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Towards the synthesis of enantiopure α-aminophosphonic acids

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Contents

1. Introduction

1.1 Organophosphorus compounds enable life as we know it

Phosphorus is the 11th most abundant element in Earth´s crust[1] and apart from being present in many inorganic minerals in our environment, it is also part of the building blocks[2, 3] involved in the chemical evolutionary processes that led to the emergence of life and still serves as a crucial macronutrient for all lifeforms. Organophosphorus compounds, i.e. organic molecules that contain phosphorus, play a major role in cell signaling pathways, in intracellular energy transfer in the form of ATP, in structural elements of cells as phospholipids and phosphonolipids, in the skeletons of vertebrates as well as in the DNA and RNA, the very backbone of life as we know it[4]. Although phosphorus is present in biological systems mostly in the form of organophosphate, there is a vast variety of other important organophosphorus compounds which were discovered in the past decades. All of these are important players in the global phosphorus cycle and influence various biochemical processes in marine and terrestrial ecosystems alike.

There are different classes of phosphorus-containing compounds according to the atoms that phosphorus is bound to. The most abundant group of organophosphorus compounds of both natural and synthetic origin belong to the so-called oxyphosphorus compounds (containing one or more P-O bonds) and carbophosphorus compounds (containing one or more P-C bonds), which can be further categorized into phosphates, phosphites,

phosphonates, phosphinates, trialkylphosphines and phosphine oxides (Figure 1). Phosphates, phosphate esters and trialkyl phosphites are exclusively oxyphosphorus compounds, trialkyl phosphines are exclusively carbophosphorus compounds, while phosphonates, phosphinates and phosphine oxides have mixed character, since they harbour both C-P and O-P bonds.

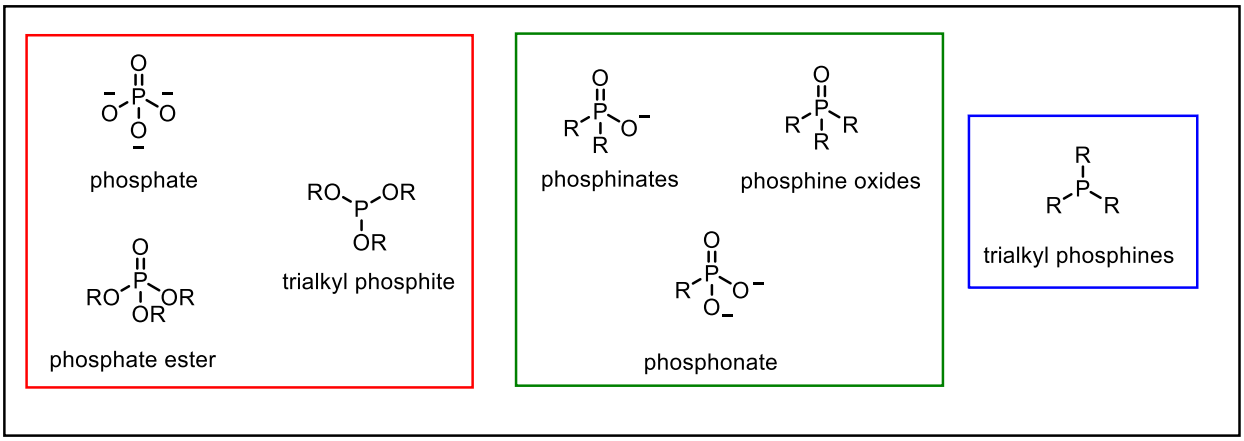


Figure 1: General structures of carbophosphorus (blue box) and oxyphosphorus (red box) compounds and compounds with mixed character (green box).

Phosphates, phosphate esters, phosphonic acids, phosphonates and phosphinates are the most important organophosphorus compounds from a biological, medicinal and industrial perspective. They can be of natural or anthropogenic origin. Figure 2 shows examples of naturally occurring and synthetic molecules from the aforementioned compound classes: **1**: adenine nucleotide, a building block for nucleic acids containing a phosphate group; **2**: triisopropyl phosphite, a common reagent employed in the synthesis of phosphonic acids; **3**: fosmidomycin, an antimalarial drug with a phosphonic acid functionality; **4**: Fosinopril, an orally active ACE inhibitor with a phosphinate functionality;

5: Brigatinib, a small molecule used in targeted cancer therapy with a phosphine oxide functionality; **6**: triphenylphosphine, a commonly used reagent in synthetic chemistry.

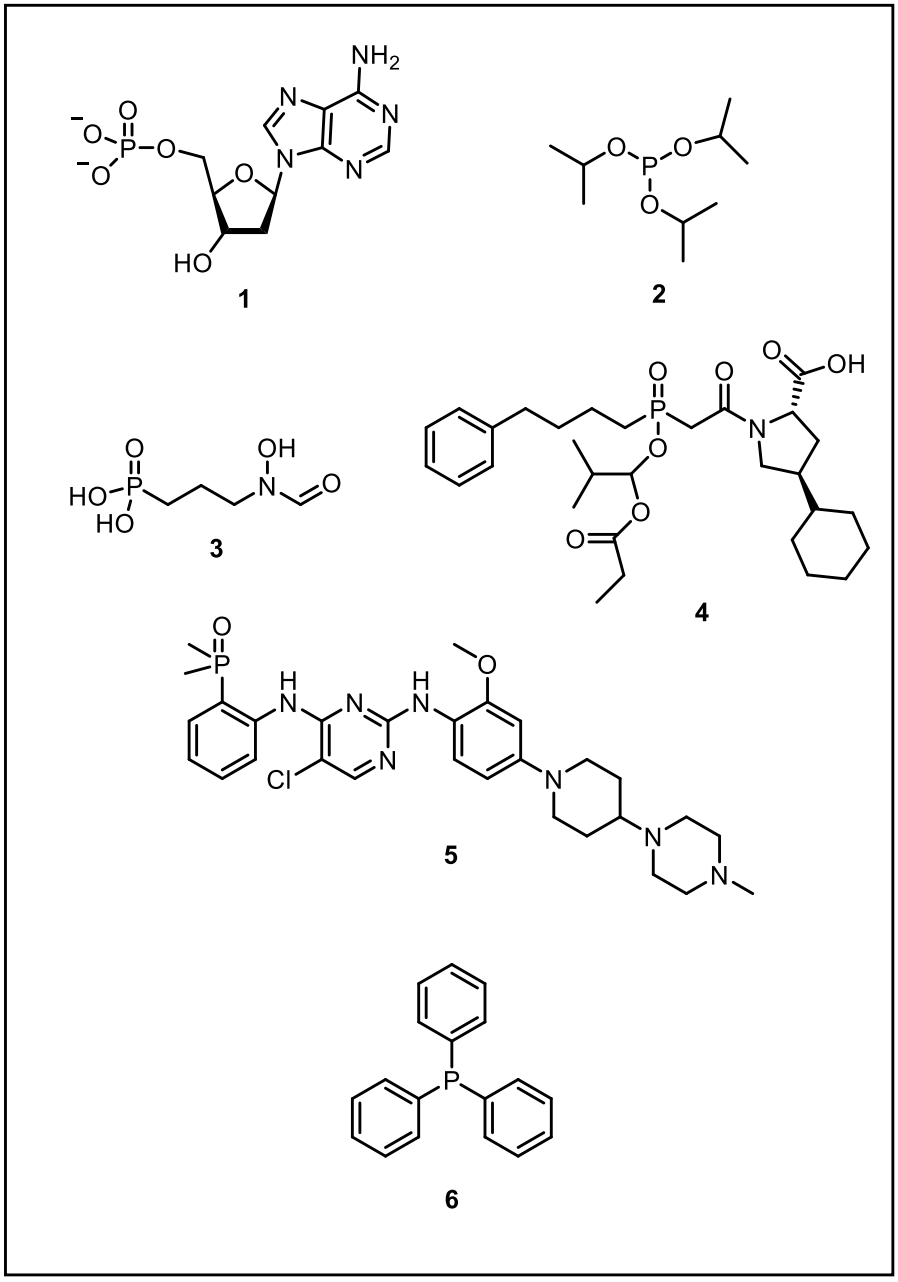


*Figure 2: Examples for naturally occurring and synthetic carbo- and oxyphosphorus compounds **1** to **6**.*

Apart from carbophosphorus- and oxyphosphorus compounds, azaphosphorus compounds (containing a P-N bond) and thiophosphorus compounds (containing a P-S bond) are also known.

Organophosphates are by far the most prominent representatives of these compound classes, and they also belong to the best studied organophosphorus compounds. Organophosphates make up the backbone of DNA and RNA, they are present in the polar headgroups of phospholipids making up cell membranes. Phosphate-containing compounds also play important industrial roles and are used as drugs,[5] agricultural chemicals,[6] flame retardants[7] and even chemical warfare agents.[8]

Phosphonic acids and phosphonates are groups of compounds that have gained the interest of the organophosphorus chemist community in the last couple of decades. They are important drugs, as the phosphonate moiety has the ability to mimic phosphate monoesters, carboxylates or, given its tetrahedral geometry, the transition state of peptide bond formation and hydrolysis (Figure 3). They can thus act as inhibitors for various enzymatically catalyzed processes.[9]

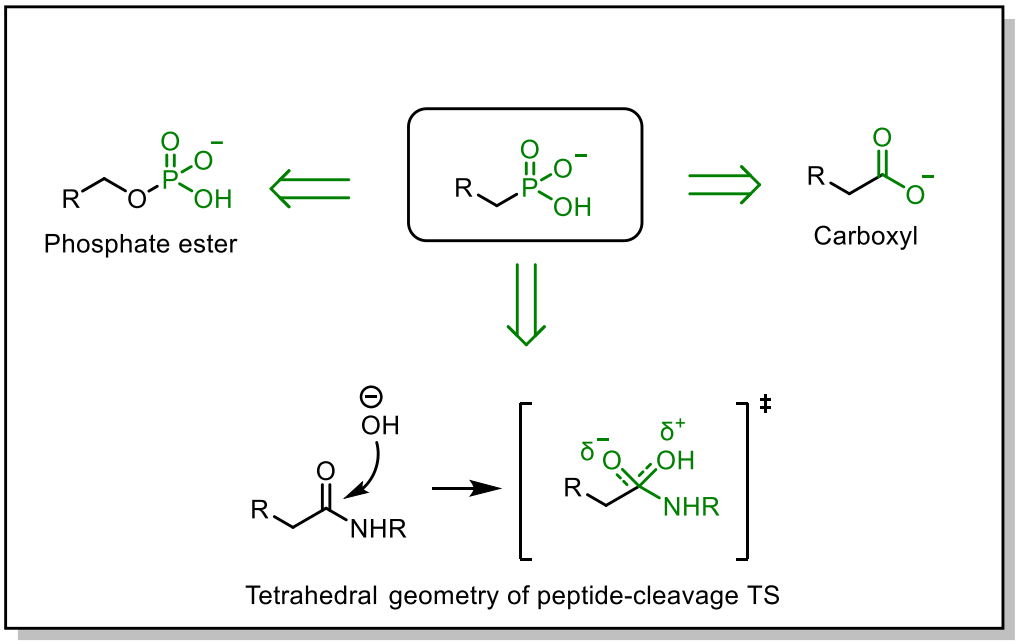


Figure 3: Geometrical and electronic comparison of the phosphonate moiety with the tetrahedral phosphate group, planar carboxylate group and the transition state of peptide bond hydrolysis.

The history of synthetic phosphonates started when Max Engelmann and Josef Pikl[10] synthesized aminomethylphosphonic acid (AMPA, **7**) during their studies for DuPont in 1942. This breakthrough in synthetic chemistry was followed by the discovery of 2-aminoethyl phosphonic acid (2-AEP, **8**) of natural origin in sheep rumen protozoa[11] in 1959. The latter was the first discovered phosphonic acid of biogenic origin and was soon after found to be a component of the sea anemone *Anthopleura elegantissima*[12]. Today it is known that phosphonates are found in various organisms and play an important role in many biochemical processes. Then in 1969, the prominent phosphonate-based antibiotic Fosfomycin (**9**) was isolated[13] from *Streptomyces* cultures and which was soon followed by the first total synthesis of this compound.[14] 1969 was also the year when the Murchison meteorite, a carbonaceous chondrite meteorite rich in organic material[15] fell

on Earth in Victoria, Australia. Chemical analysis of the meteorite by Cooper *et al.* in 1992 revealed that it contained methylphosphonic acid (**10**), ethylphosphonic acid (**11**), *n*-propyl- (**12**) and isopropylphosphonic acid (**13**) as well as *n*-butylphosphonic acid (**14**),[16] providing the first evidence for phosphonic acids of extraterrestrial origin. Figure 4 shows the structures of these phosphonic acids. The fact that there were phosphonic acids of extraterrestrial origin has led to the investigation of how phosphonates could have played a role in the evolution of life itself in the reducing atmosphere of prebiotic Earth.[17]

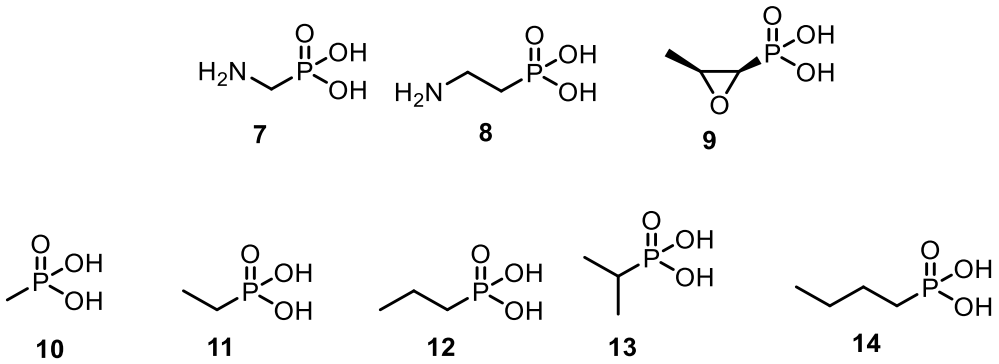


*Figure 4: Structures of the first synthetic and natural phosphonic acids to be discovered (**7** to **9**); structures of phosphonic acids found on the Murchison meteorite (**10** to **14**)*

Having discovered many naturally occurring phosphonic acids with proven biological activities in the past decades inadvertently led to the development of new and efficient synthetic methods for the production of molecules with this functional group. According to the website *ChemAnalyst* global phosphonate production had an output of 600 thousand tonnes in 2022, and this amount is projected to increase to 930 thousand tons by the year 2032.[18] Part of this output are phosphonate natural products, which have a

commercialization rate of 15%, significantly higher than the 0.1% overall commercialization rate for natural products.[19]

This has fueled the interest to find new and more efficient methods for the preparation of synthetic phosphonates and simultaneously lead to increased interest in new screening methods to find phosphonate producing microorganisms. The development of genome mining techniques has led to the identification of many organisms that produce phosphonates or use them as a P and/or C source.[20]

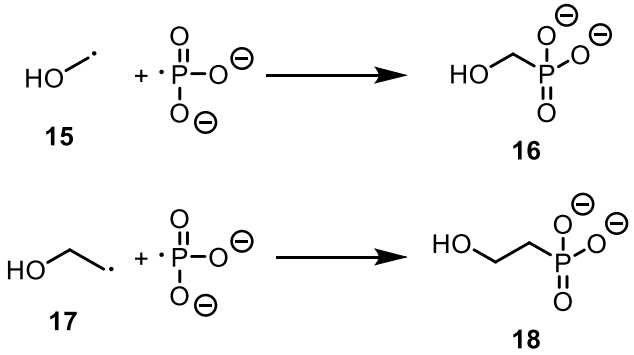
1.2 Phosphonic acids and the origin of life

Many contemporary organisms harbor enzymes that can metabolize phosphonates and phosphonic acids even though they have access to phosphates. However, if we consider the low solubility of phosphate in the marine environment due to the formation of poorly soluble apatites[3] with Ca^{2+} combined with the fact that phosphonic acids were found in extraterrestrial objects led to the question whether biochemical pathways for phosphonate biosynthesis and catabolism evolved as a possible way to circumvent the problems associated with the low availability of phosphates for metabolic purposes in a variety of ecosystems. Researchers studying the chemical evolution of terrestrial life argued that the ability of various organisms to utilize phosphonates and phosphonic acids might be an artefact from past times, when the first building blocks of life started to form and arrived on our planet during the period of the Late Heavy Bombardment 4 billion years ago. The work of cosmochemists, astrochemists, geochemists and prebiotic chemists tries to shed a light on how these compounds could have been formed in prebiotic ways in interstellar

media, under conditions that can be found on meteorites and under conditions that were present in the oceans and on the surface of early Earth.

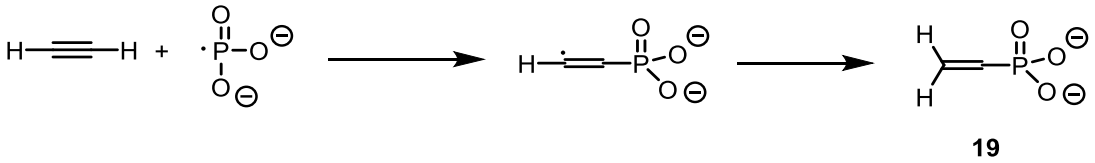
The prebiotic atmosphere on the early Earth was a complex gas-mixture with a significant hydrocarbon-component in the form of methane, and trace amounts of more complex hydrocarbons (formed through photolytic reactions of methane with other radicals resulting from strong UV-radiation[21, 22]). Additionally, the planetary surface was covered with water and different rocks, minerals and sediments and undergoing repeated wet-dry cycles in pools interconnected by streams creating flow-conditions without time restrictions.[23]

Plausible explanations for the prebiotic origin of phosphonic acids were reported by Graaf *et al.*[24] They showed experimentally that an aqueous mixture of Na_2HPO_3 and formaldehyde irradiated by UV-light can lead to the formation of hydroxymethyl phosphonic acid (**16**) and 1-hydroxyethyl phosphonic acid (**18**). They proposed a radical reaction initiated by UV-light. Photoreduction product **15** is formed by the photolysis of formaldehyde. The formation of **18** could be explained by the reaction of the phosphite radical with the photoreduction product of acetaldehyde, **17**. Acetaldehyde in turn is produced from formaldehyde when irradiated with UV-light[25](Scheme 1).[17]



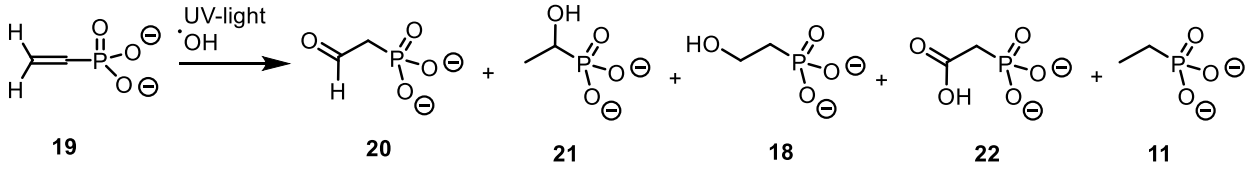
*Scheme 1: Recombination of a hydroxymethyl and hydroxyethyl radical with phosphite radicals leading to hydroxymethyl-(**16**) and 2-hydroxyethyl phosphonate (**18**), respectively.*

According to the same report, the formation of **16** and **18** was also observed in experiments where aqueous solutions of methanol and ethanol with phosphite were irradiated according to the same protocol. Graaf *et al.* further elaborated on this idea by experimentally showing the formation of vinylphosphonic acid (**19**) under neutral or basic conditions in an aqueous mixture of acetylene and Na_2HPO_3 when irradiated with UV-light (Scheme 2).[26] It has been speculated that acetylene could have been a possible component of the anoxic atmosphere of primordial Earth.[27]



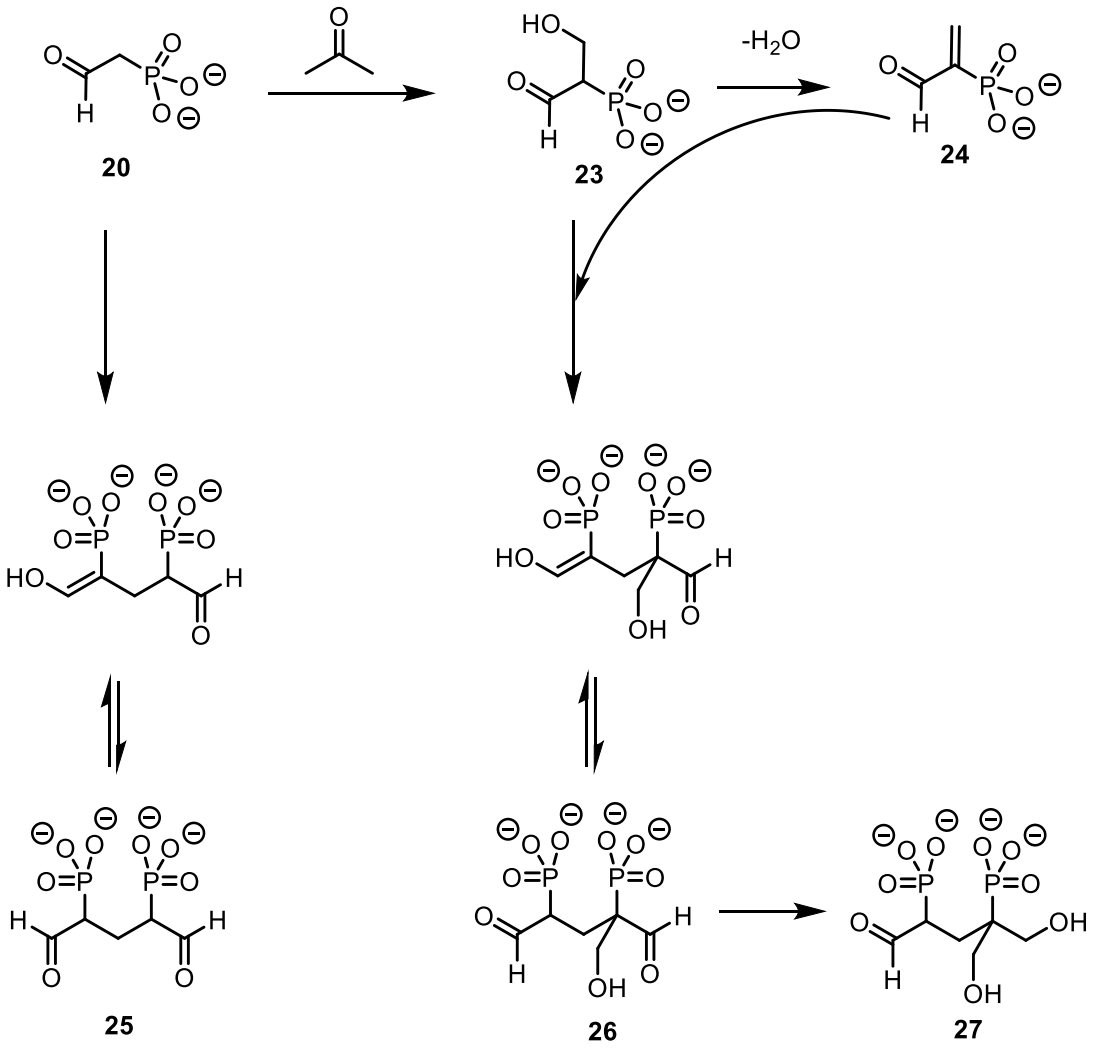
*Scheme 2: Schematic illustration of the formation of vinylphosphonic acid **19** from acetylene and a phosphite radical.*

The resulting vinylphosphonic acid (**19**) was further found to be photolyzed in the aqueous mixture leading to hydration products such as phosphonoacetaldehyde (**20**), 2-hydroxyethyl phosphonic acid (**21**), 1-hydroxyethyl phosphonic acid (**18**), phosphonoacetic acid (**22**) and ethylphosphonic acid (**11**) (Scheme 3). Among these, **20** and **21** were the major organic products with a combined yield of 17%.



*Scheme 3: Products of the photolysis of vinylphosphonic acid (**19**) under UV-light and recombination with hydroxyl radicals.*

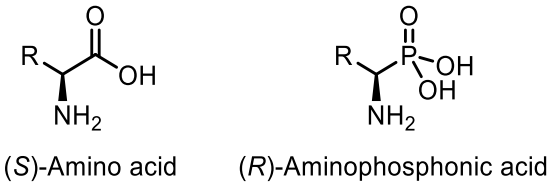
Phosphonoacetaldehyde can further serve as the starting material for other more complex organophosphonates such as 2-hydroxymethyl-2-phosphonoacetaldehyde (**23**), which can in turn undergo dehydration to give 2-methylene-2-phosphonoacetaldehyde (**24**); (1,5-dioxopentane-2,4-diyl)bisphosphonic acid (**25**) or (2-formyl-1-hydroxy-5-oxopentane-2,4-diyl)bisphosphonic acid (**26**), which can be further reduced to (1-hydroxy-2-(hydroxymethyl)-5-oxopentane-2,4-diyl)bisphosphonic acid (**27**) (Scheme 4).[28]



Scheme 4: Reactions of phosphonoacetaldehyde with formaldehyde under prebiotic conditions leading to the formation of more complex phosphonic acids.

1.3 α-Aminophosphonic acids and α-Aminophosphonates

α-Aminophosphonic acids are a special group of phosphonic acids containing an N-C-P motif with an amino group in α-position to the phosphonic acid moiety. They are structural analogs of α-amino carboxylic acids but contain a sterically more demanding, tetrahedral phosphonic acid group instead of the planar carboxylic acid group (Figure 5).

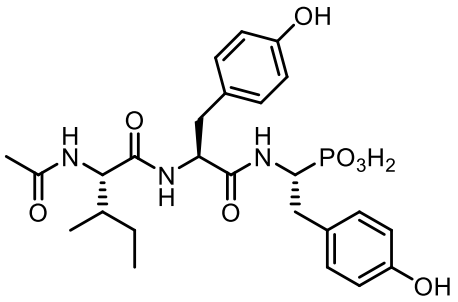


(*S*)-Amino acid (*R*)-Aminophosphonic acid

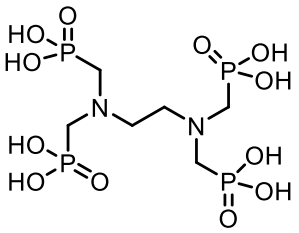
Figure 5: Structural comparison of aminophosphonic acids and amino carboxylic acids.

The tetrahedral geometry and electronic properties of this structural motif are the reason for the ability of aminophosphonic acids and aminophosphonates, to act as a transition state analogs for ester and amide bond formation and hydrolysis by mimicking the tetrahedral transition state of these enzymatic reactions.[29] Thus, aminophosphonic acids and aminophosphonates are effective inhibitors of varied proteases, peptidases and ligases.[30] Compounds like these are thus enjoying an ever growing popularity as drugs[31] with potential antiviral,[32] antifungal,[33] antibacterial,[34] antioxidative and anti-inflammatory,[35] as well as anticancer[36] effects. Apart from these medical applications, aminophosphonates and aminophospohnic acids are also widely used in modern agriculture as herbicides,[37] pesticides and insecticides.[38] Figure 6 shows the structures of selected representatives of these molecules: **28** – a naturally occurring

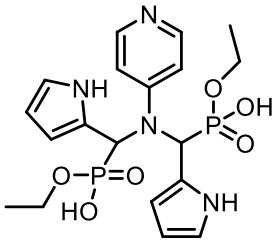
phosphonotripeptide angiotensin converting enzyme (ACE) inhibitor; **29** – a polyphosphonic acid chelating agent, constituent of the drug Samarium (^{153}Sm) lexidronam used as treatment for pain associated with bone cancer; **30** – a potential antibacterial and anti-inflammatory agent; **31** - potential lung cancer therapeutic; **32** – potential antifungal agent; **33** – glyphosate, a controversial herbicide, an inhibitor for the enzyme 5-enolpyruvylshikimate-3-phosphate synthase.



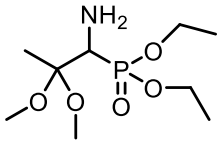
28, K-26



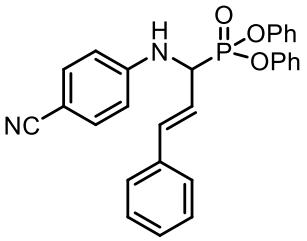
29, EDTMP



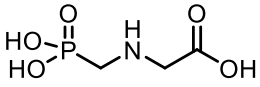
30, diethyl ((pyridin-4-ylazanediyl)bis((1*H*-pyrrol-2-yl)methylene))bis(hydrogen phosphonate)



31, diethyl (1-amino-2,2-dimethoxypropyl)phosphonate



32, (E)-diphenyl (1-((4-cyanophenyl)amino)-3-phenylallyl)phosphonate



33, glyphosate

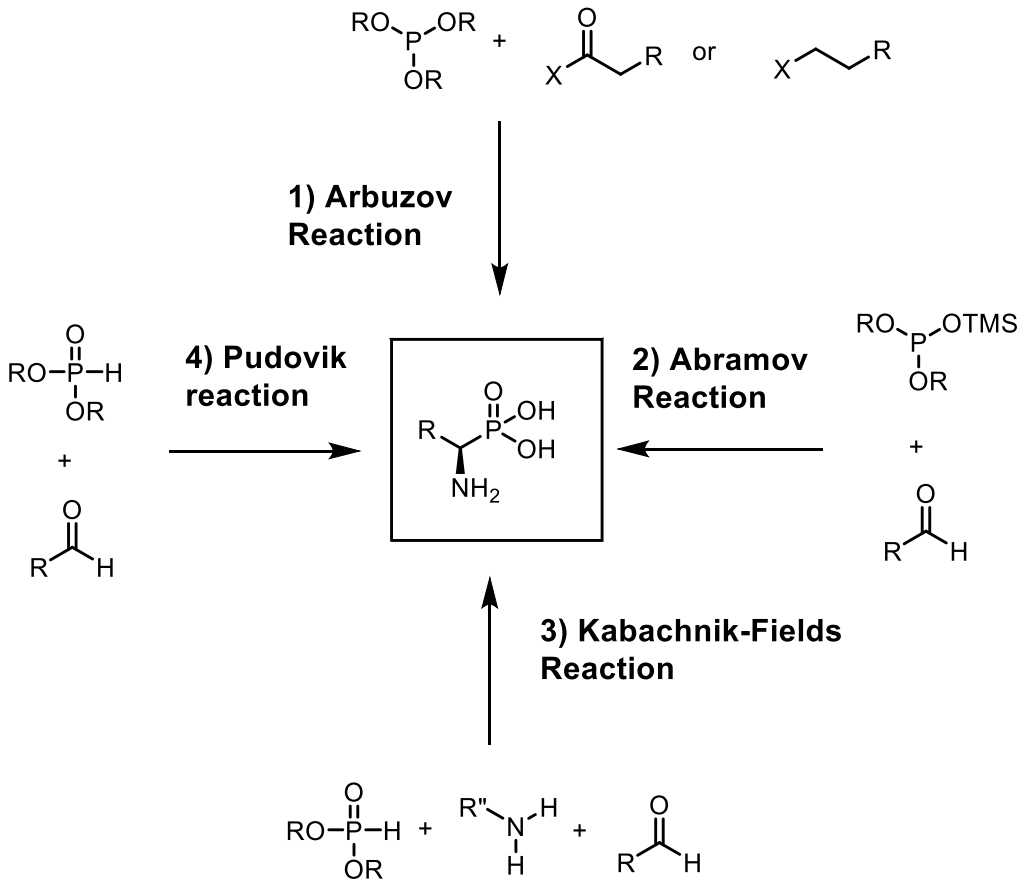
Figure 6: Structures of selected biologically active aminophosphonic acids and aminophosphonates.

Due to the industrial and medical importance of α-aminphosphonic acids and their derivatives, there is a need for reliable, synthetic methods that allow for the synthesis of these compounds in enantiopure form. Examples of such strategies will be given in the following chapters.

1.4 Synthesis of α-aminophosphonic acids and their derivatives

1.4.1 Overview of the general strategies

Introducing the phosphonate moiety is usually one of the first steps to be undertaken in the synthesis of aminophosphonic acids. Unsurprisingly, many different methods to facilitate the formation of a phosphorous-carbon bond (P-C bond) were developed in the past. Scheme 5 illustrates the most common ones used in the synthesis of aminophosphonic acids.



Scheme 5: Common methods to form a direct phosphorus-carbon bond synthetically; R = aryl or alkyl, X= Cl, Br, I.

Each of these methods has its advantages and disadvantages. In the Arbuzov reaction (also called the Michaelis-Arbuzov reaction), the P-C bond is formed by reacting a trialkyl phosphite with an acyl- or alkyl halide. In the case of alkyl halides, harsh reaction conditions (high temperatures) are needed to facilitate the reaction which limits the substrates scope.[39] The toxicity of many alkyl halides[40] is also a drawback. Arbuzov reactions using alkyl halides as electrophiles are typically not suitable for the construction of alpha-functionalized phosphonates, such as α-aminophosphonates. Acyl chlorides can be reacted with trialkyl phosphites under significantly milder conditions[41] and they result in α-oxo phosphonates (also called α-keto phosphonates), which can be easily converted to other compound classes. Thus, they can be used to finally give α-aminophosphonic acids. Furthermore, Arbuzov reactions with acyl halides allow for the use of carboxylic acids as cheap, prefunctionalized starting materials. The only prerequisite is the stability of the carboxylic acid of choice towards the conditions needed for acyl chloride formation.

The Abramov reaction allows for the direct formation of racemic α-hydroxyphosphonates from aldehydes and silylated phosphites under mild conditions.[42] List *et al.*[43] have reported a catalytic asymmetric Abramov reaction to synthesize enantiopure α-hydroxyphosphonates using a chiral disulfonimide catalyst. Enantiopureα-hydroxyphosphonates can otherwise only be obtained by oxidizing the racemic product of an Abramov reaction to the corresponding ketophosphonate and then reducing the latter again in an asymmetrical way.

Another alternative approach for the formation of a P-C bond is the Kabachnik-Fields reaction. The Kabachnik-Fields reaction, also called phospha-Mannich reaction, is a three-component condensation reaction for the synthesis of aminophosphonates

between an oxo-compound, an amine and a dialkyl or diaryl phosphite reported simultaneously by Kabachnik[44] and Fields[45] in 1952. Since the discovery, this reaction has found widespread use for the synthesis of α-aminophosphonic acids.

This three-component one-pot reaction is often conducted under microwave irradiation.[46] It often results in complex reaction mixtures and complicated reaction setups. Enantiopure α-aminophosphonic acids can be generated by employing chiral catalysts, chiral carbonyl compounds, chiral phosphorus compounds or chiral amines.[47]

The Pudovik reaction is a reaction in which carbonyl-compounds are reacted with dialkyl- or diaryl phosphites to produce α-hydroxyphosphonates. It suffers from the same drawbacks as the Kabachnik-Fields reaction. Expensive catalysts have to be used to make enantiopure α-hydroxyphosphonates by this methodology, and the resulting products often suffer from unsatisfactory *ee´*s and/or yields[48] depending on the substituents on the carbonyl-compounds (aromatic, aliphatic, electron withdrawing or electron donating groups) and steric effects. In a variant, called the aza-Pudovik reaction, α-aminophosphonates can be generated directly by reacting a dialkylphosphite with an imine. Limitations for this method are the limited commercial availability of imines and their high price, meaning that in many cases they must be prepared in the laboratory prior to usage. Imines are also prone to hydrolysis and require careful storage conditions.

Many modern synthetic routes to access α-aminophosphonates also build upon these general strategies and their variations, including microwave assisted strategies,[49] photocatalytic methods,[50,51] or synthetic routes employing organocatalysts and metal-catalysts.[52] Catalyst-free variations are also known but can only furnish racemic products

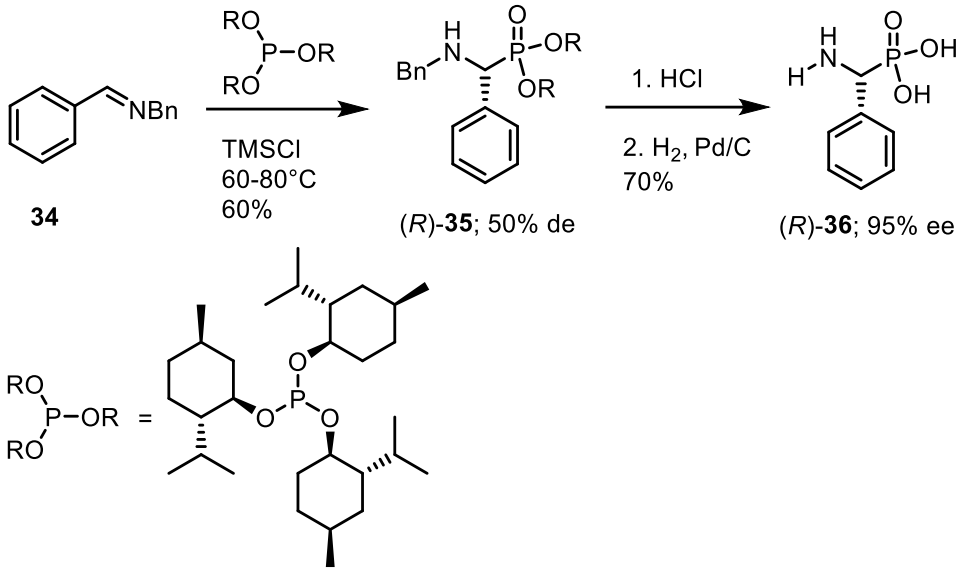
unless chiral auxiliaries are employed.[53] The same is true for the known ecologically friendly strategies[54,55] for α-aminophosphonate synthesis.

1.4.2 Synthesis of α-aminophosphonates by hydrophosphonylation – the aza-Pudovik reaction

1.4.2.1 The aza-Pudovik reaction of achiral imines with chiral phosphites

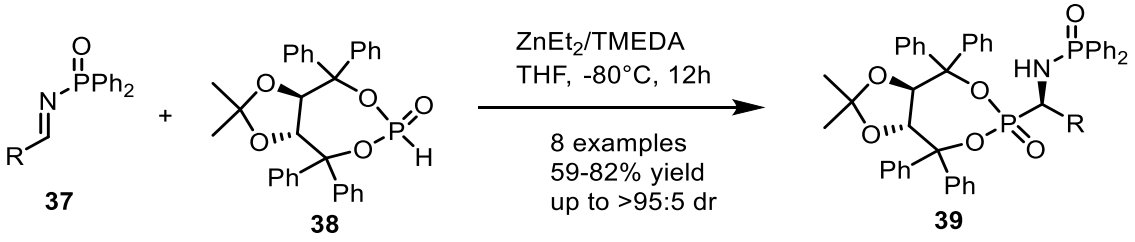
The addition of H-phosphites to imines in order to create optically pure α-aminophosphonates can be either done by using a chiral catalyst or by using chiral pool reagents such as chiral imines or chiral phosphites.

Kolodiazhnyi *et al.*[56] employed a chiral phosphite derived from (1*R*,2*S*,5*R*)-(–)-menthol for the nucleophilic addition to achiral imine **34** in the presence of trimethylsilyl chloride (TMSCl) to make *N*-protected α-aminophosphonate (*R*)-**35**, which led to (*R*)-phosphophenyl glycine [(*R*)-**36**] in 70% yield with 95% *ee* after a few additional manipulations (Scheme 6).



Scheme 6: Synthesis of (R)-phosphophenyl glycine from an achiral imine using tris[(1R, 2S, 5R)-menth-2-yl] phosphite as chiral pool reagent to induce a stereoselective reaction.

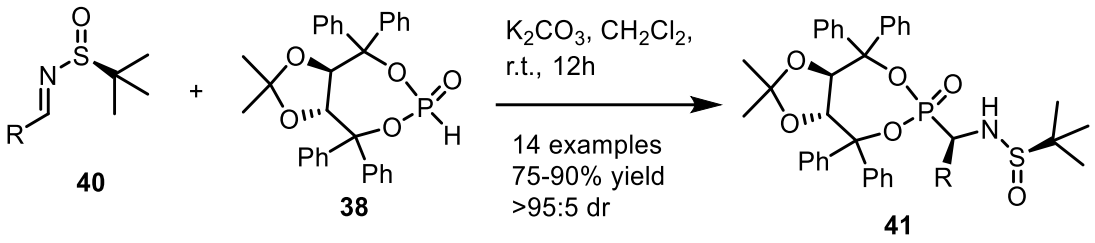
Another example of a chiral phosphite which was successfully used in aza-Pudovik reactions is (*R,R)*-TADDOL phosphite (**38**). Palacios *et al.* report the use of the latter for the synthesis of highly enantioenriched α-aminophosphonates of general structure **39** starting from *N*-diphenylphosphinylimines of type **37** (Scheme 7).[57]



Scheme 7: Synthesis of enantiopure aminophosphonates from achiral N-diphenylphosphinylimines and (R,R)-TADDOL phosphite; R = alkyl, aryl.

They report lower yields and diastereoselectivities in case of sterical hinderance.

The same chiral TADDOL phosphite was also employed for the synthesis of aminophosphonates of general structure **41** from (*S*)-*N*-*tert*-butylsulfinyl imines (general structure **40**, Scheme 8) as reported by Oszewski *et al.*[58]



*Scheme 8: Asymmetric synthesis of aminophosphonate-derivatives of general structure **41** from (S)-N-tert-butylsulfinyl imines with (R,R)-TADDOL phosphite.*

This approach affords protected aminophosphonates in higher yields and excellent distereoselectivities compared to the method employing *N*-diphenylphosphinylimines, due to the double stereoinduction. These effects were especially high in the case of aliphatic imines.

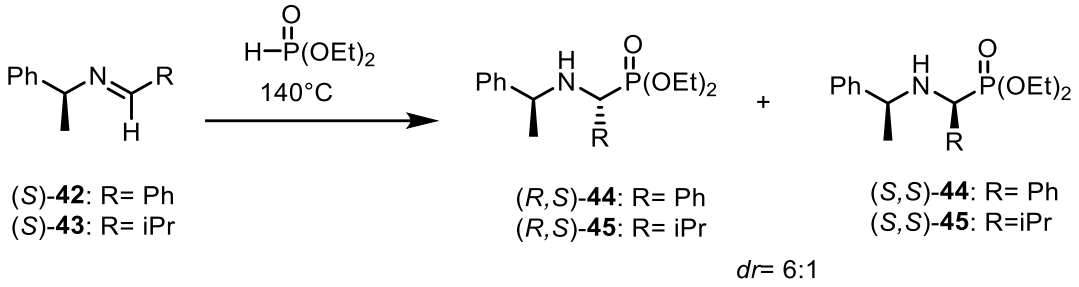
More recently, Olsziewski *et al.*[59] employed α-amido sulfones as starting materials for the synthesis of α-aminophosphonates in high *de*s, which were converted to the corresponding imines *in situ* and then reacted with the aforementioned chiral (*R,R*)- or (*S,S*)-TADDOL phosphites.

1.4.2.2 The aza-Pudovik reaction of chiral imines with achiral phosphites

An early example of the synthesis of an enantiomerically pure α-aminophosphonic acid by reacting a chiral imine and an achiral phosphite was reported by Gilmore and

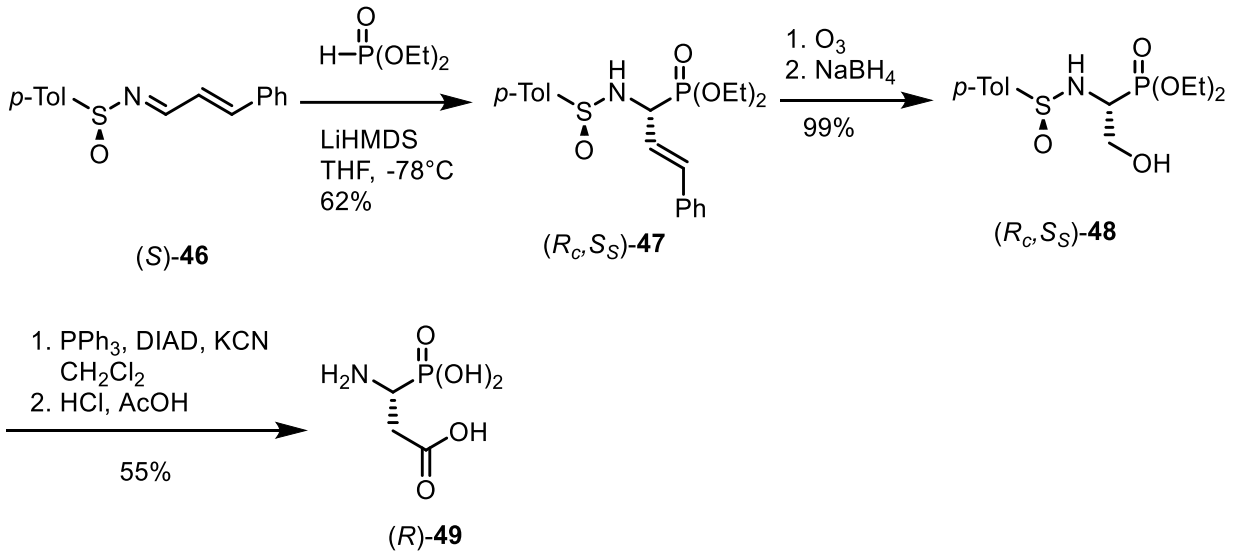
McBride[60]in 1972. They used a chiral imine derived from (*R*)-α-methylbenzylamine [(*R*)-**42**] or (*S*)-α-methylbenzylamine [(*S*)-**42**] as starting material for the synthesis of precursors for (*R*)- and (*S*)-phosphophenylglycine, namely (*R,S*)- and (*S,S*)-**44**.

5 years later[61] Goviak *et al.* showed the synthesis of the precursors for the phosphonic acid analog of the proteinogenic amino acid valine, (*R,S*)- and (*S,S*)-**45**, by the same method (Scheme 9).



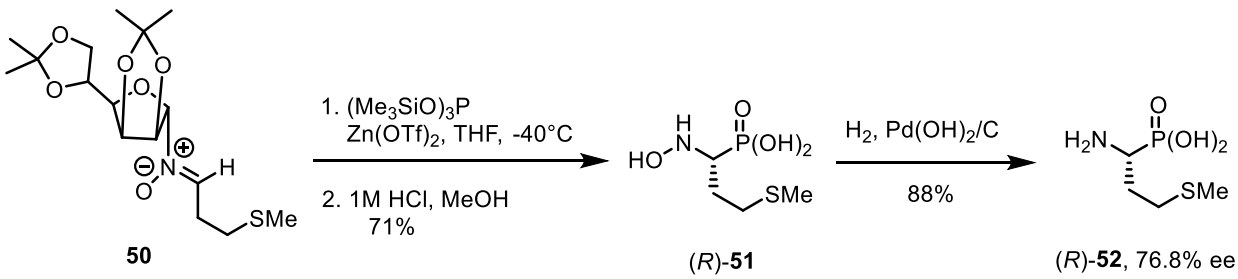
*Scheme 9: Synthesis of (R,S)-**44** and (S,S)-**44**, precursors for phosphaphenylglycine (if R= Ph) and (R,S)-**45** and (S,S)-**45**, precursors for phosphavaline (if R= iPr) from (S)-**42** and (S)-**43**.*

Mikołajczyk *et al.*[62] successfully synthesized enantiopure phosphaaspartic acid [(*R*)-**49**] by reacting (S_S)-*N*-(*p*-tolylsulfinyl)-cinnamaldimine [(*S*)-**46**] with the lithium salt of diethyl phosphite in tetrahydrofuran (THF) at −78°C in order to obtain α-aminophosphonate (R_C,S_S)-**47**, which could be elegantly converted to phosphaaspartic acid [(*R*)-**49**] in four steps (Scheme 10).



*Scheme 10: Synthesis of (R)-phosphaaspartic acid [(R)-**49**] from chiral sulfinimine (S)-**46**.*

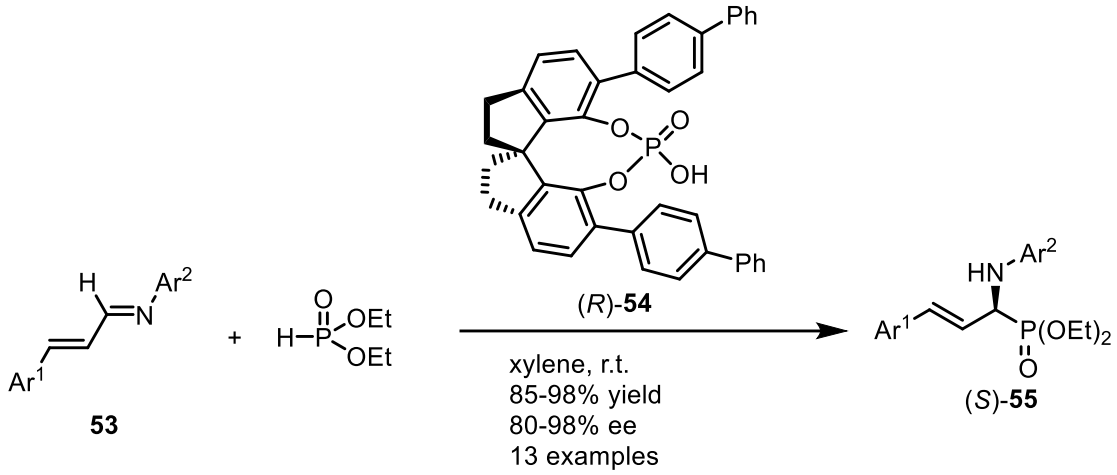
Huber and Vasella[63] have reported the synthesis of phosphamethionine [(*R*)-**52**] from *N*-glycosylnitrone **50** and $(Me_3SiO)_3P$ in the presence of catalytic amounts of $Zn(OTf)_2$ at –40°C in THF followed by catalytic hydrogenation using $Pd(OH)_2/C$ in a Parr apparatus (Scheme 11).



*Scheme 11: Synthesis of (R)-phosphamethionine [(R)-**52**] from N-glycosylnitrone **50**.*

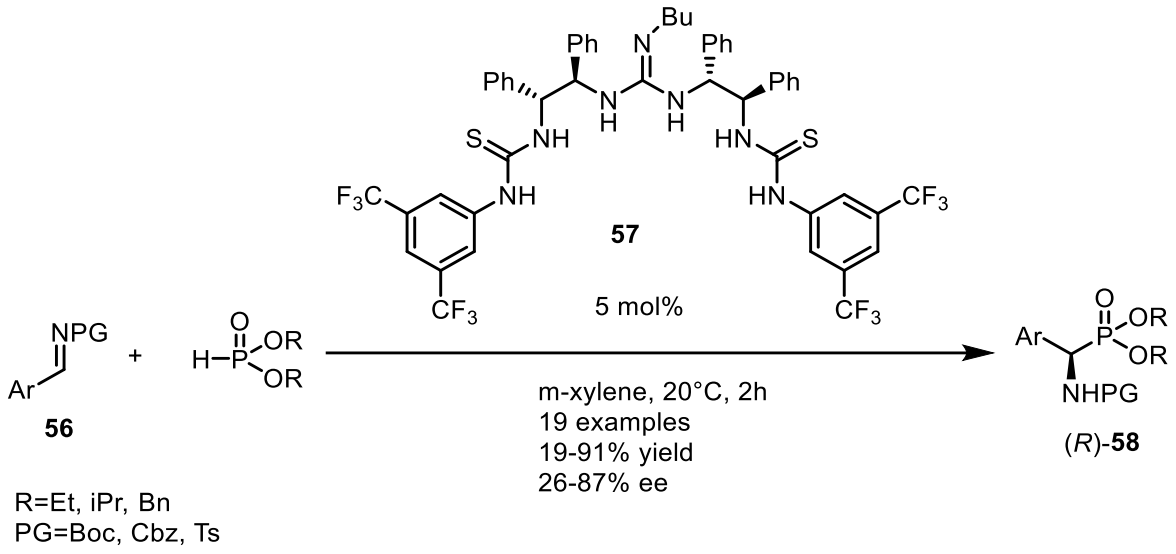
1.4.2.3 The aza-Pudovik reaction of achiral imines with achiral phosphites and a chiral organocatalyst

A recent example of a stereoselective aza-Pudovik reaction employing an organocatalyst stems from Zhao *et al.*[64] They reacted achiral cinnamaldehyde-derived aldimines with diethyl phosphite at room temperature (r.t.) in the presence of a chiral SPINOL-phosphoric acid as a highly enantioselective organocatalysts (Scheme 12).



*Scheme 12: Synthesis of aminophosphonates of type (S)-**55** from cinnamaldehyde-derived aldimines (general structure **53**) via asymmetric hydrophosphonylation with chiral SPINOL-phosphoric acid (R)-**54** as the organocatalyst.*

Another example of an asymmetric hydrophosphonylation using an organocatalyst by Chassillan *et al.*[65] uses a rigid chiral, guanidine-thiourea-derived catalyst **57** to facilitate the addition of different alkyl-phosphites to *N*-Boc (or Cbz or Ts) protected imines with various aromatic and heteroaromatic substituents (Scheme 13).



*Scheme 13: Synthesis of N-protected aminophosphonates of type (R)-**58** from N-protected imines (like **56**) and different alkyl-phosphites organocatalyst **57**.*

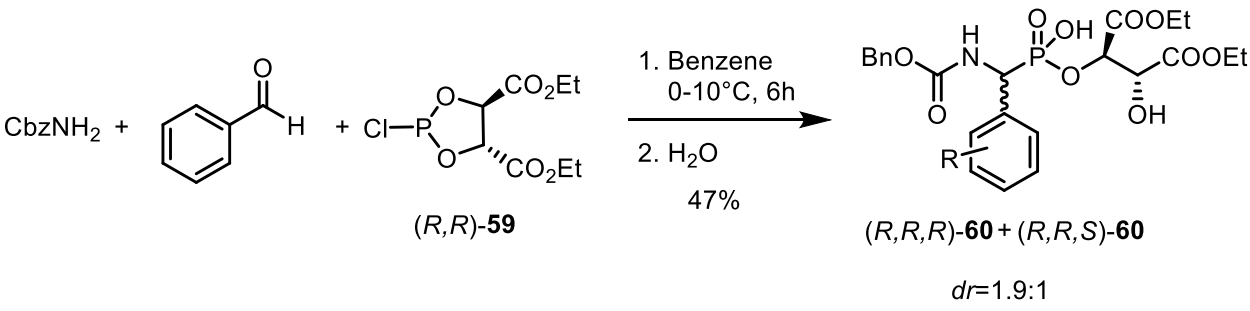
Interestingly, the guanidine-thiourea catalyst can be immobilized on polystyrene, mixed with celite and the mixture packed in a continuous-flow reactor.

1.4.3 The Kabachnik-Fields reaction

Chiral products can be obtained, similarly to aza-Pudovik reactions, by either employing chiral carbonyl compounds, chiral phosphites, chiral amines or a chiral catalyst.

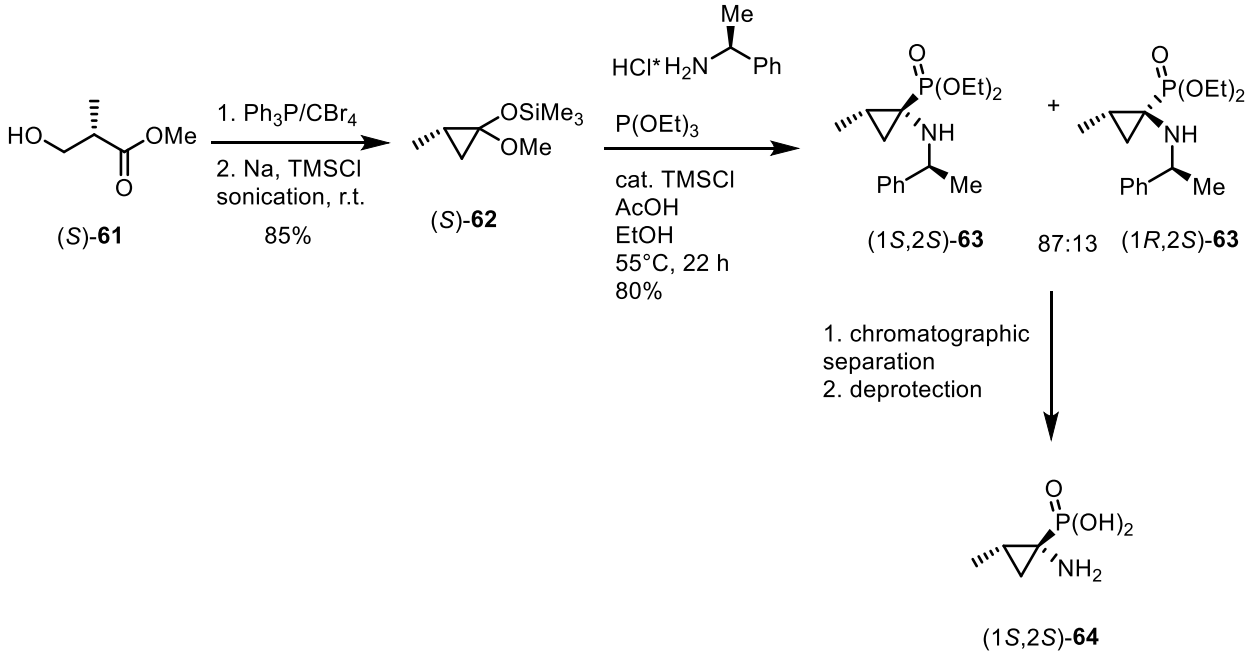
1.4.3.1 Kabachnik-Fields reaction with chiral stoichiometric reagents

Xu *et al.*[66] reported the synthesis of (*R*)- and (*S*)-*N*-Cbz-phosphonophenyl glycine precursors (*R,R,R*)-**60** and (*R,R,S*)-**60** by reacting chiral chlorophosphite (*R,R*)-**59** with benzyl carbamate and benzaldehyde. They synthesized a range of functionalized aminophosphonates by this method. The stereochemistry of the product is thus again the result of asymmetric induction with the (*R,R,R*)-diastereomer being the major and the (*R,R,S*)-diastereomer being the minor product [diastereomeric ratio (*dr*) 1.9:1, Scheme 14].



*Scheme 14: Synthesis of N-protected aminophosphonate (R,R,R)-**60** and (R,R,S)-**60** from benzaldehyde, chlorophosphite(R,R)-**59** and benzyl carbamate.*

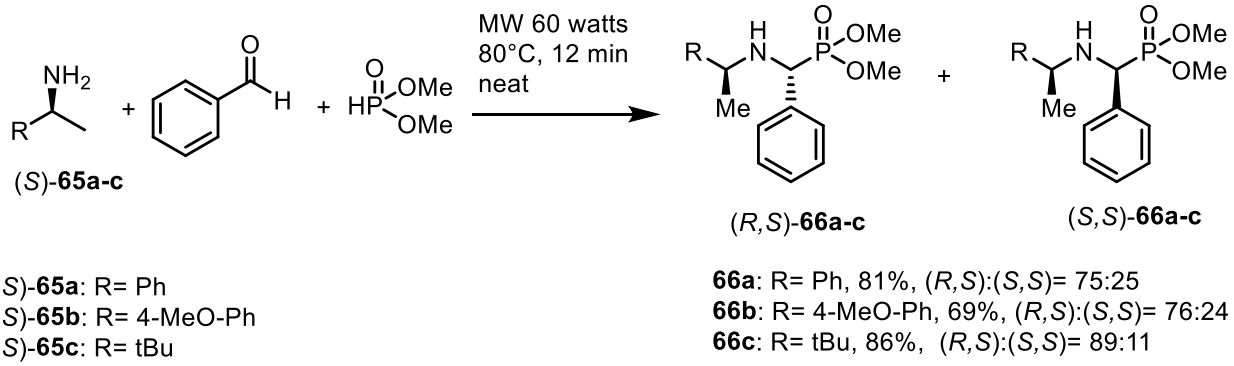
Alternatively, chiral carbonyl-compounds can also be used as shown in the work of Fadel *et al*.[67] They synthesized (1*S,*2*S*)-1-amino-2-methylcyclopropane phosphonic acid [(1*S,*2*S)*-**64**] starting from commercially available, optically pure (*S*)-3-hydroxy-2-methylpropionate [(*S*)-**61**], which they converted to 2-methylcyclopropanone ketal [(*S*)-**62**]. This ketal was further reacted in a one-pot reaction with benzyl amine and $P(OEt)_3$ in the presence of catalytic amounts of TMSCl in ethanol (EtOH) and acetic acid (AcOH) yielding (1*S,*2*S*)-**63** and (1*R,*2*S*)-**63** in 80% yield with a *dr* of 87:13. (Scheme 15). Separation of the diastereomers by column chromatography and global deprotection afforded (1*S,*2*S*)-**64** in 72% yield.



*Scheme 15: Synthesis of (1S,2S)-1-amino-2-methylcyclopropane phosphonic acid [(1S,2S)-**64**] from (S)-**61**.*

Optically pure aminophosphonic acids can also be synthesized from chiral amino components. Ordoñez *et al*.[68] reported the synthesis of optically active

aminophosphonates with good diastereomeric ratios from optically pure amino-compounds such as (*S*)-**65a-c** with benzaldehyde and dimethyl phosphite under solvent-free conditions using microwave irradiation (Scheme 16).

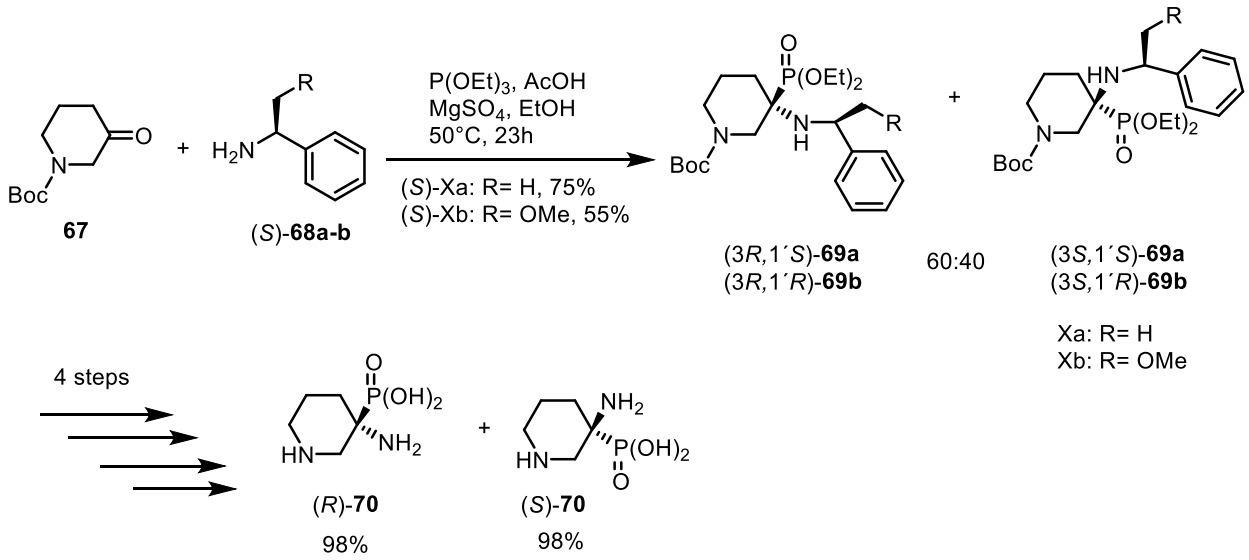


*Scheme 16: Synthesis of various aminophosphonates from chiral amines (S)-**65a-c**, benzaldehyde and dimethyl phosphite in a Kabachnik-Fields reaction under microwave irradiation.*

The (*R,S*)-diastereomer was favored in all reported cases due to the bulkiness of the substituent on the chiral amino-compound, which forced the nucleophilic attack of dimethyl phosphite on the *in situ* formed Schiff-base to occur from the less hindered face.

Fadel *et al.*[69] also reported the use of chiral amines for the synthesis of optically active, quaternary aminophosphonic acids. They synthesized both the (*R*)- and (*S*)-enantiomers of 3-aminopiperidin-3-yl-phosphonic acid [(*R*)-**70**] and [(*S*)-**70**] in a one-pot reaction from *N*-Boc-piperidin-3-one (**67**), either (*S*)-α-methylbenzylamine [(*S*)-**68a**] or (*S*)-α-methoxymethylbenzylamine [(*S*)-**68b**] and triethyl phosphite, giving diastereomers (3*R*,1´*S*)-**69a** and (3*S*,1´*S*)-**69a** in 75% and (3*R*,1´*R*)-**69b** and (3S,1´*R*)-**69b** 55% yield respectively, with both pairs of diastereomers in a diastereomeric ratio of 60:40. The diastereomers could be separated chromatographically after deprotection of the *N*-Boc

protecting group by trifluoroacetic acid (TFA). Global deprotection afforded the optically pure quaternary aminophosphonic acids (*R*)-**70** and (*S*)-**70** in 98% yield (Scheme 17).

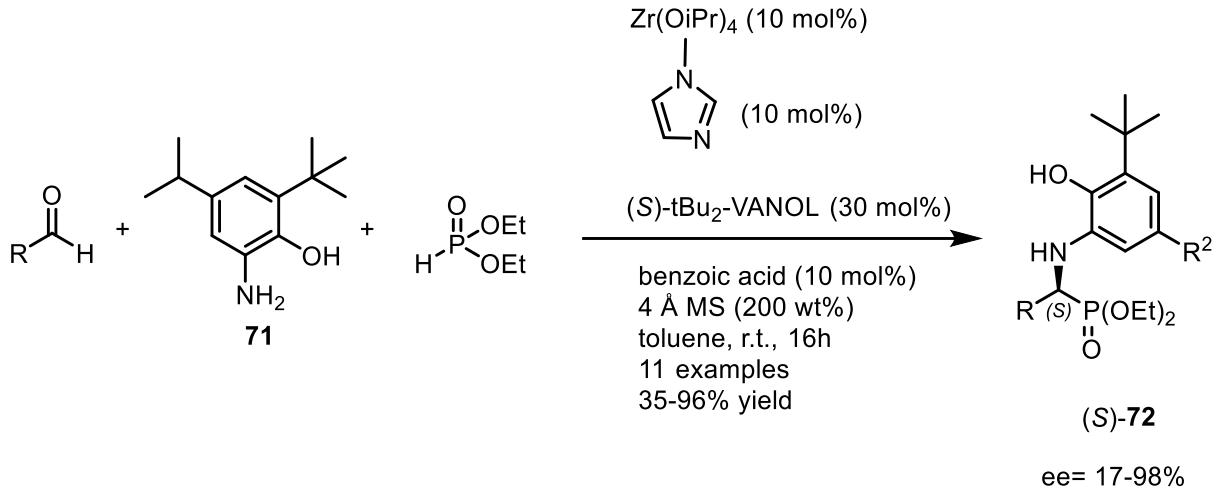


*Scheme 17: Synthesis of (R)-**70** and (S)- **70** from N-Boc-piperidin-3-one, triethylphosphite and chiral amines (S)-**68a** or (S)-**68b**.*

1.4.3.2 Kabachnik-Fields reactions with chiral catalysts

Adding a chiral organocatalyst or metal catalyst to the three-component Kabachnik-Fields reaction is an excellent way of synthesizing chiral aminophosphonates from achiral substrates.

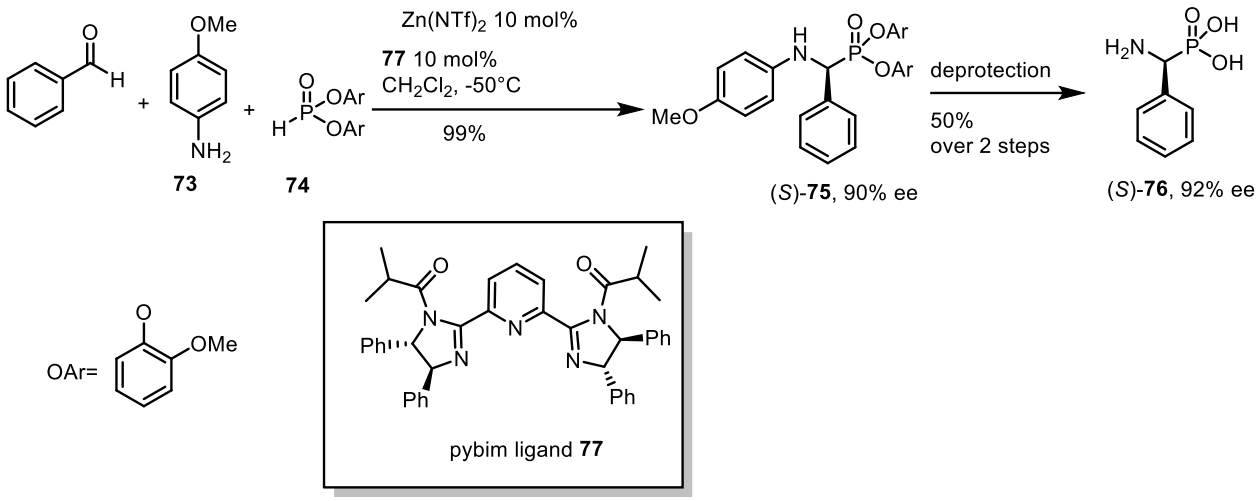
Wullf *et al.*[70] reported the synthesis of chiral aminophosphonates by an asymmetric Kabachnik-Fields reaction with a zirconium-based (*S*)-*t*Bu$_2$-VANOL catalyst from aromatic aldehydes (Scheme 18).



*Scheme 18: Synthesis of (S)-configured aminophosphonates from aldehydes with aromatic sidechains, amine **71** and diethyl phosphite catalyzed by a Zr-VANOL complex.*

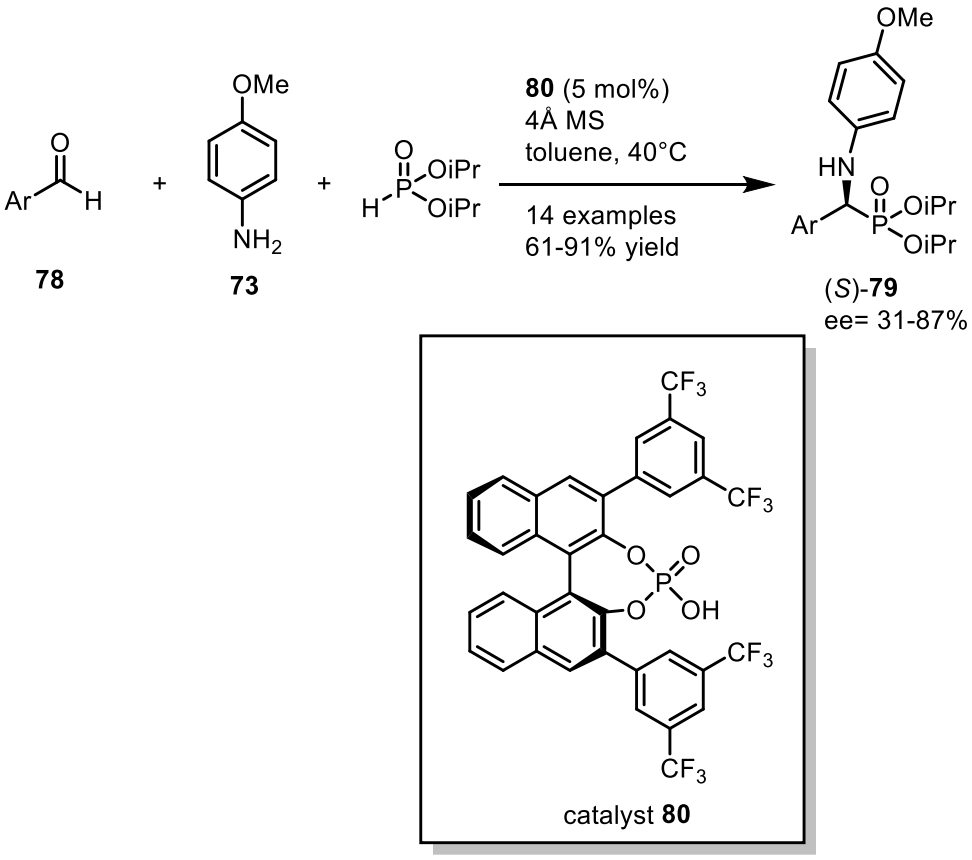
A catalytic amount of benzoic acid was needed to improve the yield and enantiomeric excess of the resulting products.

Other transition metals in combination with a chiral ligand have also been proven to be effective catalysts for Kabachnik-Fields reactions. The work of Shibata *et al*.[71] demonstrated the usefulness of a Zn(II)-2,6-bis-(1-(2-methylpropanoyl)-[4*S*,5*S*]-4,5-diphenyl-4,5-dihydro-1H-imidazol-2-yl)pyridine ligand (pybim ligand) (**77**) for stereoinduction during the reaction of benzaldehyde, *p*-anisidine (**73**) and bis(*o*-methoxyphenyl)-phosphite (**74**) (Scheme 19).



*Scheme 19: Synthesis of (S)-phosphaphenylglycine [(S)-**76**] by a Kabachnik-Fields reaction catalyzed by a Zn(II)-complex with a pybim ligand (**77**).*

(*S*)-Phosphaphenyl glycine was obtained in 92% *ee* by this method. Optically active phosphoric acid derivatives were also demonstrated to be effective catalysts for asymmetric Kabachnik-Fields reactions. Wang *et al.*[72] reported the synthesis of optically active aminophosphonates using biphenyl-based phosphoric acid **80** as an organocatalyst. They mixed aromatic aldehydes and cinnamaldehyde-derivatives **78** with *p*-MeO-aniline (**73**) and diisopropylphosphite together with **80** to obtain aminophosphonates (*S*)-**79** in good to excellent yields, however, only with moderate to good enantiomeric excess (Scheme 20).



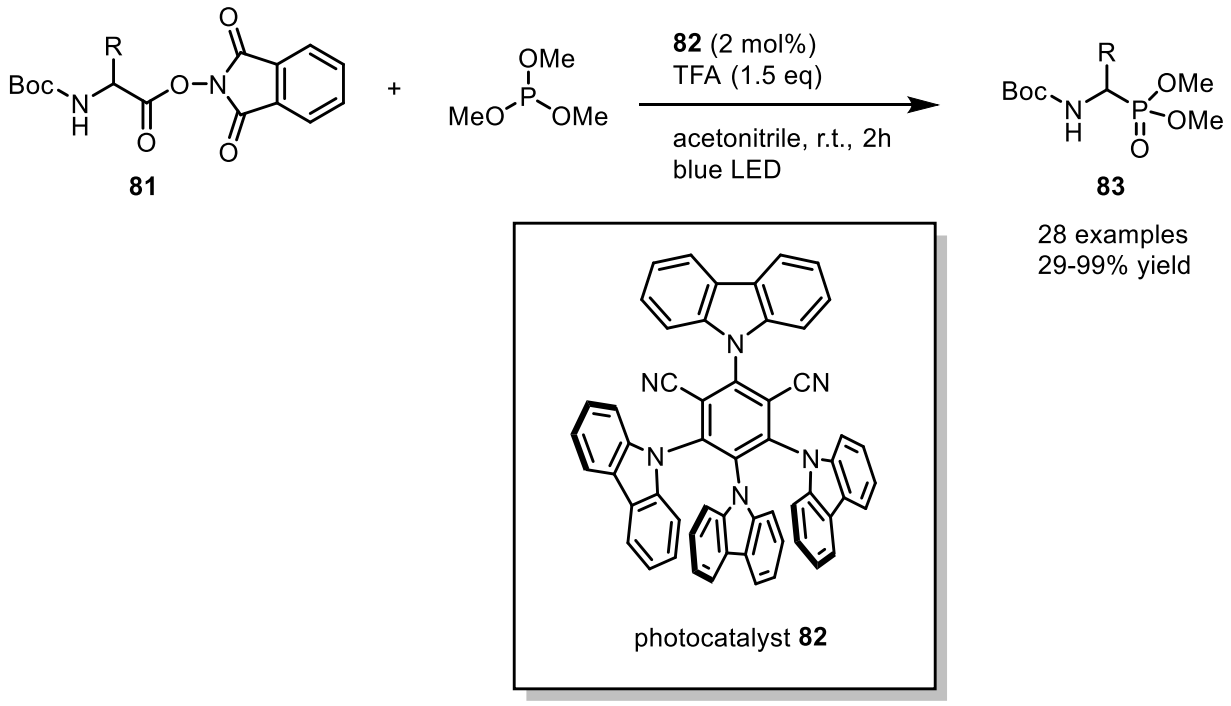
*Scheme 20: Synthesis of aminophosphonates (S)-**79** in a three-component Kabachnik-Fields reaction from aromatic aldehydes and cinnamaldehyde-derivatives (**78**), p-anisidine and diisopropylphosphite in the presence of catalyst **80**.*

The aminophosphonates that were synthesized from the cinnamaldehyde-derivatives had significantly higher *ee´*s, than those obtained from aromatic aldehydes.

1.4.4 Other methods for the synthesis of aminophosphonates and aminophosphonic acids

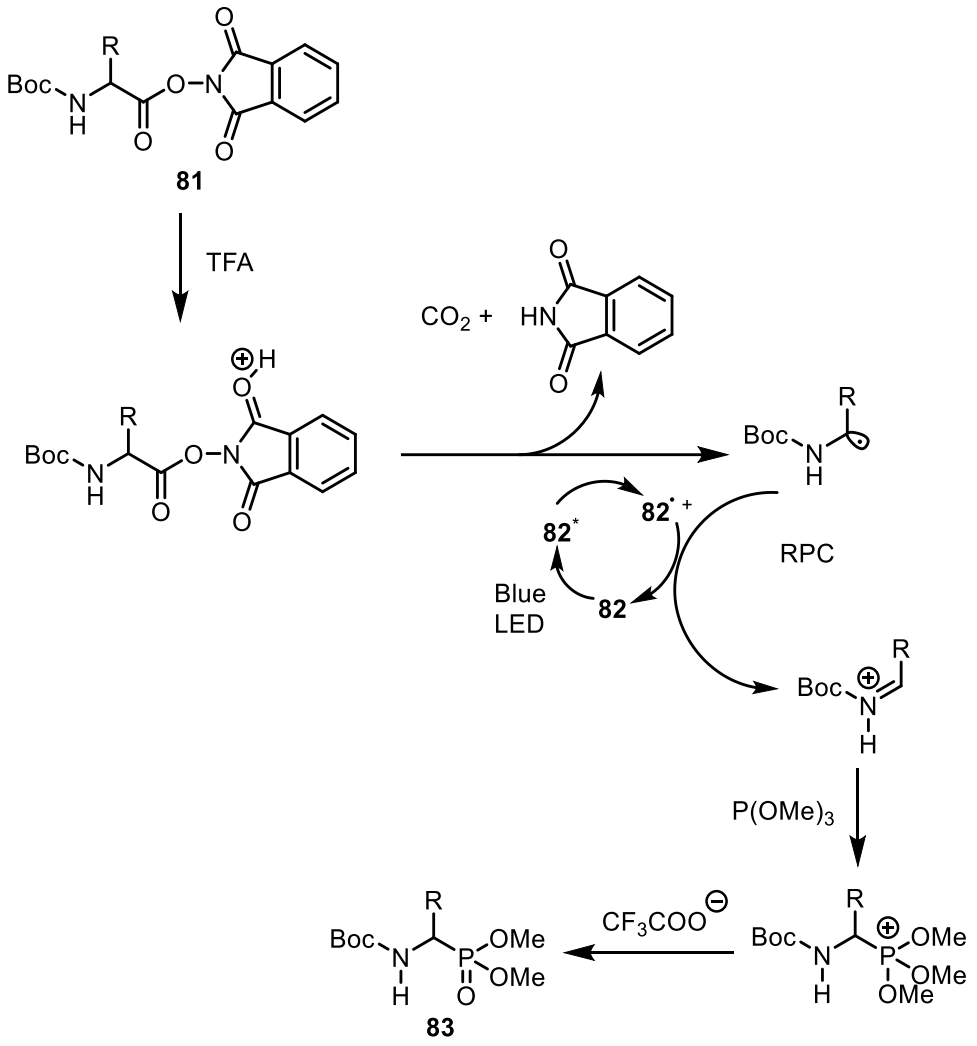
Although the synthesis of enantiomerically and diastereomerically pure α-aminophosphonic acids is of higher interest for pharmaceutical and medicinal chemists, since drugs typically need to interact with chiral, biological systems, there are still some noteworthy synthetic methods for the preparation of racemic α-aminophosphonic acids.

An example of such type was recently reported by Aggarwal *et al.*[73] They reported on the conversion of α-aminocarboxylic acids to α-aminophosphonates via decarboxylative phosphorylation using visible blue light in combination with cyanoarene-based donora-acceptor photocatalyst (**82**), With this method, they were able to prepare the phosphonate analogs of both proteinogenic and non-canonical α-amino carboxylic acids (Scheme 21).



*Scheme 21: Synthesis of N-Boc-protected aminophosphonates (of type **83**) from the hydroxyphthalimide esters of N-Boc-protected aminocarboxylic acids (of general structure **81**) and trimethylphosphite in the presence of photocatalyst **82** under irradiation with blue light.*

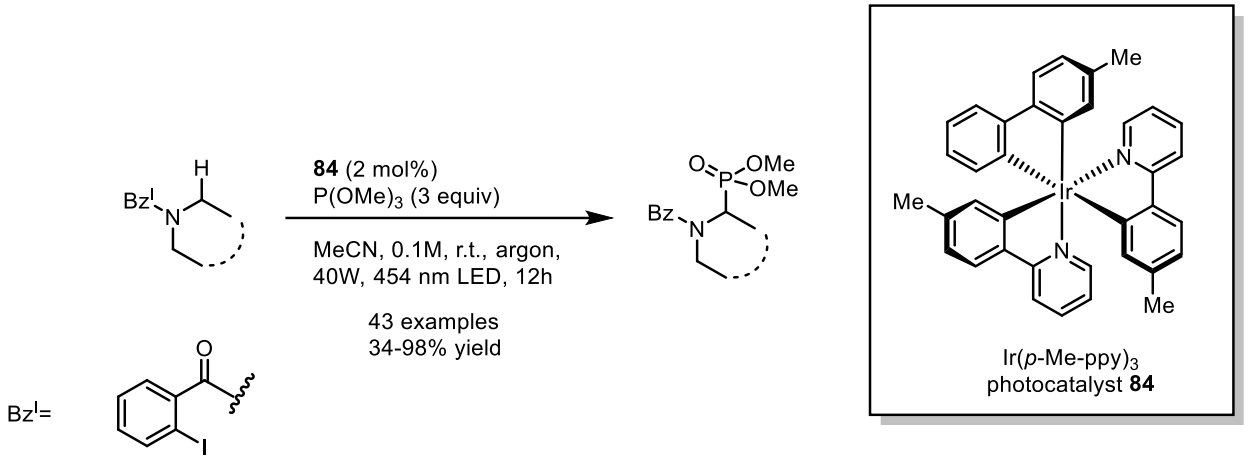
First, they prepared the hydroxyphthalimide-esters from the *N*-Boc protected amino acids, which then got protonated by TFA, which was followed by the liberation of phthalimide. Then, decarboxylation induced by the blue light and the photocatalyst, led to an α-amino radical, which was oxidized by the photocatalyst through a radical-polar crossover (RPC) to give an acyl iminimum ion which was then attacked by trimethyl phosphite in an Arbuzov-type reaction, leading to the corresponding α-aminophosphonate after demethylation (Scheme 22).



*Scheme 22: Mechanism of the decarboxylative phosphorylation of α-aminocarboxylic acids enabled by blue-light in combination with organocatalyst **82.***

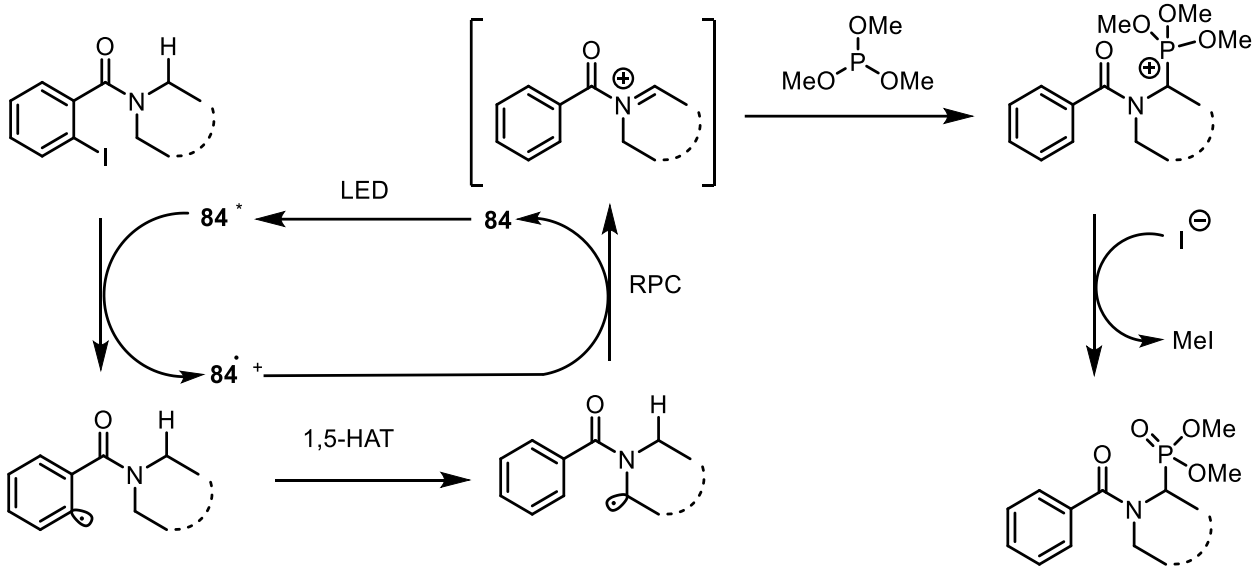
Wu *et al.*[74] reported the synthesis of a variety of aminophosphonates utilizing a photocatalytic hydrogen atom transfer (HAT)-induced α-C(sp^3) phosphonylation with Ir(*p*-Me-ppy)$_3$ (**84**) as the photocatalyst. They showed the efficacy of the method on 43 aliphatic amines, 35 of which were cyclic and 8 open-chain, bearing various functionalities, such as amides, ketones, sulfoxides, alcohols, trifluoromethyl-groups, sulfides and ethers. The reaction is very mild and redox-neutral. Both the amine and the

phosphonic acid can be liberated by hydrolysis with aqueous hydrochloric acid. Similar to the method from Aggarwal *et al.*,[73] the resulting α-aminophosphonates are obtained as racemic mixtures (Scheme 23).



*Scheme 23: Synthesis of N-benzyl-protected aminophosphonates from N-iodobenzoyl-protected aliphatic amines and trimethyl phosphite in the presence of photocatalyst **84** and visible light.*

The reaction proceeded via a HAT-RPC-Arbuzoy phosphonylation pathway (Scheme 24). The iodobenzoyl (Bz^I) protecting group serves as intramolecular HAT-reagent and generates an α-alkyl radical. The formed iodide also facilitates the demethylation leading to the phosphonate group.



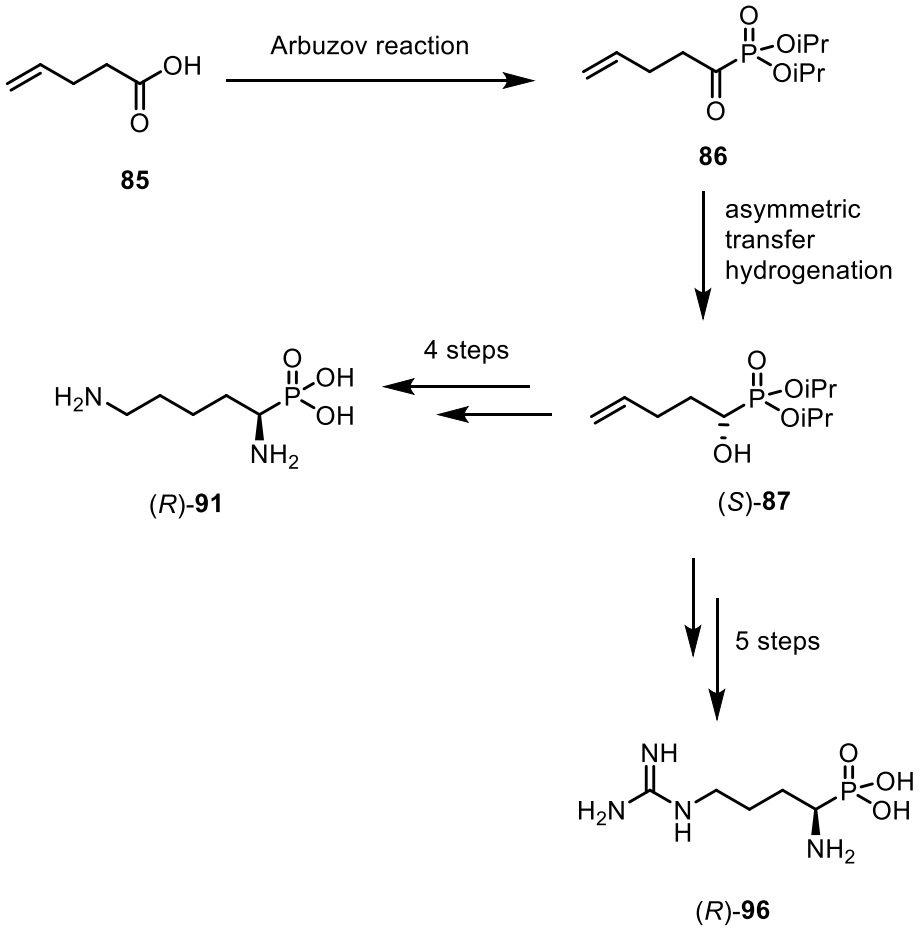
Scheme 24: Mechanism of the HAT-RPC-Arbuzov phosphonylation.

2. Aims of the thesis

Regarding the biological activity and drug-like properties of α-aminophosphonates and α-aminophosphonic acids, methods for their synthesis as pure enantiomers are needed. While there are many known methods for the synthesis of enantioenriched phosphonates, many of these utilize activated aromatic compounds, expensive catalysts or chiral starting materials and they often suffer from poor *ee´*s, mediocre yields, or both. Synthetic strategies to access enantiopure α-aminophosphonates, especially analogs of proteinogenic α-aminocarboxylic acids, lack generality and their syntheses rely on widely different approaches. Thus, the aims of this thesis were the synthesis of enantiopure phosphonic acid analogs of the proteinogenic amino acids arginine and lysine relying on the same key step to induce chirality. For this purpose, α-oxo-phosphonates were subjected to an asymmetric transfer hydrogenation. Additionally, different alternative nucleophiles for the incorporation of a nitrogen atom in the obtained α-hydroxyphosphonates via a Mitsunobu-reaction were tested. If successful, these are intended to replace the very effective but rather dangerous nucleophile hydrazoic acid (HN_3). The obtained azides can be converted to amines by hydrogenation. Thus, all tested alternative nucleophiles were chosen due to the availability of simple methods to convert them to primary amines. The alternative nucleophiles investigated were maleimide, phthalimide, trimethylsilyl azide and tetrachlorophthalimide.

The attempt was made to conceive a synthetic pathway that uses the same reagent as a starting material for both target compounds. The designed synthetic pathway branches out after a couple of steps to lead to different products.

The syntheses of the two aminophosphonic acids were attempted from 4-pentenoic acid (**85**) as the starting material and the pathway followed the same route up to the asymmetric transfer hydrogenation step. The product of the asymmetric transfer hydrogenation (ATH), the chiral hydroxyphosphonate **87**, was then subjected to different conversions as outlined below (Scheme 25).



*Scheme 25: Proposed synthetic pathway for the synthesis of enantiomerically pure (R)-phosphalysine [(R)-**91**] and (R)-phosphaarginine [(R)-**96**].*

3. Results and discussion

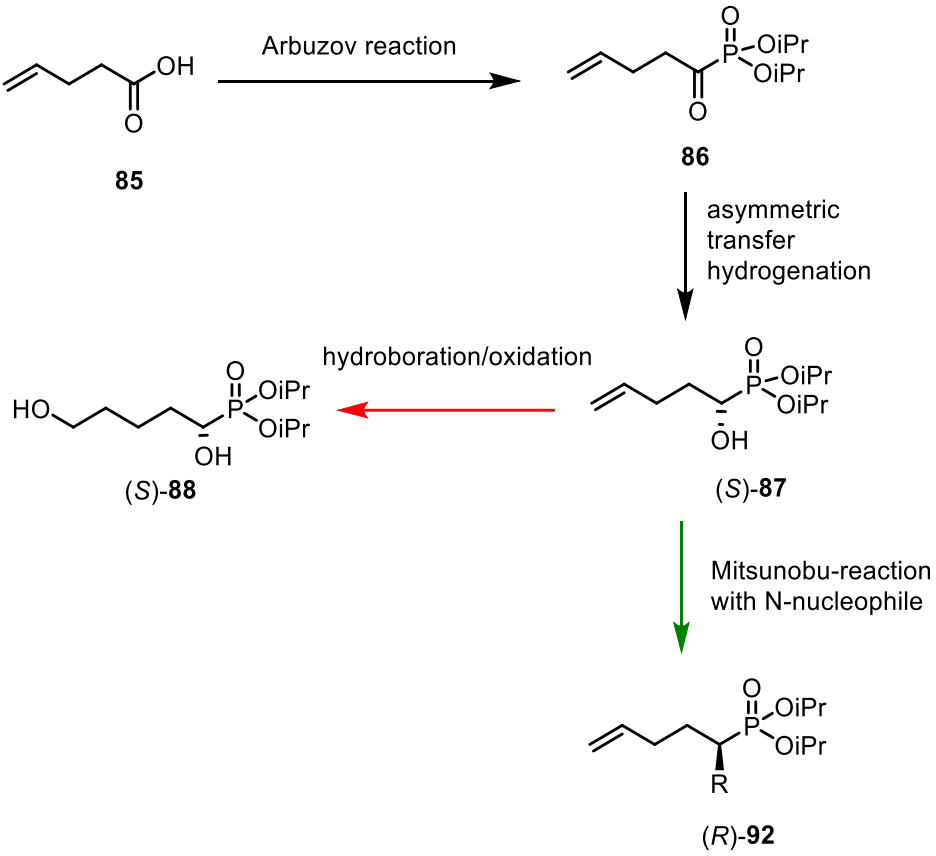
3.1 Overview of the general synthetic strategies

There are many reported synthetic routes that lead to the formation of individual phosphonic acid analogs to proteinogenic amino acids with the desired chirality, having high *ee´*s and yielding the desired products with acceptable to good yields. However, the work performed in this thesis was part of an effort to devise and streamline a synthetic protocol that can be used for the synthesis of as many phosphonic acid analogs of proteinogenic α-aminocarboxylic acids as possible. Ideally, the same keys steps can be used for the synthesis of all 21 α-aminophosphonic acids, with some minor adjustments and tweaks in some of the steps to react to the specific needs of the different functional groups. Most methods that claim to be able to produce a variety of different α-amino phosphonates are limited to aryl-substituted compounds and have a low functional group tolerance which is highly unfavorable for the synthesis of proteinogenic amino acid analogs.

The two target aminophosphonic acids are ideal model compounds to evaluate the attempted synthetic strategy regarding functional group tolerance and obtained enantiopurity using aliphatic substrates for the planned ATH. The synthesis of both target compounds was planned to start from 4-pentenoic acid (**85**). Its C_5-backbone and the terminal double bond that can be easily transformed into other functional groups make it the ideal starting material for both target compounds. It can either be used for direct incorporation of a hydroxyl-group which is needed for the synthesis of phosphalysine, or

it can also undergo ozonolysis, which leads to the addition of a hydroxyl-group while simultanously shortening the carbon backbone. The latter strategy forms the basis for the synthesis of phosphaarginine.

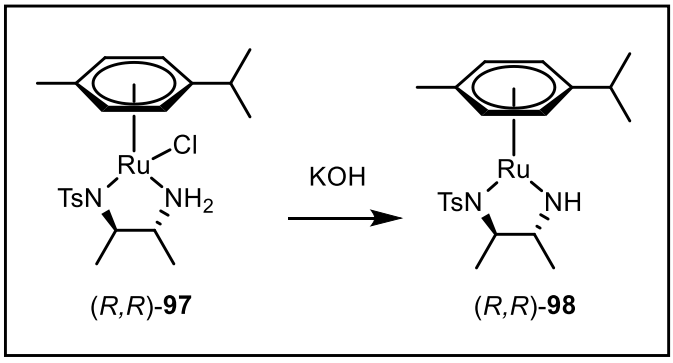
Scheme **26** illustrates the first common steps of the planned synthesis of phosphalysine and phosphaarginine, which only diverge in the steps following ATH.



Scheme 26: The first steps of the syntheses of phosphalysine and pohsphaarginine. The first 3 steps are identical, and the route diverges in the 4th step. Red arrow shows the pathway towards phosphalysine, green arrow towards phosphaarginine.

The first step of the synthetic sequence is the activation of 4-pentenoic acid with oxalyl chloride to give the corresponding acyl chloride, which is reactive enough to undergo an

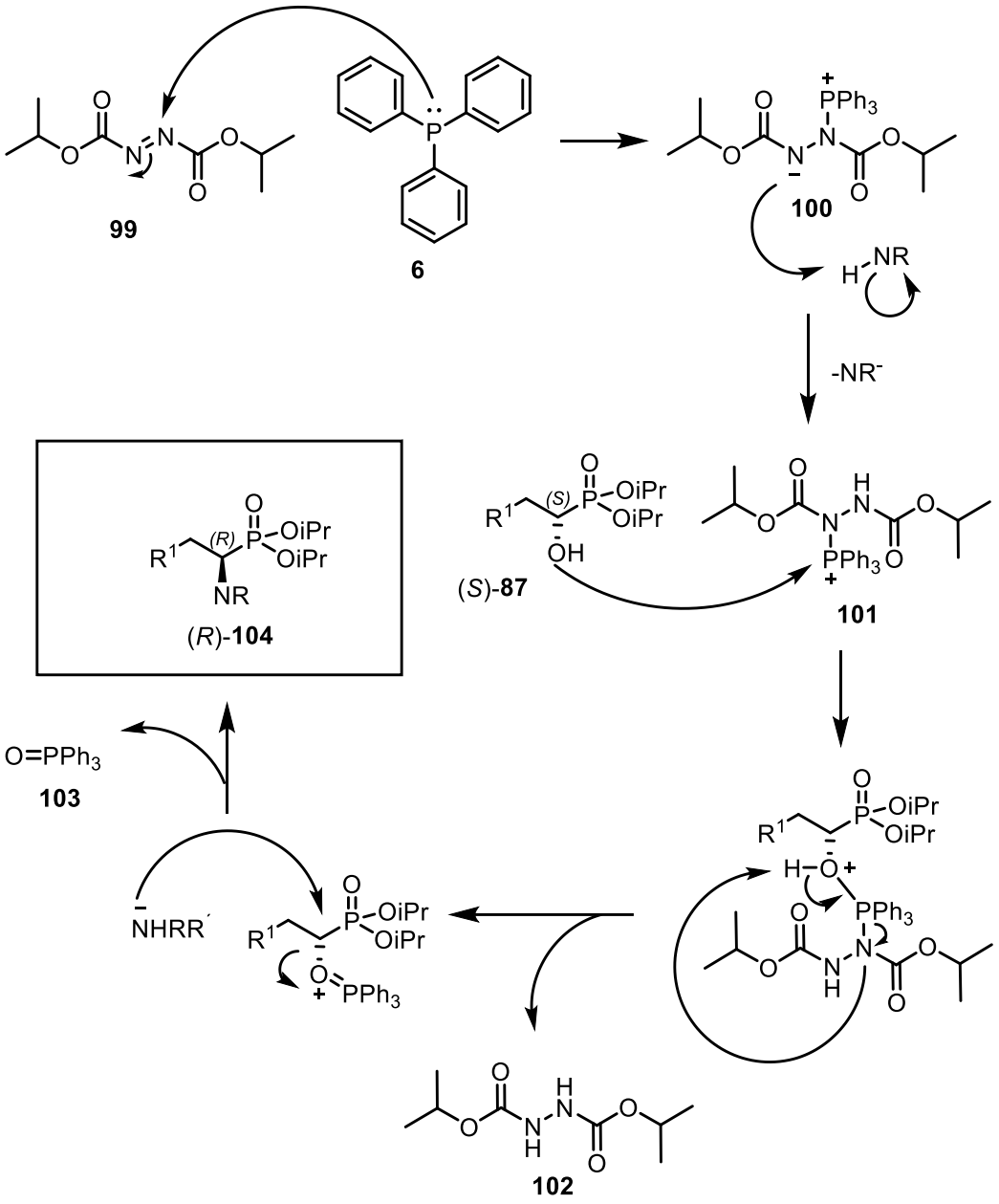
Arbuzov reaction with a trialkylphosphite – in this case triisopropylphosphite – to give the ketophosphonate **86**. This ketophosphonate is then stereoselectively converted to the corresponding hydroxyphosphonate in an asymmetric transfer hydrogenation which is a well-established method to convert ketones to chiral alcohols.[75] (*R*)- and (*S*)-**87** are obtained depending on the configuration of the used chiral Noyori-type catalyst - the (*R,R*)-catalyst yields the corresponding (S)-hydroxyphosphonate and the (*S,S*)-catalyst the (*R*)-hydroxyphosphonate. The catalyst was used in its activated form [(*R,R*)-**98** or (*S,S*)-**98**], which is easily accessible from the commercially available chlorido-catalysts (*R,R*)- and (*S,S*)-RuCl[(p-cymene)-TsDPEN] [(*R,R*)-**97** and (*S,S*)-**97**] (Scheme 27).[76]



*Scheme 27: Activation of the commercially available Noyori-catalyst (R,R)-RuCl[(p-cymene)- TsDPEN] [(R,R)-**97**] with KOH.*

The configuration of the used Noyori-catalyst is very important, as the stereochemistry of the final products is introduced at this step. In order to produce phosphonic acid analogs of proteinogenic aminocarboxylic acids with spatially similar arrangements, (*S)*-configured hydroxyphosphonates are needed and thus the Noyori catalyst with (*R,R)*-configuration is the right choice. These (*S*)-hydroxyphosphonates will then undergo a Mitsunobu reaction under inversion of configuration to finally yield (*R*)-aminophosphonic

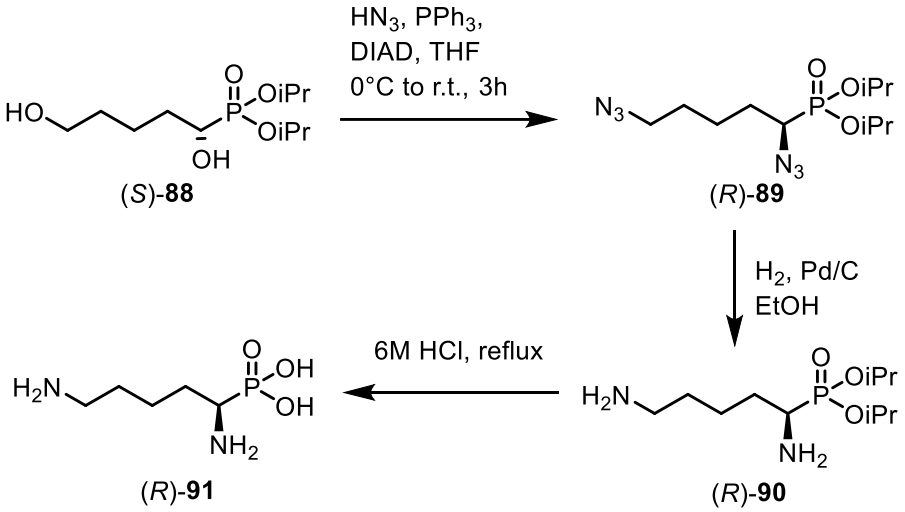
acids.[77] In the first step of a Mitsunobu reaction, an azodicarboxylate (here shown is diisopropylazodicarboxylate, DIAD, **99**) reacts with triphenylphosphine (**6**) to form betaine **100**. **100** then deprotonates the nitrogen-containing nucleophile. A nucleophilic attack by the alcohol on the phosphonium intermediate **101** follows, which results in the elimination of diisopropylhydrazine-1,2-dicarboxylate (**102**) and generates a good leaving group [triphenylphosphine oxide, $Ph_3P(O)$, **103**] allowing for the nucleophilic attack by the deprotonated nucleophile in an S_N2 reaction, resulting in the inversion of configuration at the α-position next to phosphorus (Scheme 28). If the aminophosphonic acid with opposite configuration is desired, the (*R)*-configured hydroxyphosphonate needs to be produced and the (*S,S)*-Noyori catalyst is thus needed.



*Scheme 28: Reaction mechanism of the Mitsunobu-reaction exemplified with chiral alcohol (S)-**87** as the substrate and a general N-nucleophile (HNRR´).*

The key intermediate (*S*)-**87** is then used for different transformations during the synthesis of (*R*)-**91** and (*R*)-**96**. It can either undergo hydroboration/oxidation or be directly subjected to a Mitsunobu reaction.

For the synthesis of phosphalysine, hydroxyphosphonate (*S)*-**87** is reacted with BH_3×THF in a hydroboration reaction in order to install a terminal hydroxy group and thus create the dihydroxyphosphonate (*S*)-diisopropyl-(1,5-dihydroxypentyl)-phosphonate [(*S)*-**88**]. This compound was then reacted with HN_3 in a Mitsunobu reaction, in which both hydroxyl groups were simultaneously substituted with an azide to form (*R*)-diisopropyl-(1,5-diazidopentyl)phosphonate [(*R*)-**89**]. Diazide (*R*)-**89** was then converted to enantiopure (*R*)-phosphalysine by first reducing the azide groups to amines using 3.5 atm hydrogen gas in combination with palladium on activated charcoal in a Parr-apparatus and finally deprotecting the phosphonate esters by refluxing intermediate (*R*)-**90** in half-concentrated HCl (Scheme 29). The crude compound was then purified via cation exchange chromatography to give pure, highly enantioenriched (*ee* > 99%) (*R*)-phosphalysine [(*R*)-**91**] in 18 % yield over 6 steps starting from 4-pentenoic acid.



*Scheme 29: The synthetic route from (S)-**87** to (R)-phosphalysine with HN_3 as the nucleophile in the Mitsunobu reaction.*

In order to avoid the use of harmful and difficult-to-handle hydrazoic acid, different alternative nucleophiles were tested for this transformation. Possible alternatives need to be convertible to an amine during later reaction steps but stable enough to withstand all other needed functional group manipulations.[78]

Phthalimide (**105**), maleimide (**106**) and trimethylsilyl azide (**107**) were primarily investigated as possible alternative nucleophiles for the Mitsunobu reaction of (*S*)-**88**. Later on, also tetrachlorophthalimide (**108**) was tested (Figure 7).

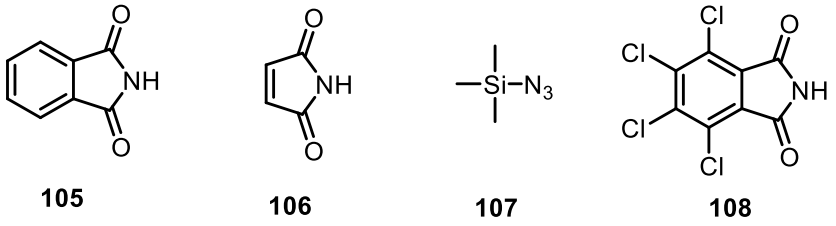


*Figure 7: Possible alternative nucleophiles to replace HN_3 in the Mitsunobu-reaction of (S)-**88**.*

Different solvents were tested (CH_2Cl_2, THF) in combination with all mentioned nucleophiles. However, none of the tested set-ups gave satisfying results. In the case of maleimide (**106**) and trimethylsilyl azide (TMS-N_3, **107**), no conversion was observed. Using phthalimide (**105**) resulted in a complex mixture of the desired product (46 %) and several side products. The purification was not feasible because of the close similarity of the polarity of the product, triphenylphosphine oxide and the formed hydrazoester. Neither any of the tested solvent systems for chromatographic separation of the mixture [ethyl acetate (EtOAc), *n*-heptane:EtOAc 1:1, 2:1, 3:1; CH_2Cl_2/2% acetone], nor attempts to precipitate triphenylphosphine oxide from the crude mixture with $ZnCl_2$[79] were successful.

Since phthalimide still led to measurable product formation, 3,4,5,6-tetrachlorophthalimide (**108**) was tested additionally.

The 4 chlorine substituents of **108** are strongly electron withdrawing resulting in a lower pKa of tetrachlorophthalimide (5.78)[80] compared to phthalimide (8.3)[81] and thus higher acidity of the imidic proton. The relatively low price of tetrachlorophthalimide is also a factor to be taken into consideration (0.27 EUR/mmol, Fluorochem – Doug Discovery, 13.9.2024).

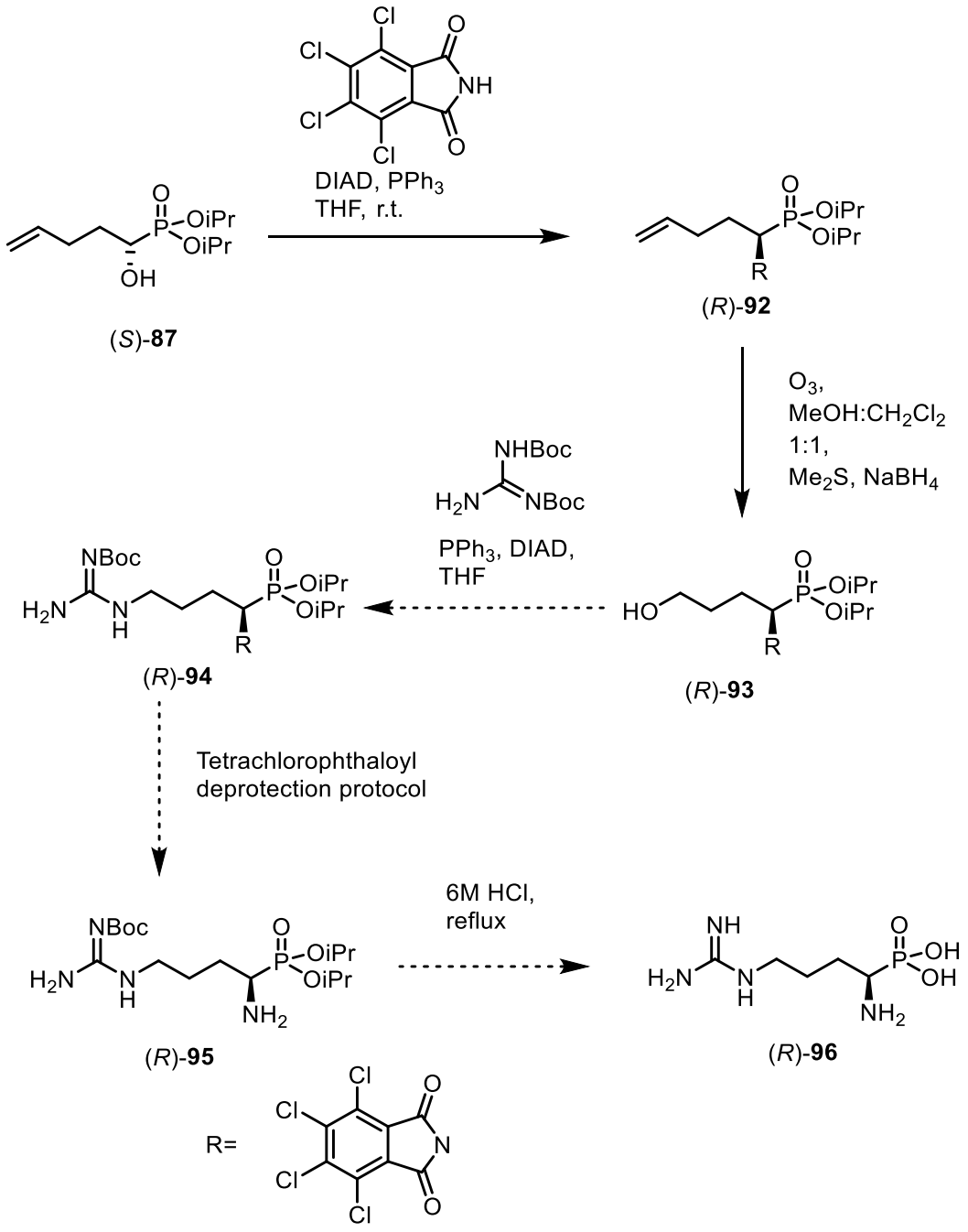
Addtional advantages of **108** include its stability under acidic conditions,[82] even in the presence of trifluoroacetic acid,[83] as well as the fact that it can be removed under milder conditions than the phthaloyl-group.[83]

Interestingly, reported biological activities of tetrachlorophthalimide-bearing molecules include a potential as α-glucosidase inhibitors,[84,85] as liver X receptor β (LXRβ)-selective agonists,[86,87] as well as anticancer properties,[88] and as carbonic anhydrase inhibitors.[89] Thus, the synthesized intermediates could be of additional pharmaceutical interest.

The Mitsunobu reaction of (*S*)-**88** with tetrachlorophthalimide as the nucleophile proceeded very smoothly, without significant side product formation. Purification of the product proved difficult again, but separation from $Ph_3P(O)$ and from the hydrazoester was possible by flash column chromatography using a suitable solvent gradient (CH_2Cl_2/2%).

For the synthesis of phosphaarginine, the carbon-backbone of (*S*)-diisopropyl-(1-hydroxypent-4-en-1-yl)phosphonate [(*S*)-**87**] had to be shortened by one carbon atom. This was achieved by ozonolysis, followed by Me_2S to reduce any remaining ozone and

a reductive workup ($NaBH_4$) which installs a terminal hydroxyl-group that can later be used for the incorporation of the guanidine moiety through a Mitsunobu-reaction. In order to be able to selectively install the guanidine moiety on the terminal hydroxyl-group, the secondary hydroxyl had to be protected first. This was done by substituting it with a tetrachlorophthaloyl-group prior to conducting the planned ozonolysis. Like this, the hydroxyl-group in alpha position to the phosphorus was both protected and already transformed to a group that can be easily converted to an amine (Scheme 30).



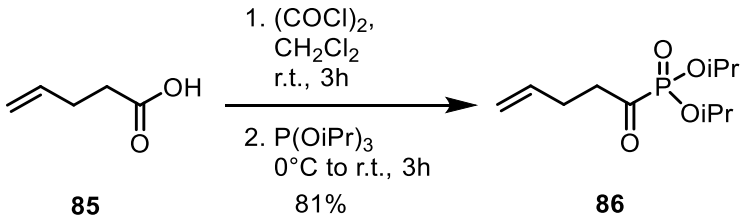
*Scheme 30: The planned synthetic path from (S)-**87** to phosphaarginine [(R)-**96**]. Dashed lines show reactions, which were not carried out as part of this thesis.*

The synthesis of phosphaarginine could not be completed within the framework of this thesis due to time constraints. However, the introduction of the guanidine-moiety by

substitution of the terminal hydroxyl-group via a Mitsunobu-reaction was reported by Hammerschmidt *et al.*,[61] as well as the conversion of the guanidine-containing phosphaarginine precursor to the finished aminophosphonic acid. Protocols for the conversion of the tetrachlorophthaloyl-group to the free amine are also literature known.[65]

3.2 Detailed discussion of the synthesis of enantiopure R-phosphalysine [(*R*)-**91**]

The first step of the synthesis of (*R*)-**91** was the conversion of 4-pentenoic acid into an α-ketophosphonate. Using a carboxylic acid as the starting material allowed for the formation of the P-C bond via an Arbuzov reaction (Scheme 31). For this purpose, 4-pentenoic acid (**85**) was first converted to the corresponding acyl chloride using 1 eq. of oxalyl chloride. Once the acid activation was complete after 3 hours, the reaction mixture was cooled to 0°C, and a slight molar excess of triisopropyl phosphite was added slowly. The mixture was stirred at 0°C for another 3 hours and then allowed to come to room temperature.

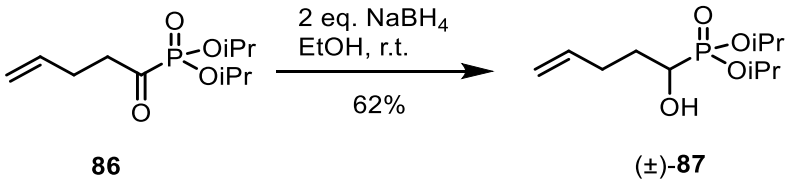


*Scheme 31: Conversion of 4-pentenoic acid (**85**) into diisopropyl pent-4-enoylphosphonate (**86**).*

After nuclear magnetic resonance (NMR) spectroscopy indicated completion of the reaction, the solvent and all formed volatiles were removed *in vacuo* and the resulting α-oxo-phosphonate (**86**) was used for the next step without further purification. Removal of the solvent is recommended to be performed in a fume hood, since the product has a very strong odor.

Enantiopure hydroxyphosphonate (*S*)-**87** was then prepared via asymmetric transfer hydrogenation of **86** using activated Noyori-catalyst (*R,R*)-**98** and a mixture of HCO_2H/Et_3N as the hydrogen source. In order to test the feasibility of the subsequent synthetic steps, these were tested before with the racemic hydroxyphosphonates [(±)-**87**].

Racemic hydroxyphosphonate (±)-**87** was accessible by using 2 eq. $NaBH_4$ in EtOH over a period of 3 h at room temperature forming (±)-**87** in 62% yield (Scheme 32).



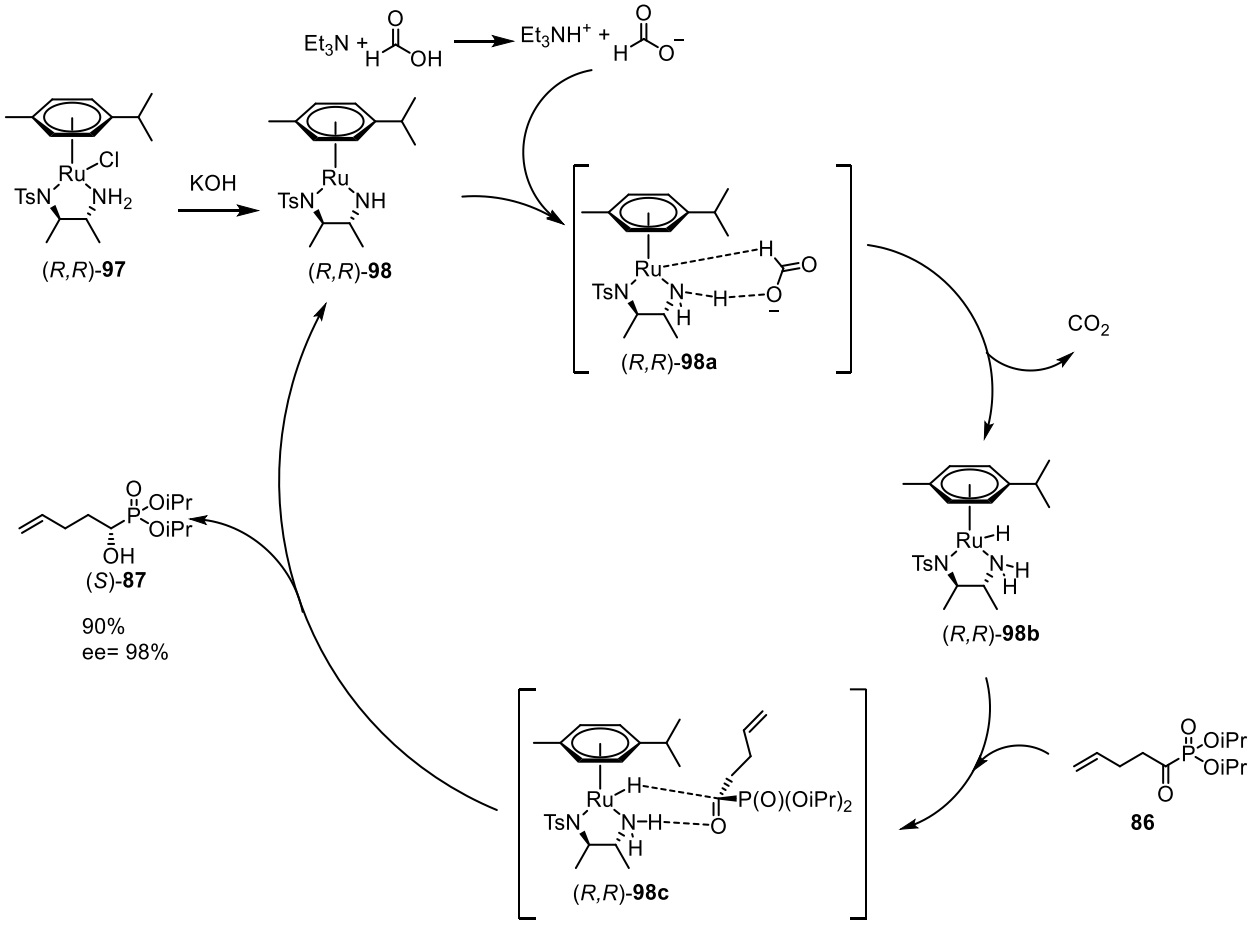
86 (±)-**87**

*Scheme 32: Synthesis of racemic α-hydroxyphosphonate (±)-**87** via reduction of **86** with $NaBH_4$.*

The asymmetric transfer hydrogenation yielded the desired enantiopure hydroxyphosphonate **87** either in its (*R*)- or (*S*)-configuration, depending on the configuration of the used catalyst (see chapter 3.1). In order to facilitate the reaction, the catalyst, (*R,R*)- or (*S,S*)-**97** had to be activated by addition of KOH first. During this process, the orange catalyst turns deep purple. It can be purified by extractive work-up

and dried over CaH_2. CaH_2 should be added in very small portions, since it reacts vigorously with water.

Different hydrogen sources can be envisaged for the asymmetric transfer hydrogenation, such as molecular hydrogen gas at high pressure, [90] or *iso*-propanol[91] (since it is an inexpensive, readily available non-toxic reagent, that gets converted to acetone) However, *iso*-propanol also has its drawbacks. Being a secondary alcohol, it can deteriorate the enantiomeric purity of the product.[92] To avoid this problem, another well-established hydrogen donor system was used for the synthesis of α-hydroxyphosphonate **87**: formic acid (HCOOH) in an azeotropic mixture with triethylamine (Et_3N).[93] Triethylamine deprotonates formic acid, generating a triethylammonium ion, a proton source, and a formate ion, which is the hydride source in this case. In the case of catalyst (*R*,*R*)- or (*S*,*S*)-**98**, the non-tosylated amine gets protonated by the triethylammonium ion and the formate ion transfers hydrogen to the central metal ion upon release of CO_2. This renders the process irreversible. The hydrido-complex then coordinates the desired ketophosphonate and generates a chiral α-hydroxyphosphonate (Scheme 33).[94,95]

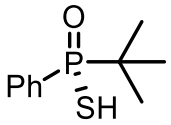


*Scheme 33: Mechanism of the performed asymmetric transfer hydrogenation of **86**.*

Handelingwise, for the ATH, ketophosphonate **86** was mixed with Et_3N/HCOOH, followed by the activated catalyst, and the reaction mixture was stirred for 3 hours.

This proved to be a very reliable method for the synthesis of enantiopure (*S*)-**87**, giving the product in 88% yield and ≥98% *ee*. The same was true for (*R*)-**87**.

The enantiomeric excess of the hydroxyphosphonates was determined by ^{1}H and ^{31}P NMR spectroscopic analysis using chiral solvating agent (*S*)-**109** (Figure 8).[96]



(*S*)-**109**

*Figure 8: Structure of chiral solvating agent tert-butyl-phenyl-phosphinothioic acid (S)-**109** used for the determination of the ee´s of (S)-, and (R)-**87** via NMR.*

The used chiral solvating agent (CSA) is an optically pure compound and binds non-covalently to the investigated substrate, thus leading to a signal splitting of NMR signals of enatiotopic protons.[97] Splitting is also observed in the phosphorus NMR spectrum. Figure 9 shows the ^{31}P-NMR spectra of racemic hydroxyphosphonate (±)-**87** without and with the mentioned CSA (top) and the ^{31}P NMR spectra of (*S*)-**87** without and with the CSA (bottom). Without the CSA the signal of the phosphorus atom appears as a singulet. If this racemic compound is mixed with chiral solvating agent (*S*)-**109**, a split in the signals of the (*R*)- and (*S*)-enantiomer can be observed.

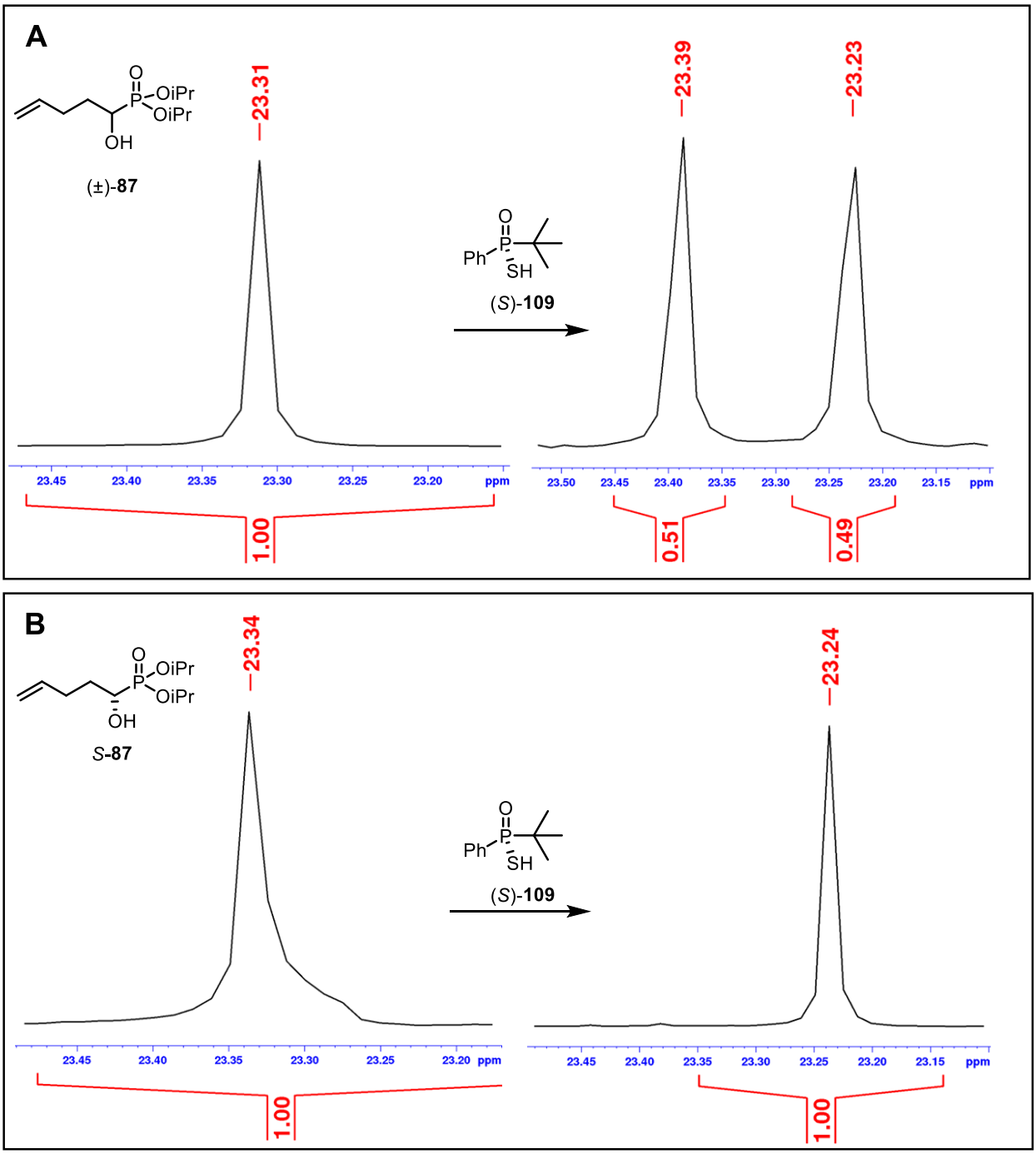


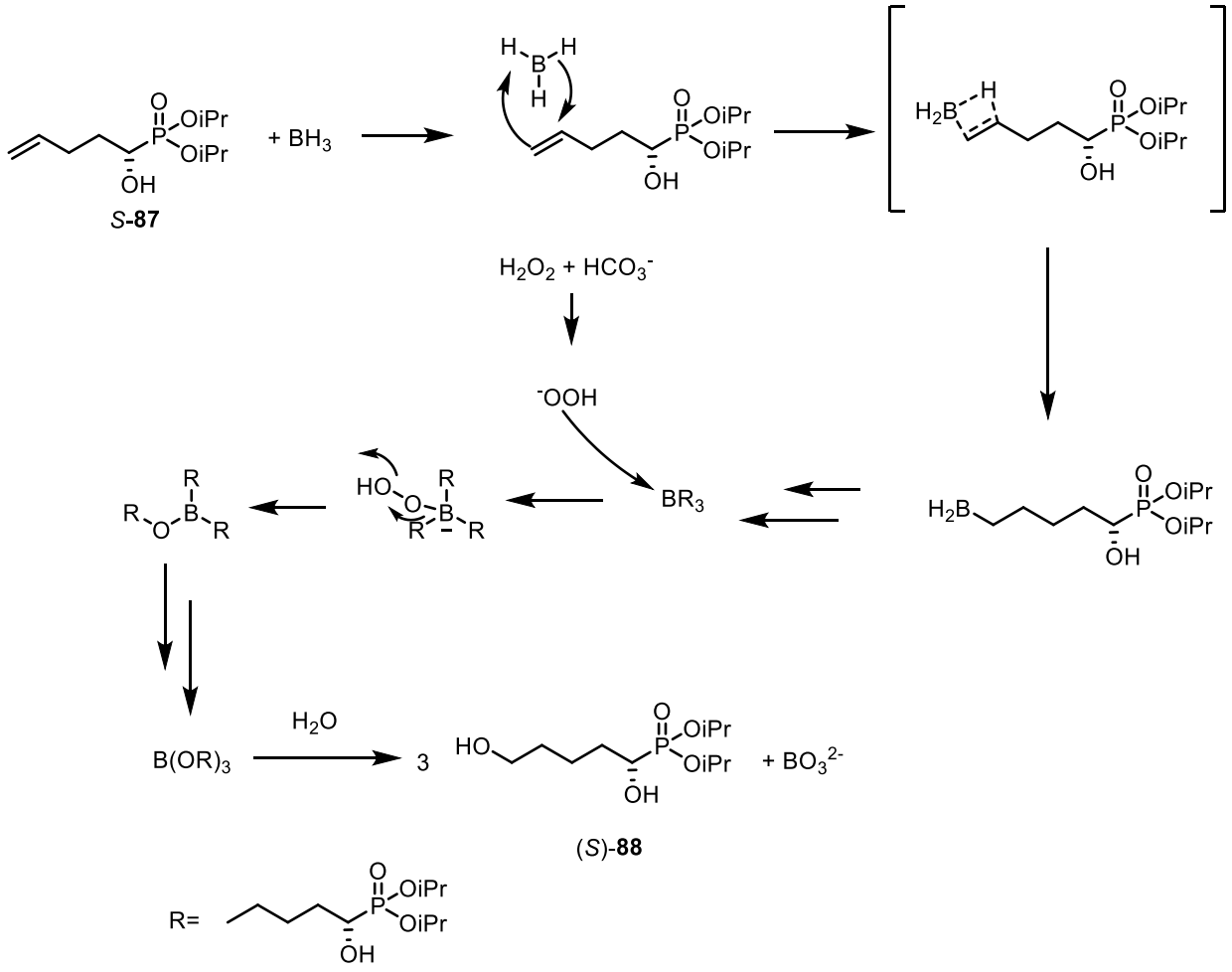
*Figure 9: ^{31}P NMR spectra of racemic (±)-**87** without (left) and with (right) the CSA (S)-**109** (**A**) and (S)-**87** without (left) and with (right) the CSA (**B**).*

The two peaks at 23.39 ppm and 23.23 ppm are centered around the original peak at 23.31 ppm and the enantiomeric ratio can be calculated by comparison of the two signal integrals. Comparing this spectrum with the spectra of the enantiomerically pure hydroxyphosphonates in combination with the CSA, allows for the determination of the *ee* of compounds of unknown enantiomeric purity without derivatization.

The peak of (*S*)-**87** is high-field shifted compared to the respective spectra without CSA. The absence of a splitting pattern in the spectra of the enantiomerically pure hydroxyphosphonate with the CSA proves their high *ee*.

109 was also used for the determination of the *ee´*s of the products obtained after the hydroboration [(*S*)-**88**] and after the Mitsunobu reaction [(*R*)-**89**, (*R*)-**92** and (*R*)-**112**].

The next step of the synthetic route towards (*R*)-phosphalysine was the synthesis of (*S*)-diisopropyl-(1,5-dihydroxypentyl)phosphonate [(*S*)-**88**]. This was done by subjecting (*S*)-**87** to a hydroboration-oxidation sequence with BH_3×THF and H_2O_2, known as Brown hydroboration. This is a well-known method for the synthesis of alcohols from terminal alkenes[98] extensively used in organic synthesis (Scheme 34).



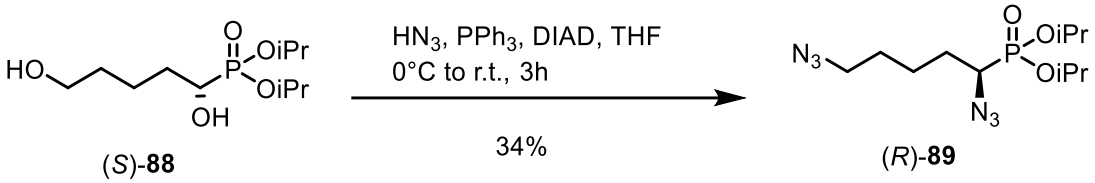
*Scheme 34: Reaction mechanism of the Brown-hydroboration exemplified on the synthesis of (S)-**88.***

First, the borane adds to the least hindered carbon making this a useful method for the installation of a ω-hydroxy group. Theoretically 1 eq. of the borane reagent should be sufficient to react with 3 eq. of the hydroxyphosphonate. However, the reaction proceeded more smoothly when employing 2 eq. of BH_3×THF.

The reaction was monitored by NMR spectroscopy. After 3 hours, no starting material was left, and excess borane was quenched with methanol. The crude mixture was purified

by flash-column chromatography with a solvent gradient (EtOAc/MeOH, 0 → 5% MeOH). (*S*)-**88** was obtained in 73% yield with an *ee* of ≥99%.

The installation of a terminal hydroxyl-group created an additional functionalization site suitable for a nucelophilic attack. Thus, it became possible to install an α- and an ω-azide, in one step via a Mitsunobu reaction (Scheme 35).



*Scheme 35: Synthesis of (R)-**89** by a Mitsunobu reaction of (S)-**88** with HN_3 as the nucleophile.*

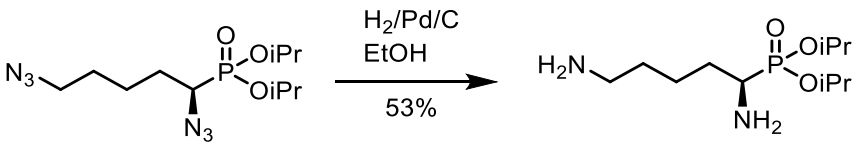
(*S*)-**88** and PPh_3 were combined at 0°C and DIAD was slowly added to this solution in order to allow for the formation of the betaine intermediate.

Both the ω and α hydroxyl-group get substituted by an azide according to the mechanism described in Scheme 28. Reaction progression was monitored with TLC (n-heptane:EtOAc 1:1). Spots were visualized by the triphenylphosphine-ninhydrine staining protocol developed by Cegielska and Kacprzak.[99] Here the azide appeared on the TLC plates as a red spot. The product (34% isolated yield, ≥99% *ee*) was purified using flash-chromatography with a solvent gradient (*n*-heptane/EtOAc, from 16 → 100% EtOAc) as the eluent. The low yield can be partly attributed to a competing reaction that can occur during the Mitsunobu reaction of primary alcohols, in which the hydrazine dicarboxylate gets *N*-alkylated.[100,101] Comparing the isolated yield of 34% to the crude yield of 59%

(calculated from the ^{31}P NMR spectrum) it can also be suggested that some of the product was lost during the purification process because of the similar polarity of the product, triphenylphosphine oxide and the formed hydrazoester. Azides also tend to be unstable on silica gel, a fact that could also contribute to the low yield.

(*R*)-Phosphalysine was synthesized from (*R*)-**89** by reducing the azides hydrogenolytically and subsequently hydrolyzing the formed aminophosphonate to give the free α-aminophosphonic acid.

Azides can be reduced to amines by different methods. One possibility would be the Staudinger reaction,[102] in which the azide is reduced with triphenylphosphine to the corresponding amine. The drawback of this method is the need for stoichiometric amounts of triphenylphosphine, and again the need for removal of the triphenylphosphine oxide side product by chromatographic purification. To prevent this, the reduction was performed by catalytic hydrogenation with palladium/carbon (10% Pd) as the catalyst in ethanol at elevated pressure (Parr apparatus, 3.5 atm H_2, Scheme 36).

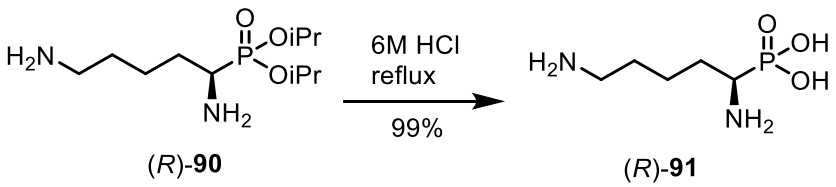


(*R*)-**89** (*R*)-**90**

*Scheme 36: Reduction of azide (R)-**89** by catalytic hydrogenation with Pd/C to give amino-phosphonate (R)-**90**.*

This elegant reduction provides the amine without any unwanted side-products and the product can be simply obtained by filtration of the resulting suspension over Celite® to remove the catalyst. The obtained amine (*R*)-**90** was stripped from the solvent and was pure enough to be used for the final deprotection. (*R*)-**90** was obtained in 53% yield.

The removal of the isopropyl-groups was accomplished by refluxing aminophosphonate (*R*)-**90** with 6 M HCl (Scheme 37).



(*R*)-**90** (*R*)-**91**

*Scheme 37: Removal of the isopropyl protecting-groups from the phosphonate ester by refluxing with 6M HCl to give (R)-phosphalysine [(R)-**91**].*

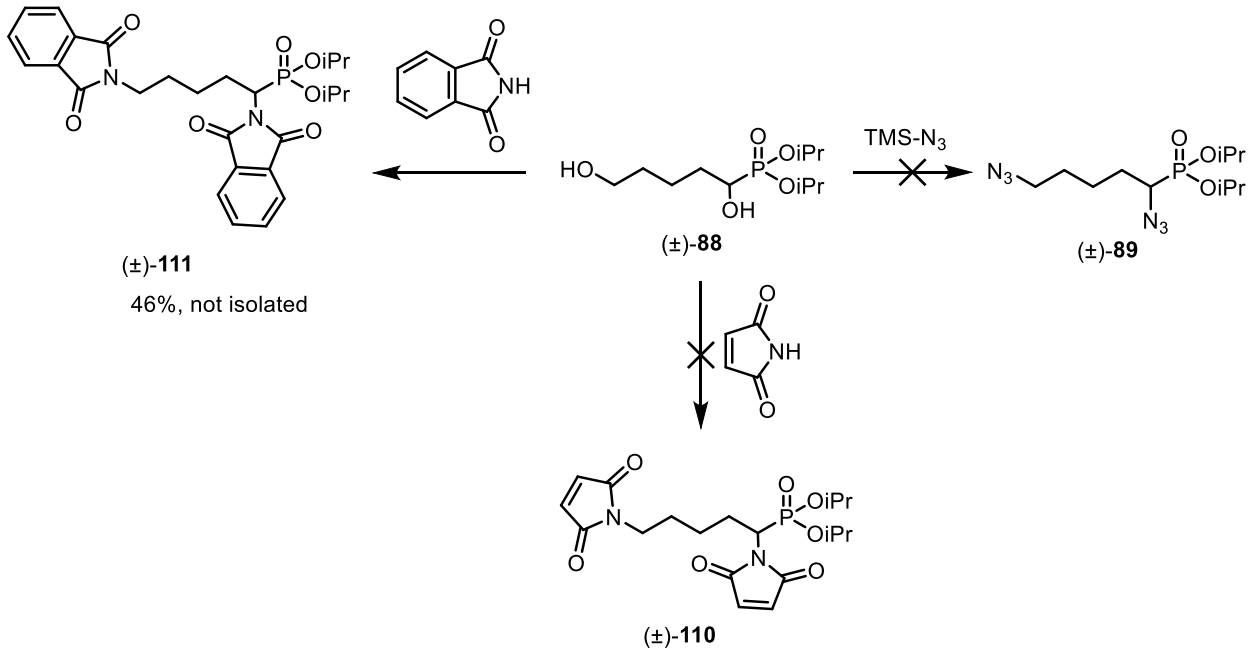
The final (*R*)-phosphalysine [(*R*)-**91**], was purified by ion exchange chromatography using Dowex W50 / H^+-form. Due to the high polarity of the product, stemming from the two free amino groups, a water/25% NH_3-solution (92:8) mixture had to be used as the eluent.

Following the synthetic pathway described in this chapter, (*R*)-phosphalysine can be obtained in 9% yield over 6 steps starting from 4-pentenoic acid with an *ee* of ≥99%.

3.3 Detailed discussion of attempts to replace hydrazoic acid in the performed Mitsunobu reactions

HN_3 proved to be a useful nucleophile for the synthesis of (*R*)-phosphalysine. However, given its hazardous nature, alternative nucleophiles would greatly improve the performed Mitsunobu reactions due to a lowered overall toxicity and due to easier handling.

For this purpose, the Mitsunobu reaction of racemic diisopropyl-(1,5-dihydroxypentyl)phosphonate (±)-**88** with trimethylsilyl-azide (**107**), maleimide (**106**) and phthalimide (**105**) as the nucleophiles was studied (Scheme 38). The reactions were performed under Mitsunobu conditions with triphenylphosphine (Ph_3P), DIAD and either THF, CH_2Cl_2 or a toluene:CH_2Cl_2 3:1 mixture as the solvent. Reactions with maleimide and phthalimide were performed at r.t. over 20 h. Reactions with TMS-N_3 were allowed to warm from 0°C to r.t. over 20h.



*Scheme 38: Reaction of (±)-**88** with TMS-N_3, maleimide and phthalimide under Mitsunobu conditions.*

TMS-N_3[103] is a good alternative to HN_3, due to its lower toxicity, higher thermal stability and since it still transfers an azide that can be easily converted to an amine, as in the case for hydrazoic acid. Unfortunately, no product formation was detected in the tested solvents (CH_2Cl_2, THF) by ^{31}P NMR (expected signal of the target compound at 19.86 ppm). However, NMR analysis of the reaction mixture showed many different P-containing degradation products. No further experiments were conducted with **107**.

The reaction with maleimide, which is also a known nucleophile for Mitsunobu reactions[104,105] led to similar results. The crude ^{31}P NMR spectrum showed a variety of phosphorus-containing substances, none of which was the desired product. The starting material completely decomposed during this attempt. Considering the high pKa of

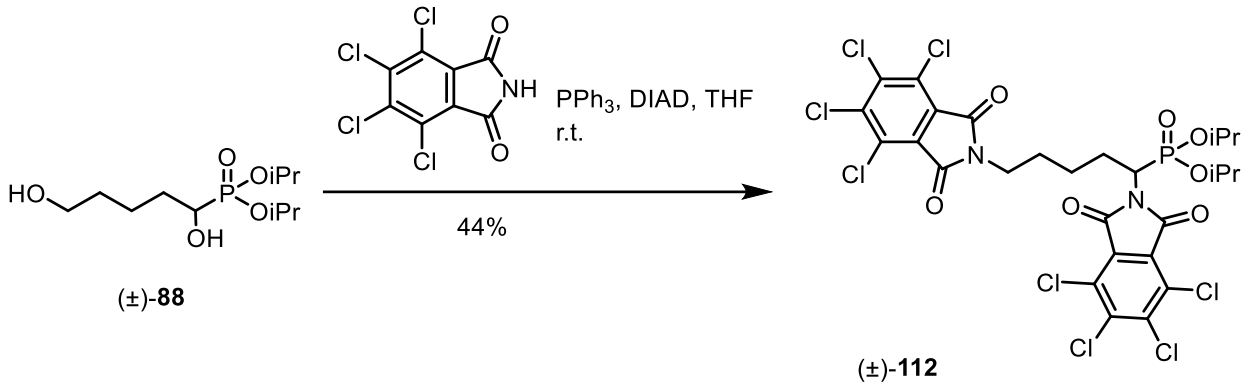
maleimide (8.52) and the unsuccessful first attempts in THF, no further experiments were performed with this nucleophile

Phthalimide performed better than the first two tested nucleophiles. The reaction of (±)-**88** with phthalimide proceeded with less byproduct formation than with maleimide, but only when performed in THF. Product formation could be observed by ^{31}P NMR spectroscopy of the crude mixture (19.97 ppm) and by high resolution mass spectrometry (HRMS) (observed: $[M+Na]^+$ 549.1756, calculated $[M+Na]^+$ 549.1762). ^{31}P NMR spectroscopy indicated that the product formed in 46% yield.

The reaction was also performed in CH_2Cl_2 and a toluene: CH_2Cl_2 3:1 mixture, but both led to a lower extent of product formation (10% and 27% respectively).

However, the isolation of the product was not successful from either of these three solvent systems. The polarity of the product and of triphenylphosphine oxide was so similar that they were inseparable by column chromatography. Attempts were made to partially separate the target compound and $Ph_3P(O)$ using *n*-heptane and ethyl acetate in a 1:1, 2:1 and 3:1 ratio. However, these remained unsuccessful. As already mentioned earlier, precipitation of $Ph_3P(O)$ with $ZnCl_2$[77] was not successful either.

Due to the results with phthalimide, tetrachlorophthalimide (**108**) was tested as an alternative nucleophile next. It was chosen due to the higher acidity of the N-H proton due to the electron-withdrawing effect of the four chlorine substituents, in combination with an expected altered polarity and thus easier purification of the product.



*Scheme 39: Reaction of (±)-**88** with tetrachlorophthalimide as the nucleophile under Mitsunobu conditions to give (±)-**112**.*

The reaction proceeded smoothly without significant by-product formation.

Tetrachlorophthalimide proved to be the best of the tested alternative nucleophiles. As expected, separation of the product from the remaining nucleophile was easier compared to the reaction with phthalimide [R_f(product)=0.19, *n*-heptane:EtOAc = 3:1].However, in this case $Ph_3P(O)$ and hydrazoester **102** were difficult to separate from the product. This separation problem could be solved by using a different eluent system [CH_2Cl_2/2% acetone; R_f(product) =0.24]. Like this, clean (±)-**112** was obtained in 44% yield.

Similarly, enantiomerically pure (*S*)-**88** was reacted with tetrachlorophthalimide. ^{31}P NMR spectroscopy in the presence of (*S*)-**109** confirmed the configurational stability of the compound during the inversion process and showed (*R*)-**112** to have an *ee* of over 99%.

The reaction time was also optimized. While the reaction needed 20 h until completion when stirred with a magnetic stirring-bar, the reaction time could be dramatically reduced to 3 h in an ultrasound bath.

Additionally, this method needed lower solvent amounts, as in this case, a higher concentration proved to be beneficial. This method did not have any negative impact on the *ee* of the resulting product, nor the yield. On the contrary, the reaction proceeded more smoothly compared to the “classical” thermal reaction conditions.

The Mitsunobu reaction of (*S*)-**88** with tetrachlorophthalimide in THF was also done with diethyl azodicarboxylate (DEAD) instead of DIAD. However, this reaction could only be done with the “classical” stirring method. DEAD must not be used with the sonication method due to its explosivity. The reaction was stirred for 20 hours at room temperature, but ^{31}P NMR still indicated that starting material was present. The sonication method proved to be superior to the classic stirring method.

The structure of (*R*)-**112** was additionally confirmed by X-ray crystallography (Figure 10).

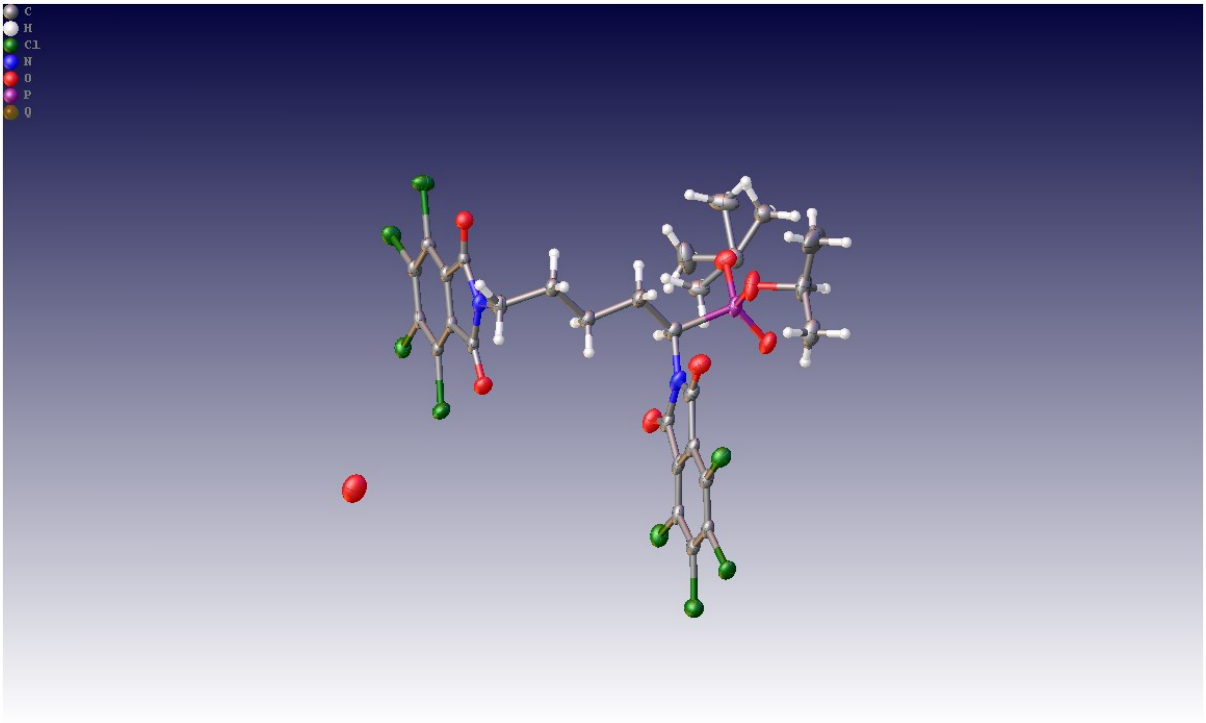
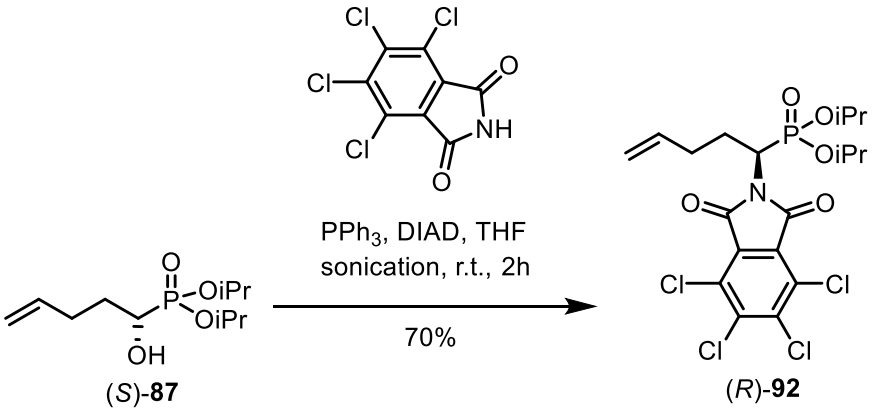


*Figure 10: Crystal structure of (R)-**112**.*

The optimized conditions for the Mitsunobu reaction with tetrachlorophthalimide were then also tested during the synthesis of (*R*)-**92** (Scheme 40).



*Scheme 40: Synthesis of (R)-**92** from (S)-**87** in a Mitsunobu reaction with tetrachlorophthalimide as the nucleophile.*

Unlike (*R*)-**112**, (*R*)-**92** could be neatly purified using *n*-heptane:EtOAc 3:1 as the eluent. The product was obtained in 70% isolated yield as a bright yellow solid of *ee*≥99% (determined by ^{31}P NMR with CSA (*S*)-**109**).

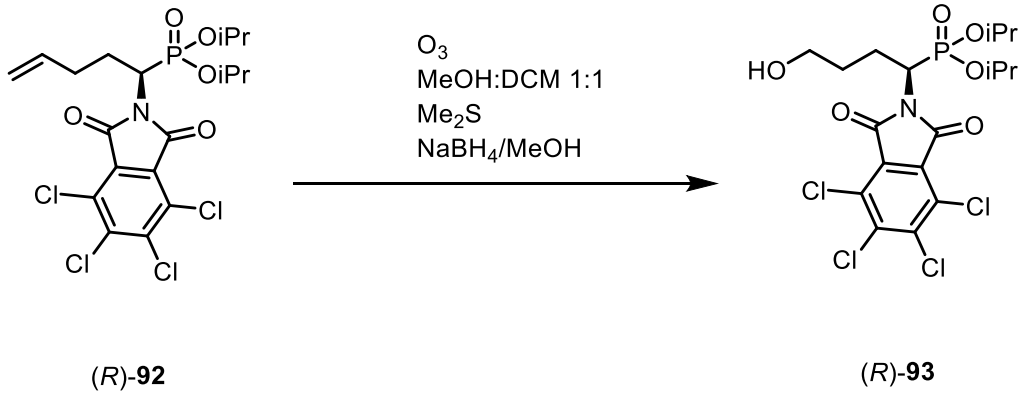
3.4 Detailed discussion of the synthesis of the (*R*)-phosphaarginine precursor (*R*)-**113**

As mentioned in chapter 3.1, the first 3 steps of the synthesis of phosphaarginine precursor (*R*)-**93** were identical to those of the synthesis of phosphalysine, Again, 4-pentenoic acid served as the starting material. For a detailed discussion of the preparation of hydroxyphosphonate (*S*)-**87**, see chapter 3.2 (Schemes 31 and 33).

Hydroxyphosphonate (*S*)-**87** was reacted with tetrachlorophthalimide as the nucleophile in a Mitsunobu reaction under similar conditions, as discussed for the synthesis of (*R*)-

112. As only one hydroxyl group had to be replaced in this case, only 1.3 equivalents of tetrachlorophthalimide, PPh_3 and DIAD were used each (Chapter 3.3, Scheme 40).

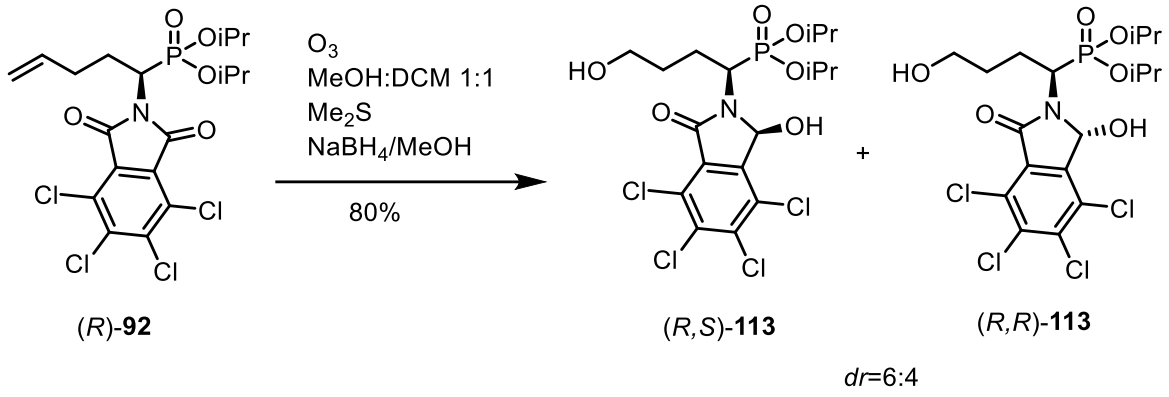
The performed Mitsunobu reaction with tetrachlorophthalimide gave (*R*)-**92** in 70% yield. (*R*)-**92** was then subjected to ozonolysis followed by a reductive work-up to install a terminal hydroxyl-group. At the same time, the carbon-backbone was shortened by one C atom to proceed with the synthesis of (*R*)-**93** (Scheme 41).



(*R*)-**92** (*R*)-**93**

*Scheme 41: Expected outcome of the ozonolysis of (R)-**92** with reductive work-up.*

While ozonolysis was successful in principle, an unexpected side reaction was observed, namely the reduction of one of the carbonyl-groups of the tetrachlorophthaloyl-group forming compounds (*R,S*)-**113** and (*R,R*)-**113** in a *dr* of 6:4 as indicated by the ^{31}P NMR of the crude mixture, while compound (*R*)-**93** was not detected (Scheme 42).



*Scheme 42: The real outcome of the ozonolysis of phosphonate (R)-**92** with reductive workup.*

The two alleged diastereomers could be separated chromatographically with *n*-heptane/EtOAc (1:4) as the eluent, since they differed enough in their polarity, with (*R,S*)-**113** having an R_f of 0.18 and (*R,R*)-**113** having an R_f of 0.29. Isolation of the compounds allowed for the measurement of high-resolution mass spectra, which indicated that both compounds have an identical mass (observed: $[M+Na]^+$ = 545.9955; calculated: $[M+Na]^+$ = 545.9959). Complete NMR analysis of the two compounds also indicated that they are diastereomers. Apart from NMR-based analysis, the structure of (*R,S*)-**113** was verified by X-ray crystallography (Figure 11). The preparation of a single crystal from (*R,R*)-**113** could not be achieved and thus its structure could not be verified by X-ray crystallography. However, the combination of the NMR-data, the mass spectrometry data and the crystallography data is strong evidence, that the more polar diastereomer is (*R,S*)-**113** and the less polar one is (*R,R*)-configured.

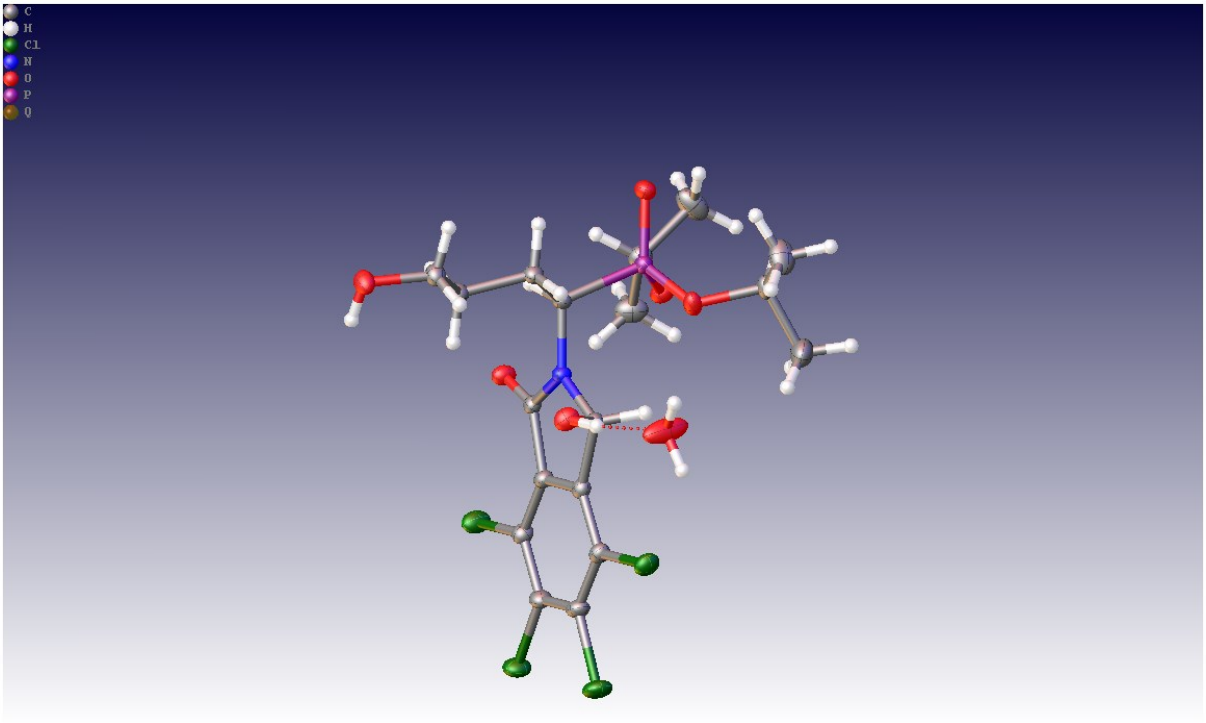


*Figure 11: Crystal structure of (R,S)-**113***

This unexpected side-reaction of the ozonolysis led to the question whether the reduction of the tetrachlorophthaloyl-group influences the subsequent reaction steps (substitution of the terminal hydroxyl-group and removal of the tetrachlorophthalyl-group). Unfortunately, due to time-constraints, these questions could not be answered within the framework of this thesis. The steric demands of the tetrachlorophthaloyl-group and the phosphonate-group might prevent the hydroxyl-group to properly react with the likewise very bulky guanidyl-group. However, experimental proof for the anticipated challenges is still missing. In summary the possible precursors for (*R*)-phosphaarginine, (*R,S*)-**113** and (*R,R*)-**113** were synthesized from 4-pentenoic acid in 5 steps in 24% and 15% yield respectively (combined yield of two diastereomers 39%) and a *dr* of 6:4. 3 more steps

would have been necessary for the synthesis of (*R*)-phosphaarginine: the substitution of the terminal hydroxyl-group with a guanidyl-group in a Mitsunobu reaction, conversion of the tetrachlorophthaloyl-group to the amine and deprotection of the phosphonate-moiety.

4. Experimental part

4.1 Instrumentation and general experimental part

Characterization data were obtained on the following devices:

Infrared Spectra (IR):

Vertex 70 IR spectrometer in ATR mode.

Specific Rotation (α_D):

Perkin-Elmer 341 polarimeter (d = 1 dm, at given temperature).

NMR spectra:

Bruker Avance AV III 600 (^{1}H: 600.25 MHz, ^{13}C: 150.93 MHz, ^{31}P: 242.99 MHz);

Bruker Avance AV 400 (^{1}H: 400.27 MHz, ^{13}C: 100.65 MHz, ^{31}P: 162.03 MHz).

The spectra were referenced to the following solvent (residual) peaks:

^{1}H NMR spectra: $CDCl_3$: $CHCl_3$ (δ_H = 7.26 ppm), D_2O: HOD (δ_H = 4.80 ppm)

^{13}C NMR spectra: $CDCl_3$: δ_C = 77.23 ppm

X-ray crystallography:

Single crystal X-ray diffraction data were collected with a Stadivari Diffractometer (STOE & Cie GmbH, Germany) equipped with an EIGER2 R500 detector (Dectris Ltd, Switzerland). Data was processed and scaled with the STOE software suite X-Area

(STOE & Cie GmbH). Structures were solved with SHELXT180 and refined with SHELXL181 or Olex2182. Model building was done with Olex2 or ShelXle183.

Chromatographic separations were carried out using the following equipment:

Medium pressure liquid chromatography (MPLC):

Column Chromatography was either performed manually or on a Biotage Isolera Prime (Biotage) flash purification system. Separation cartridges (depending on the substance amount): KP-Sil 10 g – KP-Sil 100 g, filled with Merck silica gel 60 (230-400 mesh) or Chromabond Flash RS 15 SiOH, or RS 80 SiOH (pre-packed).

Thin layer chromatography (TLC):

Merck silica gel 60 F254 glass plates (coating 0.25 mm thick)

TLCs were stained using the following solutions:

Molybdate solution: 23 g $(NH_4)_6Mo_7O_{24} \times 4\ H_2O$, 1 g $Ce(SO_4)_2 \times 4\ H_2O$ in 500 mL 10% aqueous H_2SO_4.

Ninhydrin solution: 0.2% ninhydrin in ethanol (98%).

Iodine chamber

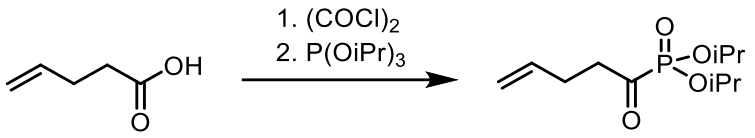
UV detection (254 nm)

Chemicals:

All chemicals were bought from TCI, Sigma-Aldrich, ABCR, Fluka or Acros and were used without any further purification.

4.2 Synthesis

4.2.1 Synthesis of diisopropyl-pent-4-enoylphosphonate **86**



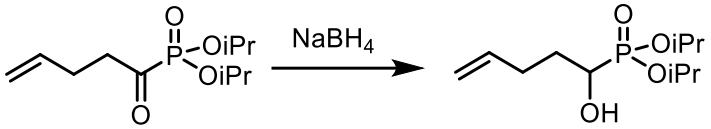
85 **86**

4-Pentenoic acid (10 mmol, 1 mL) was dissolved in CH_2Cl_2 (20 mL, 0.5 M) under argon (Ar), then $(COCl)_2$ (1 eq., 0.86 mL) was added, and the resulting mixture was stirred at r.t. for 3 h. The mixture was cooled with an ice-bath, and $P(OiPr)_3$ (1 eq., 2.46 mL) was added dropwise with a syringe. Then, stirring was continued for another 3 h and the reaction mixture allowed to warm up to r.t. The solvent was removed *in vacuo* and the resulting product, diisopropyl pent-4-enoylphosphonate (**86**) was used for consecutive reactions without further purification in 79% yield as a 1:5 mixture of its enol- and keto-form.

^{1}H NMR (400.27 MHz, $CDCl_3$, [41Dec1919/220, KB034]): δ_H=5.88-5.71 (m, 1.2H, CH= from keto- and enol form + CH-C-P enol-form), 5.29 (s, 0.2H, enol-form, OH), 5.15-4.96 (m, 2H, $=CH_2$), 4.87-4.68 (m, 2H, 2 × CH *i*Pr), 3.01-2.89 (m, 2H, CH_2 enol-form + CH_2-C(O) keto-form), 2.40-2.32 (m, 1.6H, =CH-C$\underline{H}_2$ keto-form) 1.42-1.35 (m, 12H, 4×CH_3 *i*Pr).

^{31}P NMR (162.03 MHz, $CDCl_3$, [41Dec1919/221, KB034]) δ_P: 18.16 and −2.65 (2 × d, J_{PP} = 26.9 Hz, unknown impurity, ∫ 0.13), 6.89 and −3.33 (2 × d, J_{PP} = 31.6, unknown impurity, ∫ 0.06), 4.44 (s, enol-form, ∫ 0.14), −4.41 ppm (s, keto-form, ∫ 0.67).

4.2.2 Synthesis of diisopropyl (1-hydroxypent-4-enyl)phosphonate [(±)-**87**]



86 (±)-**87**

In a 50 mL round-bottom flask equipped with a Teflon coated magnetic stir-bar, $NaBH_4$ (2 eq., 12 mmol) was dissolved in EtOH (30 mL, 0.2 M) and ketophosphonate **86** (1.49 g, corresponds to approx. 6 mmol, 1 eq.) was added dropwise under vigorous stirring. The reaction was monitored with TLC (n-heptane:EtOAc 1:1). After 3h, the reaction was quenched with water, the solvent was evaporated on a rotary-evaporator, the residue extracted with EtOAc thrice, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The obtained crude residue was purified using flash-column chromatography with 100% EtOAc as the eluent. The product, racemic diisopropyl (1-hydroxypent-4-en-yl)phosphonate [(±)**87**] was obtained in 62% yield (3.72 mmol, 0.93g).

^{1}H NMR (600.25 MHz, $CDCl_3$, [61May2920/590, KB069]) δ_H: 5.86-5.78 (m, 1H, H_2C=CH), 5.10-4.99 (m, 2H, H_2C=CH), 4.80-4.71 (m, 2H, 2×CH *i*Pr), 3.84-3.76 (m, 1H, CH-P), 2.40-2.14 (m, 2H, H_2C=CH-CH_2), 1.90-1.71 (m, 2H, CH_2-CH_2-CH-P), 1.36-1.32 (m, 12H, 4×CH_3 *i*Pr).

^{13}C NMR (150.93 MHz, $CDCl_3$, [61May2920/592, KB069]) δ_C: 137.6 (s, H_2C=CH), 115.5 (s, H_2C=CH), 71.2 (d, *J*=7.1 Hz, CH *i*Pr), 71.06 (d, *J*=7.26 Hz, CH *i*Pr), 67.8 (d, *J*=161.54 Hz, CH-P), 30.5 (s, CH_2-CH_2-CH-P), 29.8 (d, *J*=13.8 Hz, H_2C=CH-CH_2), 24.1-24.0 (m, 4×CH_3 *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [61May2920/591, KB069]) δ_P: 23.28 (s).

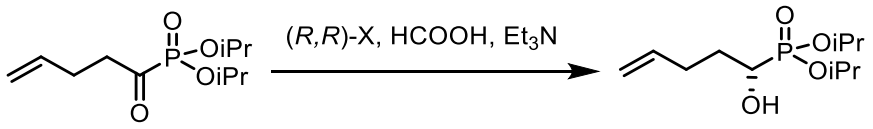
^{31}P NMR of (±)-**87** with chiral solvating agent (*S*)-**109** (242.99 MHz, $CDCl_3$, [51May1420/81, KB067 w. shift]: δ_P=95.66 [∫ 0.50, chiral solvating agent (*S*)-**109**], 23.39 [∫ 0.25, complex of chiral solvating agent with (*R*)-**87**], 23.23 ppm [∫ 0.25, complex of chiral solvating agent with (*S*)-**87**] → *ee* = 0%.

HRMS calculated for $C_{11}H_{23}O_4P$, MW=250.2748 g/mol: $[M+Na]^+$ = 273.1227;

found: $[M+Na]^+$ = 273.1225.

IR (ATR, KB075) v=3306, 2978, 1640, 1452, 1385, 1218, 1105, 978.

4.2.3 Synthesis of (*S*)- and (*R*)-diisopropyl (1-hydroxy-4-pentenyl)phosphonate [(*S*)- and (*R*)-**87**]



86 (*S*)-**87**

Prior to the reaction, (*R,R*)-RuCl[(p-cymene)-TsDPEN], [(*R,R*)-**97**, 0.02 eq., 0.105 mmol, 0.065g], was dissolved in dry CH_2Cl_2 and 0.2M aqueous KOH solution (0.75 mL) was added whereupon the reaction mixture turned deep purple. The organic phase was separated, the aqueous phase was washed twice with 1 mL dry CH_2Cl_2, and the combined organic phases were dried with CaH_2.

In parallel, HCOOH (4.4 eq., 22.11 mmol, 0.84 mL) was added dropwise to Et_3N (2.6 eq., 13.05 mmol, 1.8 mL) under an Ar atmosphere at 0°C.

The crude ketophosphonate (1.86 g, corresponding to approx. 5.025 mmol, 1 eq.) was dissolved in dry CH_2Cl_2 (6.3 mL, 0.8M) and the HCOOH/Et_3N mixture was added dropwise, followed by the activated catalyst. The reaction mixture was vigorously stirred for 3h. After the reaction was completed, the solvent was evaporated. The crude was then purified using flash column chromatography with a solvent gradient (*n*-heptane/EtOAc, 16 → 100% EtOAc) as the eluent. R_f=0.17 (*n*-heptane: EtOAc 1:1). (*S*)-Diisopropyl (1-hydroxy-4-pentenyl)phosphonate [(*S*)-**87**] was obtained as a colorless oil in 88% yield (1.12 g, 4.4 mmol).

(*R*)-diisopropyl-(1-hydroxypent-4-enyl)phosphonate [(*R*)-**87**, 1.8 mmol, 450 mg, 86 %] was obtained similarly from **86** using (*S,S*)-**97** as catalyst.

^{31}P NMR of (*S*)-**87** with chiral solvating agent (*S*)-**109** (242.99 MHz, $CDCl_3$, [61May2920/31, KB070]: δ_P=95.28 [∫ 0.37, chiral solvating agent (*S*)-**109**], 23.38 [∫ 0.004, complex of chiral solvating agent with (*R*)-**87**], 23.24 ppm [∫ 0.62, complex of chiral solvating agent with (*S*)-**87**] → *ee* ≥ 98%.

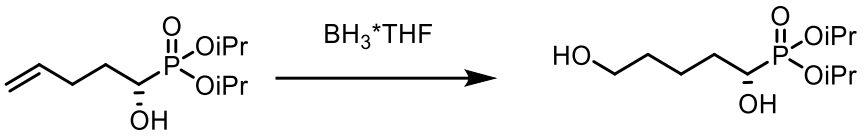
^{31}P NMR of (*R*)-**87** with chiral solvating agent (*S*)-**109** (242.99 MHz, $CDCl_3$, [51May2520/51, KB069]: δ_P=96.55 [∫ 0.64, chiral solvating agent (*S*)-**109**], 23.44 [∫ 0.36, complex of chiral solvating agent with (*R*)-**87**], complex of chiral solvating agent with (*S*)-**87** not detected → *ee*≥99%.

α_D^{20}[(*S*)-**87**] = +5.9 (c=1.050 in CH_2Cl_2).

α_D^{20} [(*R*)-**87**] = −4.6 (c=1.035 in CH_2Cl_2).

All other data were in agreement with those reported for (±)-**87**.

4.2.4 Synthesis of (*S*)-diisopropyl (1,5-dihydroxypentyl) phosphonate [(S)-**88**]



(*S*)-**87** (*S*)-**88**

(*S*)-Hydroxyphosphonate (*S*)-**87** (1eq. 1.6 mmol, 0.400 g) was dissolved in dry THF (5 mL) under an Ar atmosphere at 0°C. BH_3×THF (2 eq., 3.2 mmol, 3.2 mL) was added dropwise and the resulting mixture was vigorously stirred for 3h. MeOH (5 mL) was added slowly and stirring was continued for 30 minutes. The reaction mixture was then concentrated to 1/3 of its volume, then 5 mL THF, 3 mL H_2O_2 and 3 mL $NaHCO_3$ were added and stirring was continued for another 2h. Finally, 7 mL H_2O was added and for the mixture was stirred for another 30 minutes. The organic solvent was evaporated, and the product was extracted from the aqueous solution with 3×20 mL EtOAc. The organic phases were combined, concentrated, dried ($MgSO_4$) and the crude purified using flash-column chromatography with a solvent gradient (EtOAc/MeOH, 0 → 5% MeOH), R_f=0.29 (EtOAc with 5% MeOH). (*S*)-Diisopropyl (1,5-dihydroxypentyl)phosphonate [(*S*)-**88**] was obtained as a colorless viscous liquid in 73% yield (1.08 mmol, 0.290 g).

^{1}H NMR (600.25 MHz, $CDCl_3$, [7Aug2620/30, KB073 41-50 dried 2D]) δ_H: 4.79-4.71 (m, 2H, 2 × CH iPr), 3.81-3.76 (m, 1H, HO-CH-P), 3.67 (t, $^3J_{HH}$=6.44 Hz, 2H, HO-$\underline{CH_2}$-CH_2), 2.61 (broad s, OH), 1.83-1.76 (m, 1H, CH_2), 1.75-1.68 (m, 2H, 1×CH_2 and 1×CH_2), 1.67-1.55 (m, 2H, CH_2), 1.54-1.47 (m, 1H, CH_2), 1.36-1.32 (m, 12H, 4×CH_3 *i*Pr).

^{13}C NMR (150.93 MHz, $CDCl_3$, [7Aug2620/31, KB073 41-50 dried 2D]) δ_C: 71.2 (d, $^2J_{CP}$=7.28 Hz, CH *i*Pr), 71.14 (d, $^2J_{CP}$=7.48 Hz, CH *i*Pr), 68.2 (d, $^1J_{CP}$=161.28 Hz, C̲H-P), 62.5 (s, HO-C̲H_2), 32.1 (s, CH_2), 30.8 (s, CH_2), 24.13 (s, CH_3 *i*Pr), 24.11 (s, CH_3 *i*Pr), 24.01 (s, CH_3 iPr), 23.99 (s, CH_3 iPr), 21.9 (d, $^2J_{CP}$=13.5 Hz, CH_2).

^{31}P NMR (162.03 MHz, $CDCl_3$, [41Aug1420/121, KB073 41-50 dried] δ_P: 23.4 (s).

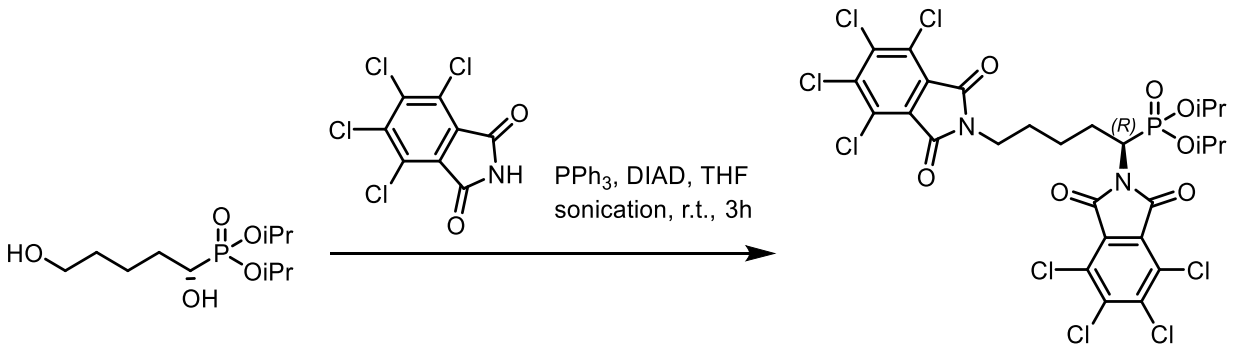
^{31}P NMR of (*S*)-**88** with chiral solvating agent (*S*)-**109** (162.03 MHz, $CDCl_3$) δ_P: 96.74 (∫ 2.49, chiral solvating agent), 23.097 (∫1.00, complex of (*S*)-**88** with chiral solvating agent), complex of chiral solvating agent with (*R*)-**88** not detected → *ee*≥99%.

HRMS calculated for $C_{11}H_{25}O_5P$, MW=268.1440 g/mol: $[M+Na]^+$ = 291.1332,Found: $[M+Na]^+$ = 291.1333.

IR (ATR, KB073) v=3462, 2980, 2937, 1454, 1385, 1375, 1217, 1104, 983.

α_D^{20}[(*S*)-**88**] = +14.9 (c=1.035 in CH_2Cl_2).

4.2.5 Synthesis of (*R*)-diisopropyl (1,5-bis(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentyl)phosphonate [(*R*)-**112**]



(*S*)-**88** (*R*)-**112**

Dihydroxyphosphonate (*S*)-**88** (0.5 mmol, 0.134 g), tetrachlorophthalimide (2.6 eq., 1.3 mmol, 0.37 g) and PPh_3 (2.6 eq., 1.3 mmol, 0.34 g) were combined in a round-bottom flask under an Ar atmosphere and dissolved in 1.25mL dry THF while sonicating. After the solids dissolved, DIAD (2.6 eq., 1.3 mmol, 0.25 mL) was added dropwise to the solution over 2 minutes. The reaction mixture was then sonicated for another 3h (reaction was monitored by NMR), and then methanol was added (3 mL). The solvent was removed *in vacuo* and the crude residue was purified by flash-column chromatography with CH_2Cl_2/2% acetone as the eluent. R_f=0.18 (CH_2Cl_2 with 2% acetone). (*R*)-Diisopropyl (1,5-bis(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentyl)phosphonate [(*R*)-**112**] was obtained as a highly hygroscopic, crystalline solid in 44% isolated yield (0.170 g, 0.22 mmol).

^{1}H NMR (600.25 MHz, $CDCl_3$, [61Aug1420/30, KB063 recryst 2D] δ_H: 4.83-4.66 (m, 2H, 2×CH iPr), 4.49-4.41 (m, 1H, N-CH-P), 3.65 (t, $^3J_{HH}$=7.03 Hz, 2H, N-CH_2), 2.21 (ABX$_2$X´P-system; A-part: m, 2.45-2.34; B-part: m, 2.06-1.97, 2H, $\underline{CH_2}$-CH-P), 1.70 (ABX$_2$X´P-system; A-part: m, 1.79-1.70; B-part: m, 1.70-1.61, 2H, N-CH_2-$\underline{CH_2}$), 1.37 (d, $^3J_{HP}$=6.13 Hz, CH_3 *i*Pr), 1.35-1.31 (m, 11H, 3×CH_3 *i*Pr and $\underline{CH_2}$-CH_2-CH-P).

^{13}C NMR (150.93 MHz, $CDCl_3$, [61Aug1420/31, KB063 recryst 2D] δ_C: 163.5 (s, N-$\underline{C}$=O), 140.1 (s, aromatic C), 129.8 (s, aromatic C), 129.6 (s, aromatic C), 127.5 (s, aromatic C), 72.1 (d, $^2J_{CP}$=6.8 Hz, CH *i*Pr), 71.5 (d, $^2J_{CP}$=6.8 Hz, CH *i*Pr), 49.1 (d, $^1J_{CP}$=157.5 Hz, CH-P), 38.2 (s, N-CH_2), 27.5 (s, N-CH_2-$\underline{CH_2}$), 26.2 (s, $\underline{CH_2}$-CH-P), 24.3 (d, $^3J_{CP}$=2.4 Hz, CH_3 *i*Pr), 24.1 (d, $^3J_{CP}$=3.9 Hz, CH_3 *i*Pr), 24.0 (d, $^3J_{CP}$=4.6 Hz, CH_3 *i*Pr), 23.9 (d, $^3J_{CP}$=12.1 Hz, $\underline{CH_2}$-CH_2-CH-P), 23.7 (d, $^3J_{CP}$=6.5 Hz, CH_3 *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [61Aug1420/35, KB063 recryst 2D] δ_P: 18.74 (s).

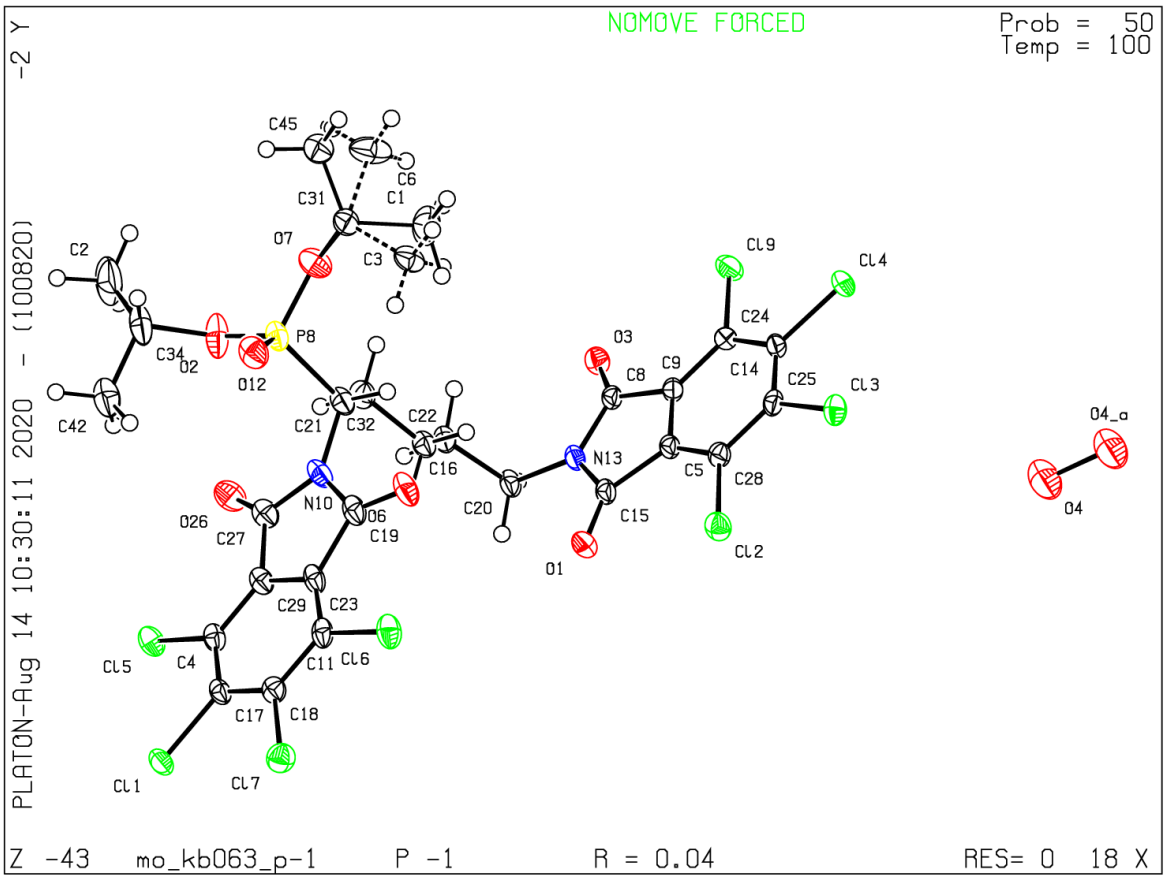
^{31}P NMR of (*R*)-**112** with chiral solvating agent (*S*)-**109** (162.03 MHz, $CDCl_3$) δ_P: 97.97 (∫1.07, chiral solvating agent), 18.65 (∫1.00, complex of (*R*)-**112** with chiral solvating agent), complex of chiral solvating agent with (*S*)-**112** not detected → *ee*≥99%.

HRMS calculated for $C_{27}H_{23}Cl_8N_2O_7P$, MW=802.0618g/mol: $[M+Na]^+$ = 824.8585; Found: $[M+Na]^+$ = 824.8567.

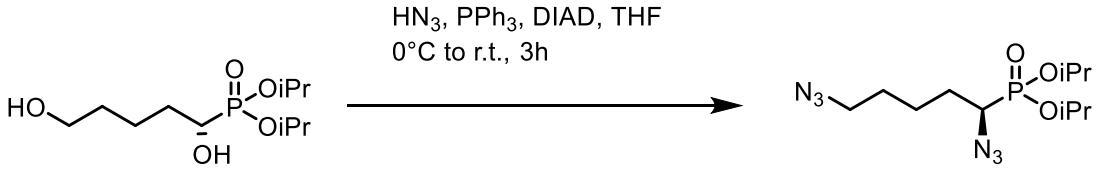
IR (ATR, KB063) v=2978, 2931, 2872, 1776, 1715, 1438, 1370, 1350, 1249, 1199, 1104, 980, 737.

α_D^{20}[(*R*)-**112**]= −2.54 (c=1.035 in CH_2Cl_2).

The structure of the product could be additionally confirmed by X-ray crystallography (data in appendix).



4.2.6 Synthesis of (*R*)-diisopropyl (1,5-diazidopentyl)-phosphonate [(*R*)-**89**]



(*S*)-**88** (*R*)-**89**

Dihydroxyphosphonate (*S*)-**88** (1 mmol, 0.270 g) and PPh_3 (2.6 eq., 2.6 mmol, 0.68 g) were dissolved in 3 mL THF under an Ar atmosphere. The solution was cooled to 0°C and then HN_3 (3.6 eq., 3.6 mmol, 2 mL) was added dropwise followed by DIAD (2.6 eq., 2.6 mmol, 0.51 mL). The mixture was allowed to slowly warm up to r.t. After 3h MeOH (3 mL) was added. The solvent was evaporated, and the crude residue was purified by flash-column chromatography using a solvent gradient (*n*-heptane/EtOAc, from 16 → 100 EtOAc) as the eluent. R_f=0.34 (*n*-heptane/EtOAc 1:1). (*R*)-Diisopropyl (1,5-diazidopentyl)phosphonate [(*R*)-**89**]was obtained as an oily liquid in 34% yield (0.34 mmol, 0.110 g).

^{1}H NMR (600.25 MHz, $CDCl_3$, [61*J*ul3120/30, KB022] δ_H: 4.83-4.75 (m, 2H, 2×C<u>H</u> *i*Pr), 3.35-3.28 (m, 3H, C<u>H</u>-P and N_3-C<u>H_2-</u>), 1.92-1.82 (m, 1H, CH_2), 1.73-1.56 (m, 4H, from three different CH_2), 1.55-1.45 (m, 1H, CH_2), 1.39-1.34 (m, 12H, 4×CH_3 *i*Pr).

^{13}C NMR (150.93 MHz, $CDCl_3$, [61*J*ul3120/31, KB022] δ_C: 71.86 (d, $^2J_{CP}$=7.5 Hz, <u>C</u>H *i*Pr), 71.8 (d, $^2J_{CP}$=7.2 Hz, <u>C</u>H *i*Pr), 57.7 (d, $^1J_{CP}$=156.84 Hz, CH-P), 51.1 (s, N_3-<u>C</u>H_2), 28.3 (s, <u>C</u>H_2), 28.2 (s, <u>C</u>H_2), 24.16 (s, <u>C</u>H_3 *i*Pr), 24.13 (s, <u>C</u>H_3 *i*Pr), 24.08 (s, <u>C</u>H_2), 24.01 (s, <u>C</u>H_3 *i*Pr), 23.98 (s, <u>C</u>H_3 *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [41*J*ul0120/151, KB022] δ_P: 19.86 (s).

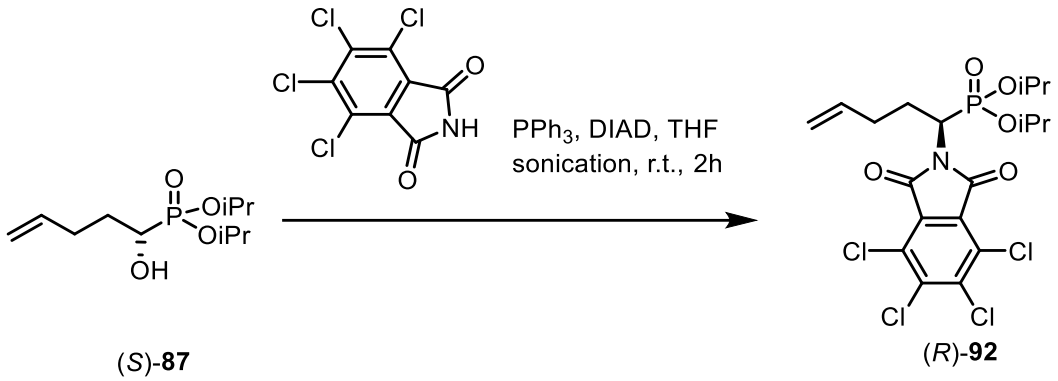
^{31}P NMR of (*R*)-**89** with chiral solvating agent (*S*)-**109** (162.03 MHz, $CDCl_3$) δ_P: 97.49 (∫ 0.63, chiral solvating agent), 19.91 (∫ 0.37, complex of chiral solvating agent with (*R*)-**89**), complex of chiral solvating agent with (*S*)-**89** not detected → *ee*≥99%.

HRMS calculated for $C_{11}H_{23}N_6O_3P$, MW=318.3178 g/mol: $[M+Na]^+$ = 341.1462; Found: $[M+Na]^+$ = 341.1466.

IR (ATR, KB022) v=2984, 2934, 2098, 1738, 1375, 1252, 1105, 988.

α_D^{20}[(*R*)-**89**] = −43.9 (c=1.100 in CH_2Cl_2).

4.2.7 Synthesis of (*R*)-diisopropyl (1-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pent-4-enyl)phosphonate [(*R*)-**92**]



(*S*)-**87** (*R*)-**92**

Hydroxyphosphonate (*S*)-**87** (2.8 mmol, 0.700 g), tetrachlorophthalimide (1.3 eq., 3.64 mmol, 1.04 g) and PPh_3 (1.3 eq., 3.64 mmol, 0.96 g) were dissolved in 7 mL dry THF under an Ar atmosphere while sonicating. DIAD (1.3 eq., 3.64 mmol, 0.7 mL) was added dropwise, and the reaction mixture was sonicated for another 2h. Methanol was added and the solvent evaporated. The crude mixture was purified using flash column chromatography with *n*-heptane:EtOAc 3:1 as the eluent. R_f=0.30 (*n*-heptane/EtOAc 3:1). (*R*)-Diisopropyl (1-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pent-4-enyl)phosphonate [(*R*)-**92**] was obtained as a bright yellow solid in 70% yield (1.013g, 1.96 mmol).

^{1}H NMR (600.25 MHz, $CDCl_3$, [61Aug1420/70, KB081 2D] δ_H: 5.77-5.69 (m, 1H, CH_2=C<u>H</u>), 5.02-4.96 (m, 2H, C<u>H$_2$</u>=CH), 4.83-4.67 (m, 2H, 2×C<u>H</u> *i*Pr), 4.53 (ddd, $^2J_{HP}$=18.9 Hz, $^3J_{XA}$=11.2 Hz, $^3J_{XB}$=4.1 Hz, 1H, N-C<u>H</u>-P), 2.30 (ABX$_2$X´P-system; A-part: m, 2.55-

2.43; B-part: m, 2.13-2.04, 2H, C$\underline{H_2}$-CH-P), 2.06 (ABX$_2$X´P-system; A-part: m, 2.13-2.06; B-part: m, 2.06-1.98, 2H, C$\underline{H_2}$-CH$_2$-CH-P), 1.37 (d, $^3J_{HH}$=6.28 Hz, 3H, C$\underline{H_3}$ *i*Pr), 1.35 (d, $^3J_{HH}$=6.14 Hz, 3H, C$\underline{H_3}$ *i*Pr), 1.34 (d, $^3J_{HH}$=6.38 Hz, 3H, C$\underline{H_3}$ *i*Pr), 1.32 (d, $^3J_{HH}$=6.48 Hz, 3H, C$\underline{H_3}$ *i*Pr).

^{13}C NMR (150.93 MHz, $CDCl_3$, [61Aug1420/71, KB081 2D] δ_C: 162.9 (s, 2×N-$\underline{C}$=O), 140.2 (s, 2×aromatic C), 136.2 (s, CH$_2$=$\underline{C}$H), 129.8 (s, 2×aromatic C), 127.3 (s, 2×aromatic C), 116.4 (s, $\underline{C}$H$_2$=CH), 72.0 (d, $^2J_{CP}$=6.75 Hz, $\underline{C}$H *i*Pr), 71.5 (d, $^2J_{CP}$=6.95 Hz, $\underline{C}$H *i*Pr), 48.7 (d, $^1J_{CP}$=157.52 Hz, N-$\underline{C}$H-P), 30.75 (d, $^3J_{CP}$=12.7 Hz, $\underline{C}$H$_2$-CH$_2$-CH-P), 25.9 (s, C$\underline{H_2}$-CH-P), 24.3 (d, $^3J_{CP}$=2.40 Hz, CH$_3$ *i*Pr), 24.1 (d, $^3J_{CP}$=3.73 Hz, CH$_3$ *i*Pr), 23.9 (d, $^3J_{CP}$=4.90 Hz, CH$_3$ *i*Pr), 23.7 (d, $^3J_{CP}$=6.50 Hz, CH$_3$ *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [61Aug1420/71, KB081 2D]) δ_P: 19.05 (s).

^{31}P NMR of (*R*)-**92** with chiral solvating agent (*S*)-**109** (162.03 MHz, $CDCl_3$) δ_P: 98.32 (∫ 0.54, chiral solvating agent), 18.96 (∫ 0.46, complex of chiral solvating agent with (*R*)-**92**), complex of chiral solvating agent with (*S*)-**92** not detected → *ee*≥99%.

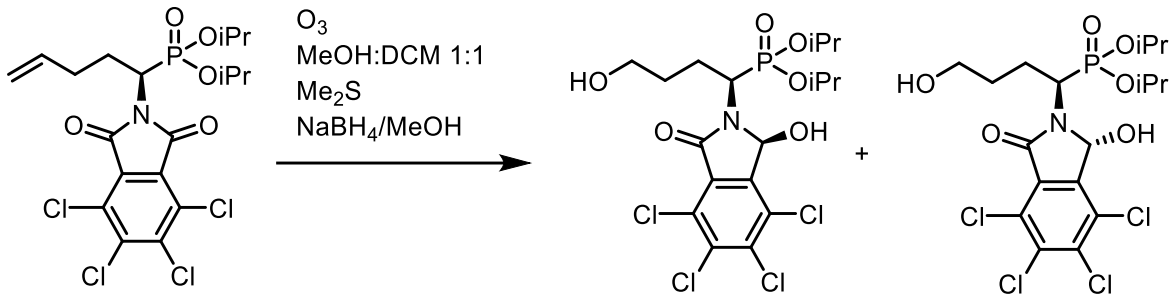
HRMS calculated for $C_{19}H_{22}Cl_4NO_5P$, MW=517.1608 g/mol: $[M+Na]^+$ = 539.9853;

Found: $[M+Na]^+$ = 539.9842.

IR (ATR, KB081) v=2979, 1781, 1725, 1386, 1372, 1252, 984, 740.

α_D^{20}[(*R*)-**92**] = −11.4 (c=1.140 in CH_2Cl_2).

4.2.8 Synthesis of (*R*)-diisopropyl 4-hydroxy-1-((*S*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate and (*R*)-diisopropyl 4-hydroxy-1-((*R*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate [(*R,S*)-**113** and (*R,R*)-**113**]



(*R*)-**92** (*R,S*)-**113** (*R,R*)-**113**

Terminal alkene (*R*)-**92** (1.55 mmol, 800 mg) was dissolved in 30 mL of a 1:1 mixture of MeOH/ CH_2Cl_2 and cooled to −78°C. O_3 (flowrate: 100N/min, O_3 level: 70%) was bubbled through the reaction mixture for 4 minutes after which the solution turned blue color. Then, a stream of O_2 was bubbled through the reaction mixture until the blue color vanished. Me_2S (1 eq., 1.55 mmol, 0.11 mL) was added and the mixture was stirred for 20 min. at room temperature. After that, the mixture was cooled to −30°C, and $NaBH_4$ (1.2 eq., 1.62 mmol, 0.062 g) in 8 mL EtOH was added dropwise. The reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. Then H_2O was added, the phases were separated, the aqueous phase was washed with EtOAc (3×20 mL), the organic phases were combined and washed with a sat. aq. $NaHCO_3$ solution, dried over $MgSO_4$, and the solvent was evaporated. The resulting crude was purified using flash column chromatography with *n*-heptane/EtOAc 1:4 as the eluent. R_f=0.18 for (*R,S*)-**113** and R_f=0.29 for (*R,R*)-**113** (n-heptane/EtOAc 1:4). (*R*)-Diisopropyl 4-hydroxy-1-((*S*)-4,5,6,7-

tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate [(*R,S*)-**113**] was obtained as a crystalline solid in 48 % yield (0.387 g, 0.74 mmol). (*R*)-Diisopropyl 4-hydroxy-1-((*R*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate [(*R,R*)-**113**] was obtained as a solid in 32 % yield (0.262 g, 0.50 mmol). The two diastereomers were obtained with a diastereomeric ratio of 6:4.

(*R,S*)-**113**:

^{1}H NMR (600.25 MHz, $CDCl_3$, [61Aug1420/60, KB078 crystal 2D]) δ_H: 6.33 (d, $^{3}J_{HH}$=7.51 Hz, 1H, N-C<u>H</u>-OH), 5.35 (d, $^{3}J_{HH}$=7.51 Hz, 1H, N-CH-O<u>H</u>), 4.82-4.63 (m, 2H, 2 × C<u>H</u> *i*Pr), 4.57 (ddd, $^{2}J_{HP}$=20.18 Hz, $^{3}J_{XA}$=11.74 Hz, $^{3}J_{XB}$=3.56 Hz, 1H, N-C<u>H</u>-P), 3.73-3.66 (m, 2H, HO-C<u>H$_2$</u>-CH_2), 2.22 (ABX_2X'P-system; A-part: m, 2.42-2.31; B-part: m, 2.11-2.02, 2H, C<u>H$_2$</u>-CH_2-CH-P), 1.95 (broad s, 1H, <u>H</u>O-CH_2-CH_2), 1.72 (m, 2H, C<u>H$_2$</u>-CH-P), 1.36 (d, $^{2}J_{HH}$=6.99 Hz, 3H, C<u>H$_3$</u> *i*Pr), 1.35 (d, $^{2}J_{HH}$=6.56 Hz, 3H, C<u>H$_3$</u> *i*Pr), 1.28 (d, $^{2}J_{HH}$=6.14 Hz, 3H, C<u>H$_3$</u> *i*Pr), 1.26 (d, $^{2}J_{HH}$=6.05 Hz, 3H, C<u>H$_3$</u> *i*Pr).

^{13}C NMR (150.93 MHz, $CDCl_3$, [61Aug1420/61, KB078 crystal 2D]) δ_C: 163.6 (d, $^{3}J_{CP}$=5.88 Hz, N-<u>C</u>=O), 141.6 (s, aromatic C), 137.5 (s, aromatic C), 135.8 (s, aromatic C), 129.5 (s, aromatic C), 128.6 (s, aromatic C), 127.3 (s, aromatic C), 80.8 (s, N-<u>C</u>H-OH), 72.5 (d, $^{2}J_{CP}$=7.14 Hz, <u>C</u>H *i*Pr), 71.9 (d, $^{2}J_{CP}$=7.32 Hz, <u>C</u>H *i*Pr), 62.1 (s, HO-<u>C</u>H$_2$-CH_2), 49.8 (d, $^{1}J_{CP}$=154.04 Hz, <u>C</u>H-P), 29.3 (d, $^{3}J_{CP}$=13.45 Hz, <u>C</u>H$_2$-CH_2-CH-P), 25.00 (s, <u>C</u>H$_2$-CH-P), 24.2 (d, $^{3}J_{CP}$=2.92 Hz, <u>C</u>H$_3$ *i*Pr), 24.0 (d, $^{3}J_{CP}$=4.10 Hz, <u>C</u>H$_3$ *i*Pr), 23.9 (d, $^{3}J_{CP}$=4.84 Hz, <u>C</u>H$_3$ *i*Pr), 23.8 (d, $^{3}J_{CP}$=5.55 Hz, <u>C</u>H$_3$ *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [61Aug1420/65, KB078 crystal 2D]) δ_P: 22.03(s).

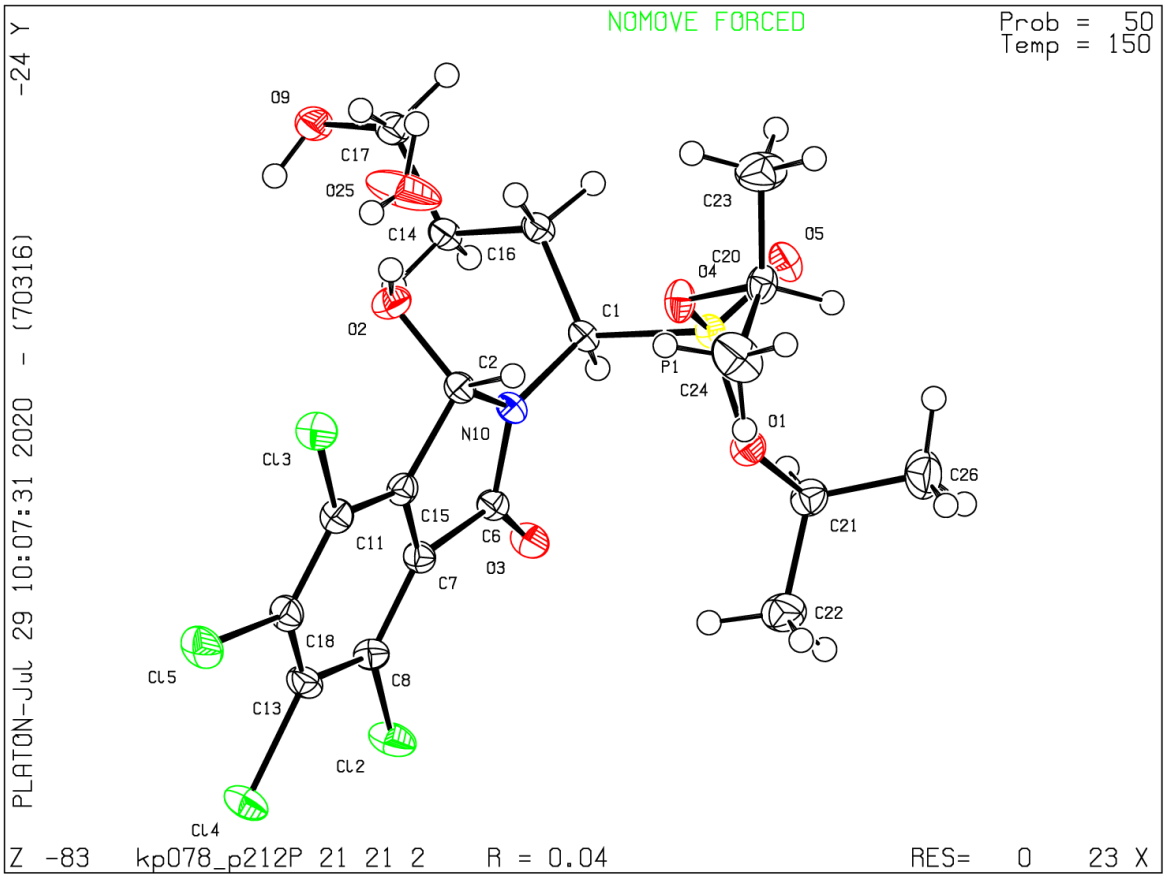
HRMS calculated for $C_{18}H_{24}Cl_4NO_6P$, MW=523.1648: $[M+Na]^+$ = 545.9959;

Found: $[M+Na]^+$ = 545.9955.

IR (ATR, KB078) v=3254, 2978, 1713, 1376, 1214, 1101, 981, 737.

α_D^{20}[(*R,S*)-**113**]= −32.0 (c=1.015 in CH_2Cl_2).

The structure of the product could be additionally confirmed by X-ray crystallography (data in appendix).



[(*R,R*)-**113**:

^{1}H NMR (600.25 MHz, $CDCl_3$, [61Jul1520/20, KB078 side C13]) δ_H: 6.74 (d, $^{3}J_{HH}$=3.66 Hz, 1H, N-C<u>H</u>-OH), 6.03 (d, $^{3}J_{HH}$=3.66 Hz, 1H, N-CH-O<u>H</u>), 4.82-4.66 (m, 3H, 2 × C<u>H</u> *i*Pr, 1 × N-C<u>H</u>-P), 3.67-3.60 (m, 2H, HO-C<u>H_2</u>-CH_2), 2.21-2.06 (m, 2H, C<u>H_2</u>-CH_2-CH-P), 1.77 (broad s, 1H, <u>H</u>O-CH_2-CH_2), 1.52-1.43 (m, 1H, C<u>H_2</u>-CH-P), 1.42-1.35 (m, 1H from C<u>H_2</u>-CH-P, 3H from C<u>H_3</u> *i*Pr), 1.31 (d, $^{2}J_{HH}$=6.16 Hz, 3H, C<u>H_3</u> *i*Pr), 1.27-1.23 (m, 3H, C<u>H_3</u> *i*Pr), 1.19 (d, $^{2}J_{HH}$=6.20 Hz, 3H, C<u>H_3</u> *i*Pr).

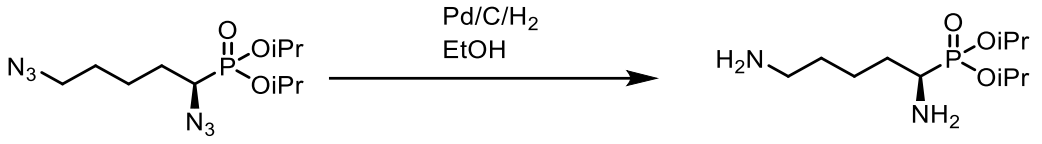
^{13}C NMR (150.93 MHz, $CDCl_3$, [61Jul1520/21, KB078 side C13]) δ_C: 164.0 (s, N-<u>C</u>=O), 141.8 (s, aromatic C), 137.7 (s, aromatic C), 135.8 (s, aromatic C), 129.7 (s, aromatic C), 129.0 (s, aromatic C), 127.1 (s, aromatic C), 77.6 (s, N-<u>C</u>H-OH), 73.2 (d, $^{2}J_{CP}$=7.46 Hz, <u>C</u>H *i*Pr), 72.3 (d, $^{2}J_{CP}$=7.79 Hz, <u>C</u>H *i*Pr), 61.5 (s, HO-<u>C</u>H_2-CH_2), 48.5 (d, $^{1}J_{CP}$=158.98 Hz, <u>C</u>H-P), 28.8 (d, $^{2}J_{CP}$=13.78 Hz, <u>C</u>H_2-CH-P), 23.3 (d, $^{3}J_{CP}$=3.17 Hz, <u>C</u>H_2-CH_2-CH-P), 24.3 (d, $^{3}J_{CP}$=2.60 Hz, <u>C</u>H_3 *i*Pr), 24.0 (d, $^{3}J_{CP}$=3.63 Hz, <u>C</u>H_3 *i*Pr), 23.6 (d, $^{3}J_{CP}$=5.79 Hz, <u>C</u>H_3 *i*Pr), 14.2 (s, <u>C</u>H_3 *i*Pr).

^{31}P NMR (242.99 MHz, $CDCl_3$, [42Jul1320/31, KB078 Fr. 40-42]) δ_P: 23.62(s).

HRMS calculated for $C_{18}H_{24}Cl_4NO_6P$, MW=523.1648: $[M+Na]^+$ = 545.9959;

Found: $[M+Na]^+$ = 545.9955.

4.2.9 Synthesis of (*R*)-diisopropyl (1,5-diaminopentyl) phosphonate [(*R*)-**90**]



(*R*)-**89** (*R*)-**90**

The azide (*R*)-**89** (0.28 mmol, 90 mg) was dissolved in 20 mL EtOH and placed in a Parr-vessel. Pd/C (61 mg, 10% Pd) was added, and the vessel was put under 3.5 bar H_2 and shaken for 3h. Pd/C was filtered off and the solvent was evaporated, yielding the aminophosphonate (*R*)-**90** in sufficient purity for the following deprotection (53%, 0.15 mmol, 40 mg).

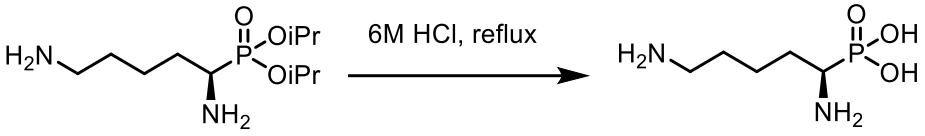
^{1}H NMR (400.27 MHz, $CDCl_3$, [42Aug0320/10, KB082] δ_H: 4.79-4.60 (m, 2×C<u>H</u> *i*Pr), 2.87-2.77 (m, 1H, N-C<u>H</u>-P), 2.73-2.64 (m, 2H, N-C<u>H$_2$</u>), 1.85-1.55 (m, 2H, C<u>H$_2$</u>-CH), 1.52-1.37 (m, 4H, -C<u>H$_2$</u>-C<u>H$_2$</u>-), 1.35-1.26 (m, 12H, 4×C<u>H$_3$</u> *i*Pr).

^{31}P NMR (162.03 MHz, $CDCl_3$, [42Aug0320/11, KB082] δ_P: 27.29 (s).

HRMS calculated for $C_{11}H_{27}N_2O_3P$, MW=266.3218: $[M+Na]^+$ = 289.1652;

Found: $[M+Na]^+$ = 289.1653.

4.2.10 Synthesis of (*R*)-phosphalysine [(*R*)-**91**]



(*R*)-**90** (*R*)-**91**

Aminophosphonate (*R*)-X (40 mg, 0.15 mmol) was refluxed in 6M HCl (5 mL) for 16h. The deprotected phosphonic acid was purified using a Dowex W 50/H^+-form ion exchange resin with water/25% NH_3-solution 92:8 as the eluent. The product was recrystallized from H_2O/EtOH, giving (*R*)-phosphalysine [(*R*)-**91**] in 93% yield (25 mg, 0.14 mmol).

^{1}H NMR (600.25 MHz, D_2O, [61Aug1320/100], KB083] δ_H: 3.08-3.01 (m, 3H, H_2N-C$\underline{H_2}$ and H_2N-C$\underline{H}$-P), 2.0-1.9 (m, 1H, H_2N-CH_2-C$\underline{H_2}$), 1.79-1.67 (m, 3H, 1H from H_2N-CH_2-C$\underline{H_2}$, 2H from H_2N-CH_2-CH_2-C$\underline{H_2}$), 1.65-1.50 (m, 2H, P-CH-C$\underline{H_2}$).

^{13}C NMR (150.93 MHz, D_2O, [61Aug1320/101], KB083] δ_C: 50.7-49.9 (d, *J*=133 Hz, H_2N-$\underline{C}$H-P), 39.0 (s, H_2N-$\underline{C}H_2$), 28.6 (d, *J*=1.37 Hz, H_2N-CH_2-$\underline{C}H_2$), 26.3 (s, H_2N-CH_2-CH_2-$\underline{C}H_2$), 22.8 (d, *J*=8.1 Hz, P-CH-$\underline{C}H_2$).

^{31}P NMR (162.03 MHz, D_2O, [41Aug1320/41, KB083 pure] δ_P: 11.51 (s).

HRMS calculated for $C_5H_{15}N_2O_3P$, MW=182.1598: $[M+Na]^+$ = 205.0713;

Found: $[M+Na]^+$ = 205.0705.

IR (ATR, KB083) v = 2931, 2861, 2554, 2349, 2138, 1611, 1562, 1469, 1042, 972, 738.

α_D^{20}[(*R*)-**91**]= −13.25 (c=0.400 in D_2O).

5. Abstracts

5.1 English abstract

α-Aminophosphonic acids and α-aminophosphonates are compounds of high interest as drugs. Hence, it is of utmost importance to find new and innovative synthetic pathways to obtain these compounds in their enantiopure form. However, most literature known methods for their synthesis only cover limited substrate scopes, use hazardous chemicals or make use of expensive chiral pool reagents. Thus, this master thesis focuses on the development of a simple, catalytic method that allows for the synthesis of a broad scope of α-aminophosphonic acids and tolerates a variety of functional groups. The thesis has three main parts. The first part concerns itself with the synthesis of enantiopure (*R*)-phosphalysine [(*R*)-**91**] from a simple starting material, 4-pentenoic acid (**85**). **85** is converted via an Arbuzov reaction to diisopropyl pent-4-enoylphosphonate (**86)**, which can be reduced in an asymmetric transfer hydrogenation with Noyori-catalyst (*R,R*)-RuCl[(p-cymene)-TsDPEN] [(*R,R*)-**97]** to chiral (*S*)-diisopropyl (1-hydroxy-4-pentenyl)phosphonate [(*S*)-**87]**. This introduces chirality into the scaffold and is the key step of the synthetic pathway. (*S*)-**87** undergoes a hydroboration/oxidation reaction, which installs a terminal hydroxyl-group on the scaffold, affording (*S*)-diisopropyl (1,5-dihydroxypentyl)phosphonate [(*S*)-**88]**. The two hydroxyl-groups can be replaced by azido-groups in a Mitsunobu reaction with HN_3. This reaction also introduces the desired (*R*)-configuration on the α-carbon next to phosphorus. Subsequent hydrogenation with H_2 and Pd/C and deprotection of the phosphonate groups affords (*R*)-**91**.

The second part of the thesis deals with an investigation of alternative nucleophiles that could be used instead of the toxic and explosive HN_3 in the performed Mitsunobu reaction. Maleimide, trimethylsilyl azide, phthalimide and tetrachlorophthalimide were investigated for this purpose. Finally, tetrachlorophthalimide turned out to be the most promising candidate. (*R*)-Diisopropyl (1,5-bis(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentyl)phosphonate [(*R*)-**112**], a possible precursor to (*R*)-**91** was synthesized this way.

Part three of the thesis deals with the synthesis of (*R*)-phosphaarginine precursors (*R*)-diisopropyl 4-hydroxy-1-((*S*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate [(*R,S*)-**113**] and (*R*)-diisopropyl 4-hydroxy-1-((*R*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonate [(*R,R*)-**113**] and it builds upon knowledge acquired in parts one and two. This synthetic pathway starts with **85** and shares its first three steps with the synthesis of (*R*)-**91**. Key intermediate (*S*)-**87** is reacted with tetrachlorophthalimide in a Mitsunobu reaction. The product of this reaction is then modified in an ozonolysis with reductive work-up to shorten the C_5-backbone by one C-atom and install a terminal hydroxyl-group at the same time, affording precursors (*R,S*)- and (*R,R*)-**113**.

5.2 Deutsche Zusammenfassung

α-Aminophosphonsäuren und α-Aminophosphonate sind Verbindungen, die als Arzneimittel von großem Interesse sind. Daher ist es von größter Bedeutung, neue und innovative Synthesewege zu finden, um diese Verbindungen in ihrer enantiomerenreinen Form zu erhalten. Die meisten in der Literatur bekannten Synthesemethoden decken jedoch nur ein begrenztes Substratspektrum ab, verwenden gefährliche Chemikalien oder greifen auf teure chirale Poolreagenzien zurück. Daher konzentriert sich diese Masterarbeit auf die Entwicklung einer einfachen, katalytischen Methode, die die Synthese eines breiten Spektrums von α-Aminophosphonsäuren ermöglicht und eine Vielzahl von funktionellen Gruppen toleriert. Die Arbeit ist in drei Hauptteile gegliedert. Der erste Teil beschäftigt sich mit der Synthese von enantiomerenreinem (*R*)-Phosphalysin [(*R*)-**91**] aus einem einfachen Ausgangsmaterial, 4-Pentensäure (**85**). **85** wird über eine Arbuzov-Reaktion zu Diisopropyl-pent-4-enoylphosphonat (**86**) umgesetzt, das in einer asymmetrischen Transferhydrierung mit Noyori-Katalysator (*R,R*)-RuCl[(p-Cymol)-TsDPEN] [(*R,R*)-**97**] zu chiralem (*S*)-Diisopropyl-(1-hydroxy-4-pentenyl)-phosphonat [(*S*)-**87**] reduziert werden kann. Dies führt Chiralität in das Gerüst ein und ist der Schlüsselschritt des Syntheseweges. (*S*)-**87** durchläuft eine Hydroborierungs-/Oxidationsreaktion, bei der eine endständige Hydroxylgruppe am Gerüst installiert wird, wodurch (*S*)-Diisopropyl-(1,5-dihydroxypentyl)phosphonat [(*S*)-**88**] entsteht. Die beiden Hydroxylgruppen können in einer Mitsunobu-Reaktion mit HN_3 durch Azidogruppen ersetzt werden. Diese Reaktion führt auch die gewünschte (*R*)-Konfiguration am α-Kohlenstoff neben dem Phosphor ein. Die anschließende Hydrierung mit H_2 und Pd/C und die Entschützung der Phosphonatgruppen ergibt (*R*)-**91**.

Der zweite Teil der Arbeit befasst sich mit der Untersuchung alternativer Nukleophile, die anstelle des giftigen und explosiven HN_3 in der durchgeführten Mitsunobu-Reaktion verwendet werden könnten. Zu diesem Zweck wurden Maleimid, Trimethylsilylazid, Phthalimid und Tetrachlorphthalimid untersucht. Schließlich erwies sich Tetrachlorphthalimid als der vielversprechendste Kandidat. Auf diese Weise wurde (*R*)-Diisopropyl-(1,5-bis(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentyl)phosphonat [(*R*)-**112**], ein möglicher Vorläufer von (*R*)-**91**, synthetisiert.

Der dritte Teil der Arbeit befasst sich mit der Synthese der (*R*)-Phosphaarginin-Vorstufen (*R*)-Diisopropyl-4-hydroxy-1-((*S*)-4,5,6,7-tetrachloro-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonat [(*R, S*)-**113**] und (*R*)-Diisopropyl-4-hydroxy-1-((*R*)-4,5,6,7-tetrachlor-1-hydroxy-3-oxoisoindolin-2-yl)butyl)phosphonat [(*R,R*)-**113**] und baut auf den in den Teilen eins und zwei erworbenen Kenntnissen auf. Dieser Syntheseweg beginnt mit **85** und teilt seine ersten drei Schritte mit der Synthese von (*R*)-**91**. Das Schlüsselzwischenprodukt (*S*)-**87** wird in einer Mitsunobu-Reaktion mit Tetrachlorphthalimid umgesetzt. Das Produkt dieser Reaktion wird dann in einer Ozonolyse mit reduktiver Aufarbeitung modifiziert, um das C_5-Backbone um ein C-Atom zu verkürzen und gleichzeitig eine endständige Hydroxylgruppe einzubauen, wodurch die Vorstufen (*R,S*)- und (*R,R*)-**113** entstehen.

6. Appendix

(*R*)-**112** crystal structure data

Table 1. Crystal data and structure refinement for (*R*)-**112**.

Identification code	mo_kb063_p-1	
Empirical formula	C27 H22 Cl8 N2 O8 P	
Formula weight	817.03	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9139(7) Å	α= 94.304(2)°.
	b = 11.4817(5) Å	β= 102.422(3)°.
	c = 14.8473(7) Å	γ = 100.144(3)°.
Volume	1613.43(16) $Å^3$	
Z	2	
Density (calculated)	1.682 Mg/m^3	
Absorption coefficient	0.800 mm^{-1}	
F(000)	826	
Crystal size	0.12 x 0.1 x 0.09 mm^3	
Theta range for data collection	1.814 to 25.350°.	
Index ranges	-11<=h<=11, -13<=k<=13, -17<=l<=17	
Reflections collected	29971	
Independent reflections	5893 [R(int) = 0.0295]	
Completeness to theta = 25.242°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.6815	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5893 / 6 / 440	
Goodness-of-fit on F^2	1.095	
Final R indices [I>2sigma(I)]	R1 = 0.0355, wR2 = 0.0873	
R indices (all data)	R1 = 0.0371, wR2 = 0.0882	
Extinction coefficient	n/a	

Largest diff. peak and hole	0.788 and -0.491 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**112**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	-5420(1)	7605(1)	2962(1)	26(1)
Cl(2)	4286(1)	4294(1)	1819(1)	27(1)
Cl(3)	7490(1)	4311(1)	2112(1)	26(1)
Cl(4)	9356(1)	6066(1)	1178(1)	28(1)
Cl(5)	-3866(1)	9525(1)	1919(1)	27(1)
Cl(6)	-526(1)	6218(1)	4298(1)	31(1)
Cl(7)	-3768(1)	5946(1)	4085(1)	30(1)
P(8)	2668(1)	11511(1)	3519(1)	25(1)
Cl(9)	8071(1)	7918(1)	14(1)	31(1)
O(1)	2282(2)	5905(2)	826(1)	27(1)
O(2)	1873(2)	12369(2)	2955(1)	41(1)
O(3)	4998(2)	8458(2)	-592(1)	26(1)
C(4)	-2953(2)	8648(2)	2605(2)	22(1)
C(5)	4775(2)	6141(2)	819(2)	20(1)
O(6)	1750(2)	8000(2)	3636(1)	32(1)
O(7)	4250(2)	11981(2)	3551(1)	32(1)
C(8)	4691(2)	7695(2)	-118(2)	20(1)
C(9)	5608(2)	6933(2)	408(2)	20(1)
N(10)	848(2)	9431(2)	2816(1)	26(1)
C(11)	-1434(3)	7152(2)	3670(2)	24(1)
O(12)	2344(2)	11343(2)	4429(1)	34(1)
N(13)	3368(2)	7322(2)	46(1)	21(1)
C(14)	7601(2)	6102(2)	1041(2)	21(1)
C(15)	3301(2)	6385(2)	594(2)	21(1)
C(16)	2221(2)	9062(2)	199(2)	23(1)
C(17)	-3639(2)	7776(2)	3049(2)	21(1)
C(18)	-2894(2)	7027(2)	3573(2)	23(1)
C(19)	762(3)	8433(2)	3292(2)	26(1)
C(20)	2157(2)	7859(2)	-335(2)	23(1)
C(21)	2220(2)	10107(2)	2750(2)	26(1)
C(22)	2129(2)	8985(2)	1203(2)	23(1)

C(23)	-768(2)	8040(2)	3260(2)	23(1)
C(24)	7030(2)	6933(2)	510(2)	21(1)
C(25)	6763(2)	5309(2)	1452(2)	21(1)
O(26)	-702(2)	10438(2)	1939(1)	33(1)
C(27)	-478(3)	9671(2)	2423(2)	26(1)
C(28)	5316(2)	5313(2)	1338(2)	21(1)
C(29)	-1507(2)	8778(2)	2736(2)	22(1)
C(31)	5410(3)	11927(2)	4350(2)	26(1)
C(32)	2330(3)	10210(2)	1748(2)	26(1)
C(34)	1287(3)	13300(3)	3403(2)	40(1)
C(42)	-245(3)	12788(3)	3359(2)	40(1)
C(45)	6299(4)	13131(4)	4580(3)	33(1)
C(2)	1503(4)	14365(3)	2908(3)	63(1)
C(1)	6201(7)	10993(5)	4100(4)	53(2)
C(6)	6744(10)	12628(9)	4060(7)	44(3)
C(3)	5554(10)	10693(8)	4409(6)	28(2)
O(4)	9359(2)	234(2)	4854(2)	52(1)

Table 3. Selected bond lengths [Å] and angles [°] for (*R*)-**112**.

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_____

Symmetry transformations used to generate equivalent atoms:

Table 4. Bond lengths [Å] and angles [°] for (*R*)-**112**.

Cl(1)-C(17)	1.717(2)
Cl(2)-C(28)	1.715(2)
Cl(3)-C(25)	1.717(2)
Cl(4)-C(14)	1.716(2)
Cl(5)-C(4)	1.717(2)
Cl(6)-C(11)	1.721(2)
Cl(7)-C(18)	1.708(3)
P(8)-O(2)	1.551(2)
P(8)-O(7)	1.5554(19)
P(8)-O(12)	1.4730(19)
P(8)-C(21)	1.831(3)
Cl(9)-C(24)	1.711(2)
O(1)-C(15)	1.194(3)
O(2)-C(34)	1.484(3)
O(3)-C(8)	1.202(3)
C(4)-C(17)	1.397(3)
C(4)-C(29)	1.385(3)
C(5)-C(9)	1.385(3)
C(5)-C(15)	1.507(3)
C(5)-C(28)	1.377(3)
O(6)-C(19)	1.209(3)
O(7)-C(31)	1.477(3)
C(8)-C(9)	1.510(3)
C(8)-N(13)	1.385(3)
C(9)-C(24)	1.385(3)
N(10)-C(19)	1.390(3)
N(10)-C(21)	1.469(3)
N(10)-C(27)	1.402(3)
C(11)-C(18)	1.403(3)
C(11)-C(23)	1.369(4)
N(13)-C(15)	1.398(3)
N(13)-C(20)	1.471(3)
C(14)-C(24)	1.401(3)
C(14)-C(25)	1.389(3)

C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(16)-C(20)	1.524(3)
C(16)-C(22)	1.521(3)
C(17)-C(18)	1.403(3)
C(19)-C(23)	1.494(3)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-H(21)	1.0000
C(21)-C(32)	1.527(3)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(22)-C(32)	1.527(3)
C(23)-C(29)	1.391(3)
C(25)-C(28)	1.408(3)
O(26)-C(27)	1.199(3)
C(27)-C(29)	1.487(3)
C(31)-C(45)	1.475(5)
C(31)-C(1)	1.505(5)
C(31)-C(6)	1.583(10)
C(31)-C(3)	1.455(9)
C(32)-H(32A)	0.9900
C(32)-H(32B)	0.9900
C(34)-H(34)	1.0000
C(34)-C(42)	1.515(4)
C(34)-C(2)	1.480(5)
C(42)-H(42A)	0.9800
C(42)-H(42B)	0.9800
C(42)-H(42C)	0.9800
C(45)-H(45A)	0.9800
C(45)-H(45B)	0.9800
C(45)-H(45C)	0.9800
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800
C(1)-H(1A)	0.9800

C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
O(4)-O(4)#1	1.460(4)

O(2)-P(8)-O(7)	104.87(12)
O(2)-P(8)-C(21)	104.62(11)
O(7)-P(8)-C(21)	104.06(11)
O(12)-P(8)-O(2)	115.40(11)
O(12)-P(8)-O(7)	114.97(10)
O(12)-P(8)-C(21)	111.77(12)
C(34)-O(2)-P(8)	122.28(17)
C(17)-C(4)-Cl(5)	121.42(18)
C(29)-C(4)-Cl(5)	121.03(19)
C(29)-C(4)-C(17)	117.6(2)
C(9)-C(5)-C(15)	108.2(2)
C(28)-C(5)-C(9)	121.7(2)
C(28)-C(5)-C(15)	130.1(2)
C(31)-O(7)-P(8)	123.67(16)
O(3)-C(8)-C(9)	129.1(2)
O(3)-C(8)-N(13)	125.8(2)
N(13)-C(8)-C(9)	105.14(19)
C(5)-C(9)-C(8)	108.20(19)
C(5)-C(9)-C(24)	121.2(2)
C(24)-C(9)-C(8)	130.6(2)
C(19)-N(10)-C(21)	120.8(2)
C(19)-N(10)-C(27)	112.7(2)
C(27)-N(10)-C(21)	126.4(2)
C(18)-C(11)-Cl(6)	120.3(2)
C(23)-C(11)-Cl(6)	121.69(19)
C(23)-C(11)-C(18)	118.0(2)

C(8)-N(13)-C(15)	113.52(19)
C(8)-N(13)-C(20)	122.6(2)
C(15)-N(13)-C(20)	123.8(2)
C(24)-C(14)-Cl(4)	119.36(18)
C(25)-C(14)-Cl(4)	119.88(18)
C(25)-C(14)-C(24)	120.8(2)
O(1)-C(15)-C(5)	128.9(2)
O(1)-C(15)-N(13)	126.2(2)
N(13)-C(15)-C(5)	104.93(19)
H(16A)-C(16)-H(16B)	107.7
C(20)-C(16)-H(16A)	108.9
C(20)-C(16)-H(16B)	108.9
C(22)-C(16)-H(16A)	108.9
C(22)-C(16)-H(16B)	108.9
C(22)-C(16)-C(20)	113.5(2)
C(4)-C(17)-Cl(1)	120.29(18)
C(4)-C(17)-C(18)	121.0(2)
C(18)-C(17)-Cl(1)	118.74(19)
C(11)-C(18)-Cl(7)	119.78(19)
C(11)-C(18)-C(17)	120.3(2)
C(17)-C(18)-Cl(7)	119.90(18)
O(6)-C(19)-N(10)	125.2(2)
O(6)-C(19)-C(23)	129.5(2)
N(10)-C(19)-C(23)	105.3(2)
N(13)-C(20)-C(16)	112.20(18)
N(13)-C(20)-H(20A)	109.2
N(13)-C(20)-H(20B)	109.2
C(16)-C(20)-H(20A)	109.2
C(16)-C(20)-H(20B)	109.2
H(20A)-C(20)-H(20B)	107.9
P(8)-C(21)-H(21)	105.8
N(10)-C(21)-P(8)	109.91(16)
N(10)-C(21)-H(21)	105.8
N(10)-C(21)-C(32)	112.8(2)
C(32)-C(21)-P(8)	115.79(18)
C(32)-C(21)-H(21)	105.8

C(16)-C(22)-H(22A)	109.1
C(16)-C(22)-H(22B)	109.1
C(16)-C(22)-C(32)	112.5(2)
H(22A)-C(22)-H(22B)	107.8
C(32)-C(22)-H(22A)	109.1
C(32)-C(22)-H(22B)	109.1
C(11)-C(23)-C(19)	130.1(2)
C(11)-C(23)-C(29)	121.7(2)
C(29)-C(23)-C(19)	108.2(2)
C(9)-C(24)-Cl(9)	121.54(18)
C(9)-C(24)-C(14)	117.9(2)
C(14)-C(24)-Cl(9)	120.59(18)
C(14)-C(25)-Cl(3)	119.96(18)
C(14)-C(25)-C(28)	120.8(2)
C(28)-C(25)-Cl(3)	119.28(19)
N(10)-C(27)-C(29)	105.2(2)
O(26)-C(27)-N(10)	126.1(2)
O(26)-C(27)-C(29)	128.6(2)
C(5)-C(28)-Cl(2)	122.24(18)
C(5)-C(28)-C(25)	117.7(2)
C(25)-C(28)-Cl(2)	120.06(18)
C(4)-C(29)-C(23)	121.4(2)
C(4)-C(29)-C(27)	130.3(2)
C(23)-C(29)-C(27)	108.3(2)
O(7)-C(31)-C(1)	109.5(3)
O(7)-C(31)-C(6)	102.5(4)
C(45)-C(31)-O(7)	106.8(2)
C(45)-C(31)-C(1)	112.9(4)
C(3)-C(31)-O(7)	109.4(4)
C(3)-C(31)-C(6)	108.8(6)
C(21)-C(32)-C(22)	111.4(2)
C(21)-C(32)-H(32A)	109.3
C(21)-C(32)-H(32B)	109.3
C(22)-C(32)-H(32A)	109.3
C(22)-C(32)-H(32B)	109.3
H(32A)-C(32)-H(32B)	108.0

O(2)-C(34)-H(34)	109.3
O(2)-C(34)-C(42)	107.6(2)
C(42)-C(34)-H(34)	109.3
C(2)-C(34)-O(2)	107.3(2)
C(2)-C(34)-H(34)	109.3
C(2)-C(34)-C(42)	114.0(3)
C(34)-C(42)-H(42A)	109.5
C(34)-C(42)-H(42B)	109.5
C(34)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(31)-C(45)-H(45A)	109.5
C(31)-C(45)-H(45B)	109.5
C(31)-C(45)-H(45C)	109.5
H(45A)-C(45)-H(45B)	109.5
H(45A)-C(45)-H(45C)	109.5
H(45B)-C(45)-H(45C)	109.5
C(34)-C(2)-H(2A)	109.5
C(34)-C(2)-H(2B)	109.5
C(34)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(31)-C(1)-H(1A)	109.5
C(31)-C(1)-H(1B)	109.5
C(31)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(31)-C(6)-H(6A)	109.5
C(31)-C(6)-H(6B)	109.5
C(31)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5

C(31)-C(3)-H(3A)	109.5
C(31)-C(3)-H(3B)	109.5
C(31)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y,-z+1

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (*R*)-**112**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	17(1)	32(1)	29(1)	1(1)	6(1)	7(1)
Cl(2)	28(1)	29(1)	29(1)	6(1)	13(1)	7(1)
Cl(3)	29(1)	27(1)	25(1)	4(1)	5(1)	14(1)
Cl(4)	16(1)	28(1)	40(1)	4(1)	3(1)	9(1)
Cl(5)	22(1)	36(1)	26(1)	8(1)	2(1)	12(1)
Cl(6)	32(1)	38(1)	27(1)	5(1)	3(1)	19(1)
Cl(7)	32(1)	29(1)	31(1)	5(1)	8(1)	7(1)
P(8)	22(1)	34(1)	19(1)	-2(1)	2(1)	12(1)
Cl(9)	19(1)	28(1)	49(1)	13(1)	10(1)	5(1)
O(1)	20(1)	31(1)	32(1)	2(1)	9(1)	6(1)
O(2)	51(1)	55(1)	26(1)	-2(1)	5(1)	37(1)
O(3)	24(1)	27(1)	28(1)	5(1)	6(1)	9(1)
C(4)	21(1)	29(1)	17(1)	-1(1)	2(1)	11(1)
C(5)	18(1)	21(1)	20(1)	-4(1)	3(1)	6(1)
O(6)	23(1)	48(1)	29(1)	2(1)	3(1)	18(1)
O(7)	24(1)	45(1)	24(1)	7(1)	1(1)	6(1)
C(8)	18(1)	19(1)	20(1)	-4(1)	3(1)	6(1)
C(9)	18(1)	20(1)	21(1)	-2(1)	3(1)	7(1)
N(10)	17(1)	40(1)	24(1)	-2(1)	6(1)	8(1)
C(11)	26(1)	30(1)	16(1)	-3(1)	3(1)	13(1)
O(12)	31(1)	45(1)	26(1)	-4(1)	10(1)	9(1)
N(13)	16(1)	24(1)	21(1)	-2(1)	2(1)	8(1)
C(14)	16(1)	21(1)	26(1)	-3(1)	2(1)	7(1)
C(15)	19(1)	24(1)	20(1)	-4(1)	4(1)	8(1)
C(16)	20(1)	26(1)	23(1)	0(1)	4(1)	9(1)
C(17)	17(1)	28(1)	19(1)	-4(1)	3(1)	7(1)
C(18)	24(1)	27(1)	18(1)	-2(1)	6(1)	6(1)
C(19)	23(1)	37(1)	18(1)	-4(1)	5(1)	11(1)
C(20)	18(1)	29(1)	22(1)	-2(1)	0(1)	11(1)
C(21)	20(1)	33(1)	26(1)	0(1)	6(1)	9(1)
C(22)	21(1)	28(1)	23(1)	1(1)	7(1)	7(1)

C(23)	20(1)	34(1)	16(1)	-4(1)	3(1)	12(1)
C(24)	18(1)	20(1)	26(1)	-1(1)	5(1)	4(1)
C(25)	23(1)	20(1)	20(1)	-3(1)	2(1)	9(1)
O(26)	27(1)	43(1)	29(1)	9(1)	5(1)	8(1)
C(27)	24(1)	36(1)	18(1)	1(1)	6(1)	8(1)
C(28)	22(1)	22(1)	19(1)	-2(1)	7(1)	6(1)
C(29)	20(1)	33(1)	15(1)	-2(1)	4(1)	7(1)
C(31)	21(1)	28(1)	26(1)	1(1)	-3(1)	8(1)
C(32)	27(1)	30(1)	24(1)	1(1)	10(1)	7(1)
C(34)	39(2)	51(2)	34(2)	-4(1)	7(1)	30(1)
C(42)	38(2)	53(2)	32(1)	0(1)	4(1)	25(1)
C(45)	30(2)	32(2)	37(2)	5(2)	10(2)	5(2)
C(2)	70(2)	60(2)	86(3)	20(2)	52(2)	39(2)
C(1)	46(3)	49(3)	58(3)	-18(3)	-5(3)	23(3)
C(6)	30(5)	47(6)	46(6)	23(5)	-4(4)	-5(4)
C(3)	21(4)	31(5)	29(4)	12(3)	0(3)	4(3)
O(4)	38(1)	66(2)	53(1)	3(1)	10(1)	20(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**112**.

	x	y	z	U(eq)
H(16A)	3115	9599	189	27
H(16B)	1437	9418	-121	27
H(20A)	1277	7311	-312	28
H(20B)	2133	7963	-993	28
H(21)	2929	9627	3010	31
H(22A)	2859	8563	1510	28
H(22B)	1197	8512	1215	28
H(32A)	3267	10682	1745	32
H(32B)	1605	10637	1441	32
H(34)	1811	13505	4068	48
H(42A)	-745	12528	2711	60
H(42B)	-675	13399	3620	60
H(42C)	-307	12106	3717	60
H(45A)	6652	13365	4039	49
H(45B)	7096	13130	5101	49
H(45C)	5740	13698	4753	49
H(2A)	2513	14700	3025	94
H(2B)	1018	14961	3131	94
H(2C)	1122	14137	2240	94
H(1A)	5561	10215	3948	80
H(1B)	6976	10962	4628	80
H(1C)	6582	11194	3562	80
H(6A)	6855	12219	3485	66
H(6B)	7587	12661	4555	66
H(6C)	6616	13440	3961	66
H(3A)	4708	10240	4553	41
H(3B)	6380	10663	4899	41
H(3C)	5670	10347	3813	41

Table 7. Selected torsion angles [°] for (*R*)-**112**.

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y,-z+1

Table 8. Torsion angles [°] for (*R*)-**112**.

Cl(1)-C(17)-C(18)-Cl(7)	1.6(3)
Cl(1)-C(17)-C(18)-C(11)	-179.07(17)
Cl(3)-C(25)-C(28)-Cl(2)	-2.3(3)
Cl(3)-C(25)-C(28)-C(5)	178.78(17)
Cl(4)-C(14)-C(24)-Cl(9)	-0.9(3)
Cl(4)-C(14)-C(24)-C(9)	179.59(17)
Cl(4)-C(14)-C(25)-Cl(3)	1.0(3)
Cl(4)-C(14)-C(25)-C(28)	-179.13(17)
Cl(5)-C(4)-C(17)-Cl(1)	-3.1(3)
Cl(5)-C(4)-C(17)-C(18)	176.98(17)
Cl(5)-C(4)-C(29)-C(23)	-177.39(17)
Cl(5)-C(4)-C(29)-C(27)	5.4(4)
Cl(6)-C(11)-C(18)-Cl(7)	0.4(3)
Cl(6)-C(11)-C(18)-C(17)	-179.00(17)
Cl(6)-C(11)-C(23)-C(19)	-3.6(4)
Cl(6)-C(11)-C(23)-C(29)	178.56(17)
P(8)-O(2)-C(34)-C(42)	-94.8(3)
P(8)-O(2)-C(34)-C(2)	142.2(3)
P(8)-O(7)-C(31)-C(45)	-129.7(2)
P(8)-O(7)-C(31)-C(1)	107.7(4)
P(8)-O(7)-C(31)-C(6)	-174.5(5)
P(8)-O(7)-C(31)-C(3)	70.1(5)
P(8)-C(21)-C(32)-C(22)	172.33(16)
O(2)-P(8)-O(7)-C(31)	145.94(18)
O(2)-P(8)-C(21)-N(10)	-82.70(19)
O(2)-P(8)-C(21)-C(32)	46.6(2)
O(3)-C(8)-C(9)-C(5)	-177.3(2)
O(3)-C(8)-C(9)-C(24)	2.4(4)
O(3)-C(8)-N(13)-C(15)	177.5(2)
O(3)-C(8)-N(13)-C(20)	-1.8(3)
C(4)-C(17)-C(18)-Cl(7)	-178.49(17)
C(4)-C(17)-C(18)-C(11)	0.9(3)
C(5)-C(9)-C(24)-Cl(9)	-179.34(17)
C(5)-C(9)-C(24)-C(14)	0.2(3)

O(6)-C(19)-C(23)-C(11)	5.8(4)
O(6)-C(19)-C(23)-C(29)	-176.2(2)
O(7)-P(8)-O(2)-C(34)	-104.6(2)
O(7)-P(8)-C(21)-N(10)	167.50(16)
O(7)-P(8)-C(21)-C(32)	-63.22(19)
C(8)-C(9)-C(24)-Cl(9)	1.0(4)
C(8)-C(9)-C(24)-C(14)	-179.4(2)
C(8)-N(13)-C(15)-O(1)	-179.5(2)
C(8)-N(13)-C(15)-C(5)	0.8(2)
C(8)-N(13)-C(20)-C(16)	-77.1(3)
C(9)-C(5)-C(15)-O(1)	-179.2(2)
C(9)-C(5)-C(15)-N(13)	0.5(2)
C(9)-C(5)-C(28)-Cl(2)	-177.77(17)
C(9)-C(5)-C(28)-C(25)	1.1(3)
C(9)-C(8)-N(13)-C(15)	-1.7(2)
C(9)-C(8)-N(13)-C(20)	179.03(18)
N(10)-C(19)-C(23)-C(11)	-175.2(2)
N(10)-C(19)-C(23)-C(29)	2.9(2)
N(10)-C(21)-C(32)-C(22)	-59.8(3)
N(10)-C(27)-C(29)-C(4)	175.4(2)
N(10)-C(27)-C(29)-C(23)	-2.1(2)
C(11)-C(23)-C(29)-C(4)	0.0(3)
C(11)-C(23)-C(29)-C(27)	177.7(2)
O(12)-P(8)-O(2)-C(34)	23.0(3)
O(12)-P(8)-O(7)-C(31)	18.1(2)
O(12)-P(8)-C(21)-N(10)	42.9(2)
O(12)-P(8)-C(21)-C(32)	172.13(17)
N(13)-C(8)-C(9)-C(5)	1.9(2)
N(13)-C(8)-C(9)-C(24)	-178.4(2)
C(14)-C(25)-C(28)-Cl(2)	177.80(17)
C(14)-C(25)-C(28)-C(5)	-1.1(3)
C(15)-C(5)-C(9)-C(8)	-1.5(2)
C(15)-C(5)-C(9)-C(24)	178.8(2)
C(15)-C(5)-C(28)-Cl(2)	2.8(3)
C(15)-C(5)-C(28)-C(25)	-178.3(2)
C(15)-N(13)-C(20)-C(16)	103.7(2)

C(16)-C(22)-C(32)-C(21)	179.5(2)
C(17)-C(4)-C(29)-C(23)	2.4(3)
C(17)-C(4)-C(29)-C(27)	-174.8(2)
C(18)-C(11)-C(23)-C(19)	175.8(2)
C(18)-C(11)-C(23)-C(29)	-2.0(3)
C(19)-N(10)-C(21)-P(8)	-105.6(2)
C(19)-N(10)-C(21)-C(32)	123.5(2)
C(19)-N(10)-C(27)-O(26)	-175.9(2)
C(19)-N(10)-C(27)-C(29)	4.1(3)
C(19)-C(23)-C(29)-C(4)	-178.2(2)
C(19)-C(23)-C(29)-C(27)	-0.5(2)
C(20)-N(13)-C(15)-O(1)	-0.2(4)
C(20)-N(13)-C(15)-C(5)	-179.90(18)
C(20)-C(16)-C(22)-C(32)	174.75(19)
C(21)-P(8)-O(2)-C(34)	146.2(2)
C(21)-P(8)-O(7)-C(31)	-104.4(2)
C(21)-N(10)-C(19)-O(6)	-4.3(4)
C(21)-N(10)-C(19)-C(23)	176.54(19)
C(21)-N(10)-C(27)-O(26)	3.2(4)
C(21)-N(10)-C(27)-C(29)	-176.9(2)
C(22)-C(16)-C(20)-N(13)	-64.1(3)
C(23)-C(11)-C(18)-Cl(7)	-179.07(17)
C(23)-C(11)-C(18)-C(17)	1.6(3)
C(24)-C(14)-C(25)-Cl(3)	-179.20(17)
C(24)-C(14)-C(25)-C(28)	0.7(3)
C(25)-C(14)-C(24)-Cl(9)	179.33(18)
C(25)-C(14)-C(24)-C(9)	-0.2(3)
O(26)-C(27)-C(29)-C(4)	-4.6(4)
O(26)-C(27)-C(29)-C(23)	177.9(2)
C(27)-N(10)-C(19)-O(6)	174.8(2)
C(27)-N(10)-C(19)-C(23)	-4.4(3)
C(27)-N(10)-C(21)-P(8)	75.4(3)
C(27)-N(10)-C(21)-C(32)	-55.5(3)
C(28)-C(5)-C(9)-C(8)	179.0(2)
C(28)-C(5)-C(9)-C(24)	-0.7(3)
C(28)-C(5)-C(15)-O(1)	0.3(4)

C(28)-C(5)-C(15)-N(13)	179.9(2)
C(29)-C(4)-C(17)-Cl(1)	177.11(17)
C(29)-C(4)-C(17)-C(18)	-2.8(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y,-z+1

Table 9. Hydrogen bonds for (*R*)-**112** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

(*R,S*)-**113** crystal structure data

Table 1. Crystal data and structure refinement for (*R,S*)-**113**.

Identification code	kp078_p21212	
Empirical formula	C18 H26 Cl4 N O7 P	
Formula weight	541.17	
Temperature	150.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 32.4871(12) Å	α= 90°.
	b = 8.2499(3) Å	β= 90°.
	c = 8.9481(4) Å	γ = 90°.
Volume	2398.23(16) $Å^3$	
Z	4	
Density (calculated)	1.499 Mg/m^3	
Absorption coefficient	0.599 mm^{-1}	
F(000)	1120	
Crystal size	0.3 x 0.3 x 0.3 mm^3	
Theta range for data collection	2.508 to 30.049°.	
Index ranges	-45<=h<=37, -9<=k<=11, -8<=l<=12	
Reflections collected	14553	
Independent reflections	6885 [R(int) = 0.0449]	
Completeness to theta = 25.242°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.6875	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6885 / 0 / 289	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.0817	
R indices (all data)	R1 = 0.0482, wR2 = 0.0857	
Absolute structure parameter	0.02(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.282 and -0.246 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R,S*)-**113**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(2)	218(1)	12027(1)	4621(1)	28(1)
Cl(3)	685(1)	10897(1)	11328(1)	24(1)
Cl(4)	-370(1)	13190(1)	7157(1)	28(1)
Cl(5)	-125(1)	12739(1)	10492(1)	29(1)
P(1)	1681(1)	6699(1)	6553(1)	17(1)
O(1)	1264(1)	6171(2)	5792(2)	21(1)
O(2)	1513(1)	10863(2)	9226(2)	22(1)
O(3)	1068(1)	10175(2)	4560(2)	22(1)
O(4)	1591(1)	6494(2)	8261(2)	22(1)
O(5)	2046(1)	5844(2)	5977(2)	22(1)
O(9)	2654(1)	13679(2)	6659(3)	24(1)
N(10)	1339(1)	9695(2)	6897(3)	16(1)
C(1)	1713(1)	8889(3)	6344(3)	16(1)
C(2)	1227(1)	9885(3)	8478(3)	16(1)
C(6)	1049(1)	10249(3)	5918(3)	16(1)
C(7)	711(1)	10941(3)	6857(3)	17(1)
C(8)	347(1)	11722(3)	6460(3)	19(1)
C(11)	556(1)	11216(3)	9488(3)	19(1)
C(13)	86(1)	12259(3)	7606(3)	21(1)
C(14)	2174(1)	11368(3)	6435(3)	18(1)
C(15)	812(1)	10696(3)	8342(3)	17(1)
C(16)	2116(1)	9607(3)	6929(3)	18(1)
C(17)	2544(1)	12108(3)	7208(3)	21(1)
C(18)	191(1)	12026(3)	9102(3)	21(1)
C(20)	1558(1)	4859(3)	8930(3)	20(1)
C(21)	1249(1)	5774(3)	4189(3)	23(1)
C(22)	822(1)	6199(4)	3662(4)	33(1)
C(23)	1913(1)	4643(4)	9963(4)	38(1)
C(24)	1145(1)	4790(4)	9670(5)	39(1)
C(26)	1354(1)	4011(4)	3991(4)	39(1)
O(25)	1634(1)	9648(4)	11979(3)	54(1)

Table 3. Selected bond lengths [Å] and angles [°] for (*R*,*S*)-**113**.

Symmetry transformations used to generate equivalent atoms:

Table 4. Bond lengths [Å] and angles [°] for (*R,S*)-**113**.

Cl(2)-C(8)	1.717(3)
Cl(3)-C(11)	1.720(3)
Cl(4)-C(13)	1.718(3)
Cl(5)-C(18)	1.718(3)
P(1)-O(1)	1.5786(19)
P(1)-O(4)	1.566(2)
P(1)-O(5)	1.4726(19)
P(1)-C(1)	1.819(2)
O(1)-C(21)	1.472(4)
O(2)-C(2)	1.400(3)
O(3)-C(6)	1.218(3)
O(4)-C(20)	1.480(3)
O(9)-C(17)	1.432(3)
N(10)-C(1)	1.470(3)
N(10)-C(2)	1.469(3)
N(10)-C(6)	1.365(3)
C(1)-C(16)	1.530(3)
C(2)-C(15)	1.511(3)
C(6)-C(7)	1.497(4)
C(7)-C(8)	1.391(3)
C(7)-C(15)	1.384(4)
C(8)-C(13)	1.403(4)
C(11)-C(15)	1.390(4)
C(11)-C(18)	1.402(4)
C(13)-C(18)	1.394(4)
C(14)-C(16)	1.530(3)
C(14)-C(17)	1.515(4)
C(20)-C(23)	1.488(4)
C(20)-C(24)	1.498(4)
C(21)-C(22)	1.508(4)
C(21)-C(26)	1.505(4)
O(1)-P(1)-C(1)	106.15(11)
O(4)-P(1)-O(1)	103.27(11)

O(4)-P(1)-C(1)	102.58(11)
O(5)-P(1)-O(1)	114.11(11)
O(5)-P(1)-O(4)	116.19(12)
O(5)-P(1)-C(1)	113.24(12)
C(21)-O(1)-P(1)	120.64(17)
C(20)-O(4)-P(1)	120.45(16)
C(2)-N(10)-C(1)	125.2(2)
C(6)-N(10)-C(1)	120.3(2)
C(6)-N(10)-C(2)	114.3(2)
N(10)-C(1)-P(1)	111.64(17)
N(10)-C(1)-C(16)	114.6(2)
C(16)-C(1)-P(1)	113.44(17)
O(2)-C(2)-N(10)	111.0(2)
O(2)-C(2)-C(15)	112.0(2)
N(10)-C(2)-C(15)	101.0(2)
O(3)-C(6)-N(10)	126.1(2)
O(3)-C(6)-C(7)	128.0(2)
N(10)-C(6)-C(7)	105.9(2)
C(8)-C(7)-C(6)	131.1(3)
C(15)-C(7)-C(6)	108.0(2)
C(15)-C(7)-C(8)	121.0(2)
C(7)-C(8)-Cl(2)	121.4(2)
C(7)-C(8)-C(13)	118.2(3)
C(13)-C(8)-Cl(2)	120.4(2)
C(15)-C(11)-Cl(3)	120.8(2)
C(15)-C(11)-C(18)	118.2(3)
C(18)-C(11)-Cl(3)	121.0(2)
C(8)-C(13)-Cl(4)	119.5(2)
C(18)-C(13)-Cl(4)	119.8(2)
C(18)-C(13)-C(8)	120.7(2)
C(17)-C(14)-C(16)	110.4(2)
C(7)-C(15)-C(2)	110.8(2)
C(7)-C(15)-C(11)	121.4(2)
C(11)-C(15)-C(2)	127.8(3)
C(1)-C(16)-C(14)	112.0(2)
O(9)-C(17)-C(14)	114.0(2)

C(11)-C(18)-Cl(5)	119.4(2)
C(13)-C(18)-Cl(5)	120.1(2)
C(13)-C(18)-C(11)	120.6(2)
O(4)-C(20)-C(23)	107.8(2)
O(4)-C(20)-C(24)	106.1(2)
C(23)-C(20)-C(24)	114.5(3)
O(1)-C(21)-C(22)	106.5(2)
O(1)-C(21)-C(26)	108.8(2)
C(26)-C(21)-C(22)	113.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (*R,S*)-**113**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(2)	22(1)	40(1)	21(1)	4(1)	-2(1)	9(1)
Cl(3)	24(1)	32(1)	17(1)	0(1)	3(1)	1(1)
Cl(4)	18(1)	34(1)	32(1)	2(1)	1(1)	9(1)
Cl(5)	24(1)	37(1)	27(1)	-5(1)	9(1)	7(1)
P(1)	18(1)	15(1)	18(1)	0(1)	2(1)	1(1)
O(1)	19(1)	24(1)	20(1)	-3(1)	2(1)	-1(1)
O(2)	20(1)	28(1)	19(1)	-3(1)	-2(1)	-2(1)
O(3)	22(1)	27(1)	16(1)	1(1)	1(1)	5(1)
O(4)	32(1)	15(1)	18(1)	0(1)	3(1)	-1(1)
O(5)	22(1)	18(1)	27(1)	1(1)	5(1)	4(1)
O(9)	18(1)	20(1)	34(1)	4(1)	-2(1)	-2(1)
N(10)	15(1)	17(1)	17(1)	1(1)	2(1)	3(1)
C(1)	15(1)	16(1)	18(1)	1(1)	1(1)	3(1)
C(2)	17(1)	16(1)	16(1)	1(1)	1(1)	1(1)
C(6)	15(1)	16(1)	18(1)	2(1)	1(1)	-1(1)
C(7)	15(1)	18(1)	19(1)	0(1)	2(1)	0(1)
C(8)	16(1)	22(1)	20(1)	0(1)	0(1)	-1(1)
C(11)	19(1)	20(1)	17(1)	-1(1)	2(1)	-1(1)
C(13)	14(1)	22(1)	26(1)	1(1)	2(1)	3(1)
C(14)	16(1)	18(1)	22(1)	2(1)	1(1)	2(1)
C(15)	17(1)	16(1)	18(1)	-1(1)	1(1)	-2(1)
C(16)	15(1)	18(1)	22(1)	2(1)	1(1)	2(1)
C(17)	19(1)	19(1)	25(2)	2(1)	-2(1)	0(1)
C(18)	18(1)	22(1)	23(1)	-4(1)	5(1)	1(1)
C(20)	28(1)	14(1)	17(1)	2(1)	0(1)	-2(1)
C(21)	24(1)	26(1)	19(1)	-2(1)	0(1)	-1(1)
C(22)	28(2)	43(2)	27(2)	-9(1)	-4(1)	4(1)
C(23)	37(2)	36(2)	40(2)	12(2)	-14(2)	-3(1)
C(24)	33(2)	34(2)	50(2)	15(2)	10(2)	1(1)
C(26)	55(2)	29(2)	33(2)	-9(2)	-11(2)	10(1)
O(25)	32(1)	108(2)	22(1)	10(1)	0(1)	29(2)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (*R*,*S*)-**113**.

	x	y	z	U(eq)
H(2)	1538	10542	10112	34
H(9)	2442	14257	6590	36
H(1)	1716	9088	5242	20
H(2A)	1202	8805	8976	20
H(14A)	2213	11410	5339	22
H(14B)	1924	12000	6684	22
H(16A)	2350	8950	6558	22
H(16B)	2118	9555	8034	22
H(17A)	2485	12192	8291	25
H(17B)	2782	11372	7085	25
H(20)	1572	4023	8122	24
H(21)	1455	6453	3641	28
H(22A)	619	5590	4246	49
H(22B)	794	5920	2602	49
H(22C)	775	7364	3794	49
H(23A)	2171	4734	9401	57
H(23B)	1897	3572	10432	57
H(23C)	1904	5483	10738	57
H(24A)	1118	5698	10369	59
H(24B)	1118	3766	10216	59
H(24C)	929	4862	8910	59
H(26A)	1626	3794	4427	58
H(26B)	1359	3746	2924	58
H(26C)	1147	3343	4494	58
H(25A)	1451	9825	12669	81
H(25B)	1867	9383	12395	81

Table 7. Selected torsion angles [°] for (*R*,*S*)-**113**.

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