Synthesis of 4-phosphono β-lactams and related azaheterocyclic phosphonates

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Synthesis of 4-phosphono β-lactams and related azaheterocyclic phosphonates

Thesis submitted in fulfillment of the requirements
for the degree of Doctor (PhD) in Applied Biological Sciences:
Chemistry

Dutch translation of the title:

Synthese van 4-fosfono-β-lactamen en aanverwante azaheterocyclische fosfonaten

*W*oord *V*ooraf

Toen ik op een hete dag in de voorbije zomer dit woord vooraf schreef, stond ik voor één van de laatste horden te nemen in de weg naar het "doctoraat". Het ideale moment voor een nostalgische terugblik op een zeer fijne periode, hoewel het onzinnig zou zijn te beweren dat alles rozegeur en maneschijn was. En op het einde van de rit komt dan ook het moment waarop je eindelijk een aantal mensen kunt bedanken, omwille van sterk uiteenlopende redenen.

Te beginnen met de mensen met wie ik het geluk heb gehad intensief te mogen samenwerken in één of meerdere onderzoeksprojecten. Ellen, Davy en Nicolai, voor mij zijn dit de meest verrijkende momenten geweest in de voorbije vier jaar. Het uitwisselen van ideeën en meningen heeft voor een zekere "drive" gezorgd die me toeliet elke morgen met vernieuwde krachten het lab in te stappen. Ik denk dat we fier kunnen zijn op de bereikte resultaten!

Ook van harte bedankt aan mijn promotor, professor Chris Stevens. We hebben meerdere malen met onze handen in het haar gezeten omwille van de rare kronkels van de chemie en het onderzoeksproject is uiteindelijk helemaal anders uitgedraaid dan het initieel was voorzien. Ik hoop alleszins dat de bereikte resultaten een stevige basis kunnen vormen voor je verdere onderzoek rond azaheterocyclische fosfonaten.

De collega's hebben gezorgd voor de goede sfeer, ook buiten de standaard chemische bezigheden. Volleybal, voetbal, film, bbq's, talloze trouwfeesten (en het voorbereiden van de bijbehorende cadeaus) en noem maar op. Bedankt Thomas, Bart, Inge, Tina, Guido, Nicola, An, Sven M., Matthias, Bert, Nicolai, Davy, Griet, Dominick, Sven C., Berten, Yves, Jan, Eva, Kurt, Diederica, Mirjana, Laurent, Viviane, Sandra en Pieter. Ook meer in het bijzonder aan mijn bureaugenoten: Ellen, David, Willem en Bram! Mijn appreciatie gaat ook uit naar de

thesisstudenten die mij als hun begeleider moeten verdragen hebben: Wouter, Vicky, Annelies, Bart, Miet en Steve. We komen elkaar vast nog wel eens tegen.

Ook bedankt aan Prof. Waroquier, Veronique en Karen van het *"Center for Molecular Modeling"*. Samenwerken tussen sterk gespecialiseerde mensen is niet gemakkelijk. Het heeft een tijd geduurd, maar *in the end* kunnen we fier zijn op het resultaat! *Also many thanks to prof. Zhdankin and his colleagues for their kind help with the x-ray analyses.*

Tenslotte kom ik bij de mensen die alles van op de eerste rij hebben meegemaakt, misschien soms zonder te begrijpen waarrond het eigenlijk altijd draaide. Het was niet gemakkelijk om al die verhalen te volgen, maar ik hoop dat vandaag alles misschien iets duidelijker of concreter wordt. Als jullie de draad toch verliezen, onthou dan maar dat het *au fond* gewoon gaat om *spelen met molecuultjes.* Veel belangrijker was jullie rol buiten de chemie, bij die dingen die zorgen voor een stabiel evenwicht in leven en werk, zoals vriendschap, een goede babbel, een gezellig thuiskomen, hulp in noodgevallen en de ongelofelijke steun bij alles wat we ondernemen! Daarom, aan mijn ondertussen sterk uitgebreide en nog steeds groeiende familie - Miriam, Tom, Ingrid, Peter, Astrid, Katrien, Arne, Stefaan, Bert, Yvette, Katleen, Kris, Myriam en Cesar - bedankt voor alles wat is geweest en nog moet komen.

Tenslotte nog een woordje voor Vera, alias *Bera Ban*. We varen al een tijd in hetzelfde schuitje en veel van de gebeurtenissen en gevoelens die hierboven beschreven staan, hebben we samen beleefd. Professioneel zijn onze wegen ondertussen uit elkaar gegaan en dat geeft misschien aanleiding tot meer gevarieerde gesprekken, 's avonds aan tafel: we hebben nu elk ons verhaal van de dag te vertellen. Ik sta hier nu met en dankzij jouw steun. Ik ben er zeker van dat we binnen een paar jaar hier weer staan, maar dan met de rollen omgekeerd!

<div align="right">

Kristof Moonen
29 september 2006

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List of Abbreviations

Ac	Acetyl
4-ABSA	4-Acetamido-benzenesulfonyl azide
AP	α-Aminoalkyl phosphonate
ATP	Adenosine triphosphate
Bn	Benzyl
Bt	Benzotriazole
cAMP	Cyclic adenosine monophosphate
CAN	Cerium ammonium nitrate
CNS	Central nervous system
COSY	Correlated spectroscopy
CPP	4-(3-phosphonoprop-1-yl)piperazine-2-carboxylic acid
CSE	Coordination solvation energy
DAP	Dialkyl phosphite
DAPTMS	Dialkyl trimethylsilyl phosphite
DCC	Dicyclohexyl carbodiimide
DEP	Diethyl phosphite
DEPT	Distortionless enhancement by polarization transfer
DEPTMS	Diethyl trimethylsilyl phosphate
DIFNOE	Difference nuclear Overhauser effect
DMAP	4-Dimethylamino pyridine
DME	Dimethoxy ethane
DMEt	Dimethyl ether
DMP	Dimethyl phosphite
DMPO	5,5-dimethyl-1-pyrroline *N*-oxide
DMPTMS	Dimethyl trimethylsilyl phosphite
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPP IV	Dipeptidyl peptidase IV
DQFCOSY	Double quantum filtered correlated spectroscopy

Edg	Endothelial differentiation gene
EPR	Electron paramagnetic resonance
EPSPS	5-Enolpyruvoylshikimate 3-phosphate synthase
FAP	Fibroblast Activating Protein
HLE	Human leukocyte elastase
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethyl phosphoramide
HSAB	Hard-soft, acid-base
HSQC	Heteronuclear single quantum correlation
IMDAF	Intramolecular Diels-Alder with furane
*i*Pr	iso-Propyl
KOTMS	Potassium trimethyl silanolate
LA	Lewis acid
LiHMDS	Lithium 1,1,1,3,3,3-hexamethyldisilazane
Ms	Mesyl
MM	Molecular mechanics
MW	Microwave
NMDA	*N*-Methyl D-aspartic acid
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser and exchange spectroscopy
PAP	3-Phosphonyl 1-aminoalkyl phosphonate
PBP	Penicillin binding protein
PE	Petroleum ether
PEP	Phosphoenol pyruvate
Ph	Phenyl
PMB	*p*-Methoxy benzyl
PPE	Porcine pancreatic elastase
PNZ	*p*-Nitrobenzyloxycarbonyl
RCM	Ring closing metathesis
ROESY	Rotating-frame Overhauser enhancement spectroscopy
ROM	Ring opening metathesis
RRM	Ring rearrangement metathesis
Rt	Room temperature
SRS	Self regeneration of stereocenters
TAP	Trialkyl phosphite
*t*Bu	Tertiary butyl
TCQ	Tetrachloroquinone (chloranil)
TEP	Triethyl phosphite
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-tetramethyl 1,2-ethanediamine
TMP	Trimethyl phosphate
Z	Phenylmethoxycarbonyl

Introduction and Goal

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1 Biological importance of amino phosphonates

Nature has chosen phosphates as essential chemicals in many critically important biological processes and materials. They are so versatile and fundamentally important in the chemistry of living systems, in so many ways, that it would be difficult to imagine any other chemical types that would be able to meet the manifold demands of living systems as we know.[1] The phophate group is present in (i) structural elements of the cell (e.g. DNA, phospholipids and protein phosphates), in (ii) intermediates of important biochemical pathways (e.g. sugar phosphates, isopentenyl pyrophosphate), in (iii) the energy management of the cell (e.g. ATP, phosphoenol pyruvate (PEP)) and in (iv) messenger molecules (e.g. myoinositol triphosphate, cAMP).

Their phosphonate counterparts are found far less widespread in living organisms.[2] Ciliatine or 2-aminoethane phosphonic acid **1** was the first one to be discovered.[3] Even more exciting was the discovery of naturally occurring phosphonates possessing remarkable biological activity despite their relatively simple structural features, as for instance the antibacterial fosfomycin[4] **2** and the antimalarial fosmidomycin[5-8] **3**, isolated from fermentation broths of *Streptomyces* species. These and other examples caused organophosphorus chemistry to achieve an important and well-recognized place in the search for new drugs.[9,10] The biological potential of phosphonic acid derivatives may arise from several rationales. Firstly, the methylene group attached to phosphorus is isosteric with an oxygen of a phosphate. However, the high stability of the C-P bond would block any natural process involving hydrolysis of a phosphate group. This can be applied in the development of antiviral agents based on naturally occurring nucleotides.[11-14]

H_2N — P(OH)_2 (O)

Ciliatine (**1**)

P(OH)_2 (O)

Fosfomycin (**2**)

OH, N, P(OH)_2 (O)

Fosmidomycin (**3**)

(HO)_2P — P(OH)_2, OH

Etidronate (**4**)

(HO)_2P — P(OH)_2, OH, H_2N

Pamidronate (**5**)

(HO)_2P — P(OH)_2, OH, N N

Zoledronate (**6**)
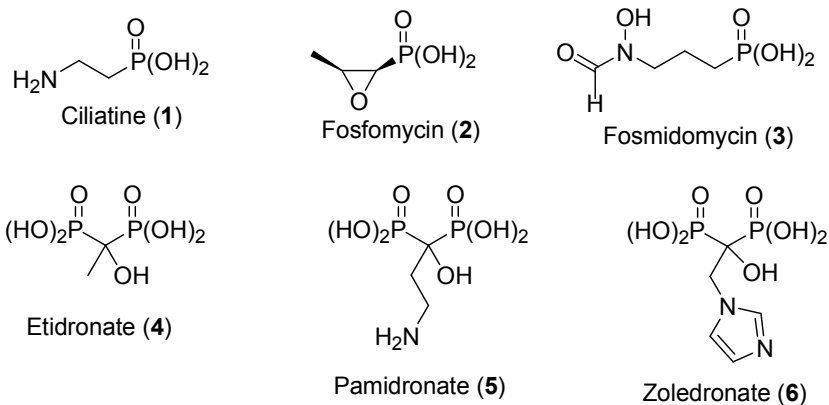
Application of the same principle resulted in a major breakthrough in the treatment of bone diseases such as osteoporosis and Paget's disease. Bisphosphonic acids (e.g. **4**-**6**) are isosteric with pyrophosphoric acid but are hydrolytically stable, in this way blocking bone resorption.[15,16] Their activity additionally results from the second interesting property of the phosphonate group, namely its ability to complex divalent cations such as Ca^{2+}. Current clinical research in the field of bisphosphonates is focussing on derivatives containing nitrogen atoms in their side chains (e.g. Zoledronate **6**) which are showing enhanced activities and pharmacological properties.[17-20]

Finally, phosphonic acids are considered to resemble their naturally occurring carboxylic acid counterparts, notwithstanding substantial differences with respect to size, shape and acidity.[21,22] This is of particular importance in the field of amino acids (amino phosphonates). More generally, the tetrahedral structure of the phosphonate group resembles that of the transition state of a nucleophilic attack on an acyl group (e.g. a peptide). Since enzymes act as catalysts because they are more closely complementary to the transition states than to the substrates or products of a reaction, phosphono peptides emerge as inhibitors of a wide range of enzymes,[23] such as elastase (e.g. **7**),[24-26] dipeptidyl dipeptidase IV (e.g. **8**),[27-30] thrombin (e.g. **9**),[31-33] HIV-protease (e.g. **10**),[34,35] etc... Good results are also obtained with metalloproteases (such as carboxypeptidase A (e.g. **13**)[36]) because of the good recognition of the tetrahedral transition state analogue together with the Zn^{2+} complexing properties of the phosphonic acid.[37]

Compounds 7, 8, 9, 10, 11, 12, 13

Boc-Val-Pro-HN–CH(P(O)(OPh)₂)–CH(CH₃)₂ **7**

N-Pro pyrrolidine-P(O)(OPh)₂ **8**

Boc-D-PhePro-HN–CH(P(O)(OPh)₂)–C₆H₄–C(=NH)NH₂ **9**

Boc-Asn-HN–CH(P(O)(OH)–N-pyrrolidine)–CH₂Ph; NH-Ile-NH-iBu **10**

H₂N–CH(CH₃)–C(O)–NH–CH(CH₃)–P(OH)₂(O) **11**

HOOC–CH₂–NH–CH₂–P(OH)₂(O) **12**

Z-HN–CH₂–P(O)(OH)–NH–CH(COOH)–CH₂Ph **13**
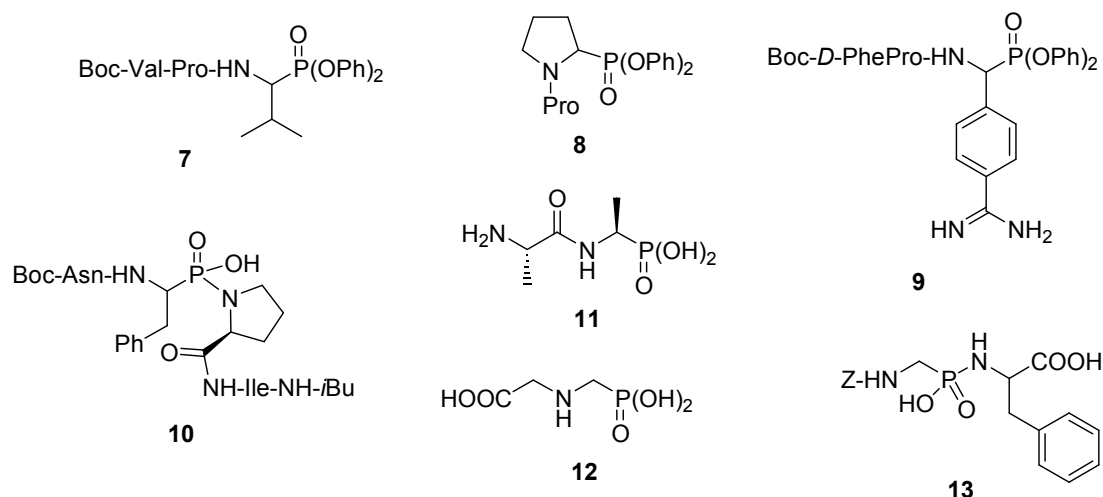
Phosphonic acid containing enzyme inhibitors have already found practical use in the past. The first is alafosfalin **11** which is readily transported into the bacterial cell and is subsequently hydrolysed. The resulting phosphono alanine is a good inhibitor of the alanine racemase, which is essential to the bacterial cell wall synthesis.[38] Phosphonomethyl glycine (glyphosate) **12** on the other hand was developed by Monsanto as an environmentally friendly total herbicide with very low mammalian toxicity. Glyphosate selectively inhibits 5-enolpyruvoylshikimate 3-phosphate synthase (EPSPS), blocking the biosynthesis of aromatic plant metabolites, including the aromatic amino acids.[39]

Apart from their enzyme inhibitory activity, also neuroactive amino phosphonic acid derivatives have been found.[40] Phosphonylated analogues of glutamate, the most important excitatory neurotransmitter in the mammalian CNS, act as specific agonists or antagonists of certain glutamate receptor subtypes. Furthermore, a considerable enhancement of antagonist potency was achieved by synthesizing conformationally restricted analogues of AP5 **14**. This can be performed by incorporating the amino group into a heterocyclic ring system (e.g. CPP **15**, CGS19755 **16**).[41,42] This illustrates the potential of azaheterocyclic phosphonates. Because of the success of constrained amino acids in drug design and biomechanistic investigation of receptor-bound ligand conformations,[43] also the corresponding amino phosphonates deserve appropriate attention.

(S)-AP5 (**14**)   (R)-CPP (**15**)   CGS19755 (**16**)
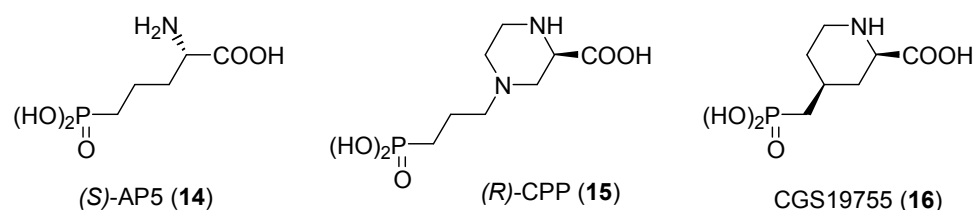
More recently phosphonates have also found application as antigens for the preparation of catalytic antibodies, because of their excellent transition state analogy with the hydrolysis of amino acids. The mammalian immune system is capable of synthesizing large folded polypeptides (immunoglobulins or antibodies) that bind virtually any natural or synthetic molecule with high affinity and exquisite selectivity. Being carboxylate hydrolysis transition state analogues, phosphonates (e.g. **17**) can be used as antigens to generate specific antibodies that catalyze the hydrolysis of the parent carboxylate (e.g. **18**).[44]
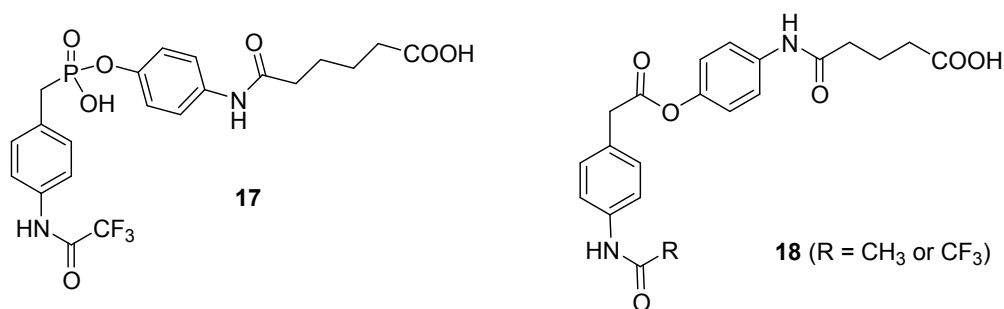
2 Goal of the current research

Despite the interesting potential of the azaheterocyclic phosphonates, this class of compounds is less well studied. Therefore, additional synthetic methods are required to obtain a wider variety of compounds belonging to this class. Mainly two strategies can be applied covering this challenge: (i) phosphonylation of a preformed azaheterocyclic ring, or (ii) cyclization of a phosphonylated precursor. The latter can be considered to be the most versatile pathway (see chapter 2 for an overview). Furthermore, it offers the opportunity to use an eminent property of the phosphonate group, namely its ability to stabilize carbanions in the α-position.

The β-lactam heterocycle is the active part of an important class of antibiotics, including penicillin.[45] In this regard, preliminary investigation at the department of organic chemistry, faculty of bioscience engineering, Ghent University has revealed an interesting pathway for the synthesis of 4-phosphono β-lactams.[46,47] Although the use of anionic organophosphorus reagents for carbon-carbon single bond formation pales in comparison to their applications in olefinations,[48] intramolecular alkylation of the phosphorus stabilized anion was selected to construct the four-membered ring in **23**. The starting *N*-chloroacetyl aminoalkyl phosphonates **21** were synthesized via one-pot acylation – phosphonylation of suitable imines **19**. However, the obtained reaction mixtures were generally impure, hence leading to low yields of the desired products **23** after laborious chromatographic separations. Further

investigation will be performed in order to study the different conversions happening in the one-pot reaction. Aliphatic and α,β-unsaturated imines merit special attention. An optimization of the reaction and broadening of the scope should allow for the synthesis of more diverse phosphono β-lactams. Also further modification including nitrogen deprotection and phosphonate dealkylation will be evaluated in the light of potential biological activity.
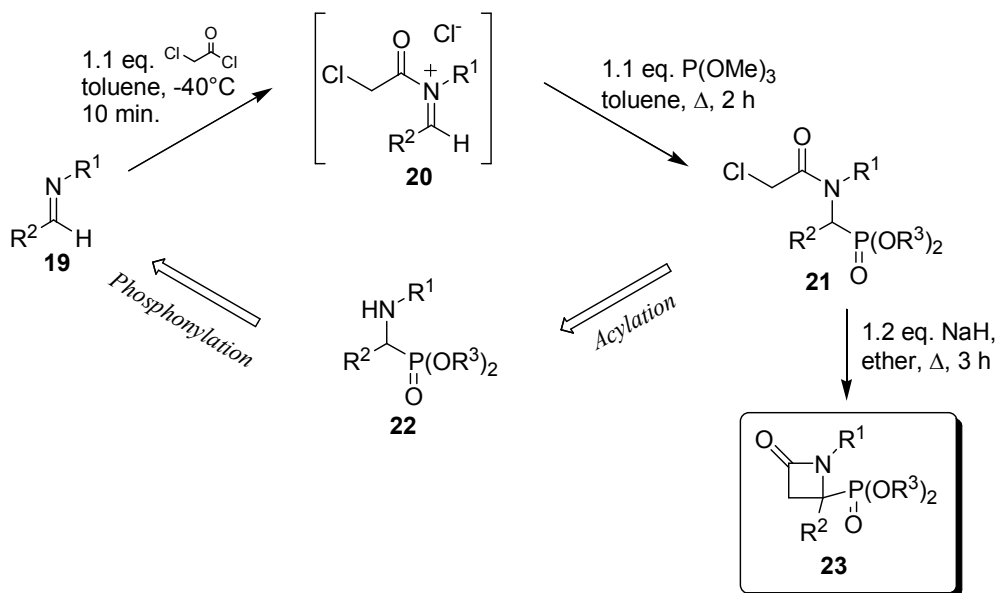
Next to the one-pot acylation – phosphonylation protocol, also a reversed, 2-step pathway towards the *N*-chloroacetyl aminoalkyl phosphonates **21** will be evaluated. Several methods are known for the phosphonylation of imines **19**. The most promising results were reported by Afarinkia and coworkers[49] when using highly nucleophilic silylated phosphite reagents: high yields and short reaction times. Furthermore, only 1,2-adducts are formed under these conditions when using α,β-unsaturated imines. Subsequent acylation should then proceed smoothly using acid chlorides and a base. Using chlorobutyryl chloride, six-membered rings can be formed via intramolecular alkylation.
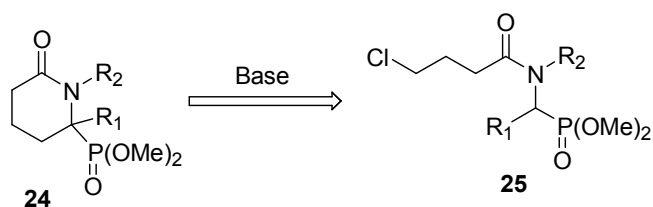
Special attention should be given to *N*-chloroacetyl aminoalkenyl phosphonates **21a-f**. Upon deprotonation with a strong base, an ambident anion is formed which can lead to a six-membered or a four-membered lactam. In initial experiments, only the four-membered rings have been formed, which was quite surprising given the high ring strain compared to the

six-membered lactams. Further research is necessary to determine the scope and to discover the underlying reasons of this unexpected selectivity.
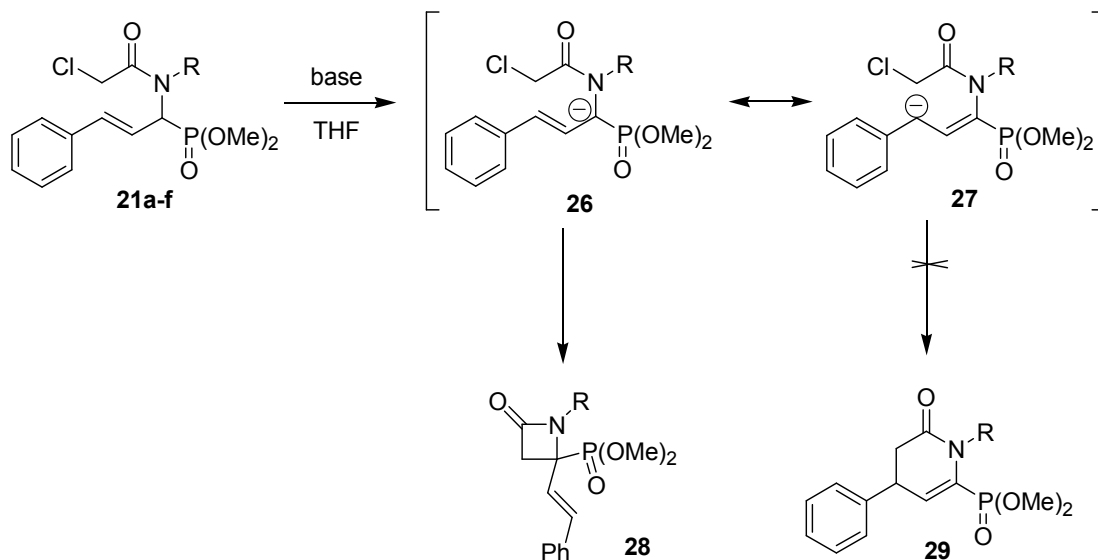
For this reason, the stabilizing effect of the phenyl group will be evaluated by substituting it with an alkyl group. An electron withdrawing nitro substituent can be introduced on the aromatic ring to favour six membered ring formation. Also the ambident nature of the anion will be investigated using protonation and intermolecular acylation experiments. Finally, *ab initio* calculations in collaboration with the Center for Molecular Modelling (under the guidance of Prof. Waroquier, Faculty of Sciences, Ghent University) will be performed to find an explanation for the unexpected regioselectivity in agreement with the experimental results.

Development of a satisfactory method for the preparation of α-aminoalkyl phosphonates should allow these as starting materials for the synthesis of more diverse azaheterocyclic phosphonates. Ring-closing metathesis (RCM) has been generally recognized as a valuable approach for the formation of medium-sized rings. Therefore, phosphonylated diallylamines **32** will be evaluated as substrates of an RCM reaction for the synthesis of phosphono pyrrolines **31** and the corresponding phosphono pyrroles **30** via oxidation.
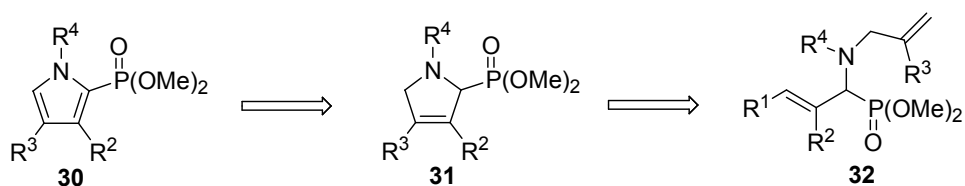
RCM would also offer an approach to phosphonylated bicyclic carbapenem-type lactams **33**. The four-membered ring **23c** can be formed first as described

before, followed by five-membered ring formation via RCM. Also the reverse pathway is possible, starting with the formation of the five-membered ring **34**.
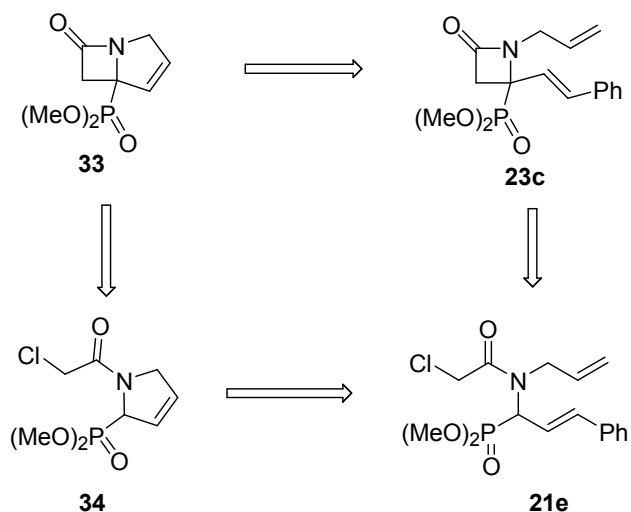
Although the Diels-Alder reaction is a much older reaction than RCM, it is still of current interest for the synthesis of cyclic compounds. Furans have been widely used as dienes in this type of reactions. *N*-acyl aminoalkyl phosphonates **36** derived from furfuraldehyde should be perfectly suitable as substrates for an intramolecular Diels-Alder reaction yielding tricyclic phosphono pyrrolidines. Furthermore, this type of reactions is known to show excellent stereoselectivity.
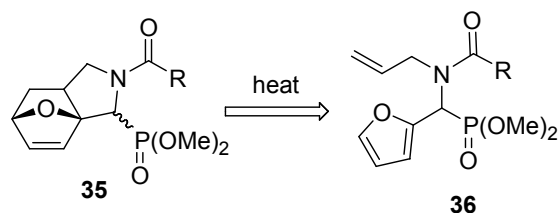
In summary, three types of C-C bond formation will be evaluated for the synthesis of azaheterocyclic phosphonates: (i) intramolecular alkylation of a phosphonate stabilized carbanion, (ii) ring closing metathesis (RCM) and (iii) [2+4] cycloaddition. Although all three are valuable methods for the construction of heterocycles, only the first one has been modestly explored for the synthesis of azaheterocylic phosphonates (see the overview in chapter 2). Furthermore, a satisfactory method for the phosphonylation of imines should be acquired, in order to obtain suitable α-aminoalkyl phosphonates as starting materials

Literature Overview on Azaheterocyclic Phosphonates

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Since the first synthesis of aminoalkyl phosphonates,[50,51] their isolation from natural sources[2,3] and the discovery of their biological activity, many researchers have also focussed their attention to azaheterocyclic phosphonates.[52] Numerous synthetic pathways have been developed towards these interesting compounds that can mainly be subdivided into two classes: the phosphonylation of a preformed azaheterocycle or the cyclization of a suitable phophonylated substrate. From this perspective, the synthesis of non-aromatic three-, four-, five-, six- and larger membered rings has been fully reviewed.[53] Within the scope of this research, an overview will be presented dealing with the most interesting synthetic routes towards four- and five-membered phosphonylated azaheterocycles and demonstrating their biological potential. For a comprehensive overview, the reader is kindly invited to look up our review article.[53]

1   Four membered rings: azetidines and azetidinones

1.1   Ring closure by nucleophilic substitution

Although *L*-azetidin-2-carboxylic acid is a potent proline mimetic,[54] very little is still known about the biological activity of its phosphonate analogue. Racemic azetidinyl-2-phosphonic acid **42** can be prepared from 3-(benzyloxy)propanal **37** which is converted to the corresponding hydroxyphosphonate by a Pudovik reaction with diisopropyl phosphite. Selective substitution of the primary mesylate with an amine followed by

intramolecular substitution of the secondary mesylate in the presence of K_2CO_3 finally yields azetidinyl phosphonate **41**.[55]
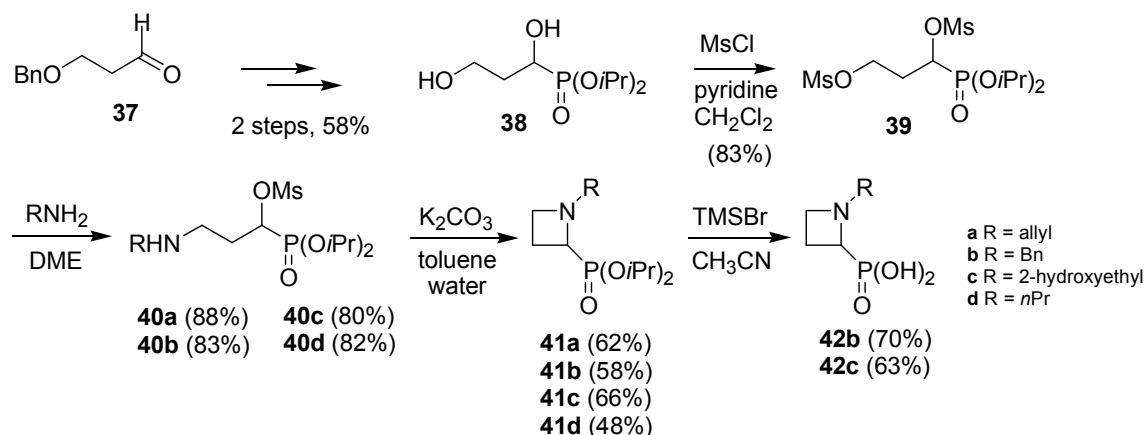
More recently, the first asymmetric synthesis of azetidinyl-2-phosphonic acids was published.[56] Starting from readily available β–amino alcohols, the required aminomethyl phosphonates **45a-c** are prepared via a two-step sequence involving: (i) oxazolidine-formation in the presence of formaldehyde, and (ii) acid-catalyzed ring opening of the oxazolidine followed by nucleophilic addition of diethyl phosphite to the iminium intermediate. Intramolecular alkylation of the phosphonate stabilized carbanion generated in chloroamine **46** using LiHMDS, then yields the azetidin-2-yl phosphonates **47**. During these transformations total retention of configuration at the stereogenic centers is observed. Only with compound **45a**, a rearrangement occurs leading to **46a** in good yield.
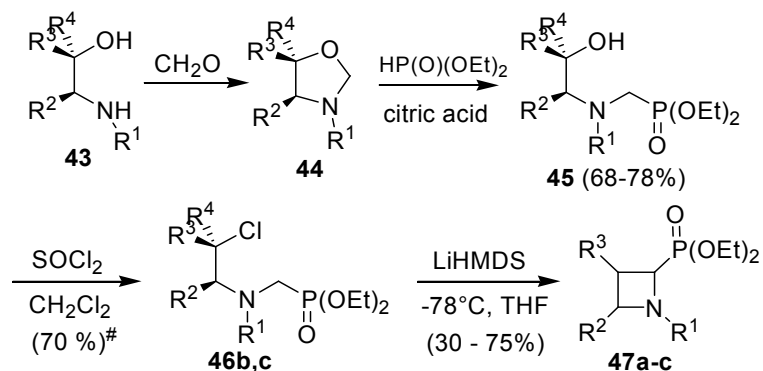
a R^1 = Bn, R^2 = Ph, R^3 = R^4 = H
b R^1 = Me, R^2 = Me, R^3 = H, R^4 = Ph
c R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = H

[#]Compound **45a** having a benzylic amine gives rearranged chloride **46** in good yield:
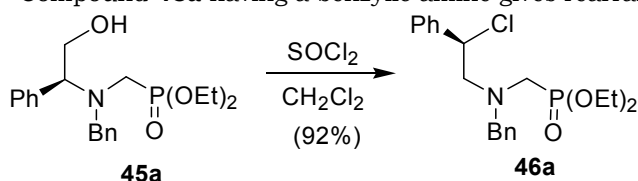
During ring closure, exclusively 2,3-*trans* azetidines **47** are formed, due to the bulkiness of the lithiated phosphoenolate. Similar experiments with an ester group instead of a phosphonate group yield a mixture of 2,3-*cis* and 2,3-*trans* azetidines **49**. Clearly, the steric interaction between the *sp²* ester enolate and the α-phenyl substituent is less severe in this case.

(2S,3R)-**47a**   *(2S,3R,4S)*-**47b**   *(2R,3S,4S)*-**47c**

48   LiHMDS, -78°C, THF   *(2S,3S)*-**49**   +   *(2R,3S)*-**49**

36% *de*
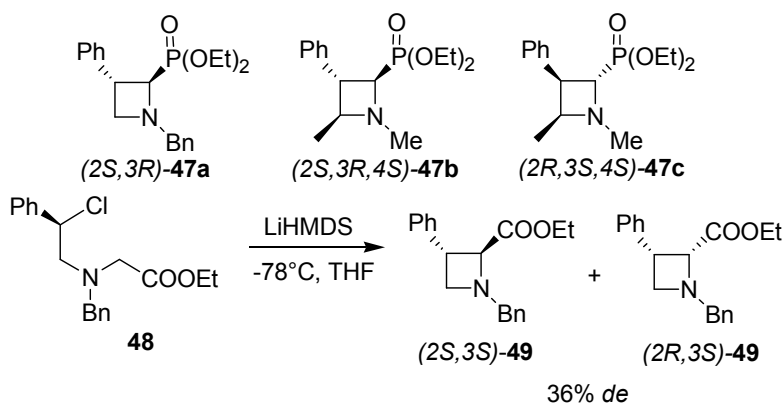
Ring closure through intramolecular alkylation of a phosphonate stabilized carbanion has also been applied in the synthesis of phosphono β-lactams. The epoxide **51** is formed *in situ* by addition of one equivalent of LiHMDS to amide **50**. A second equivalent was used to form the lactam **52** in a stereospecific manner: only the *trans*-β-lactams are formed. Nitrogen deprotection can then be performed using cerium ammonium nitrite (CAN) and the obtained 4-phosphono β-lactams **53** are potential precursors for the synthesis of carbapenems.[57-59]

(2S,3R)-**50**
R = *p*-MeOPh, *p*-MeOBn

51   LiHMDS, rt. (37 - 61%)

(3S,4R,1'R)-**53**   CAN   *(3S,4R,1'R)*-**52**
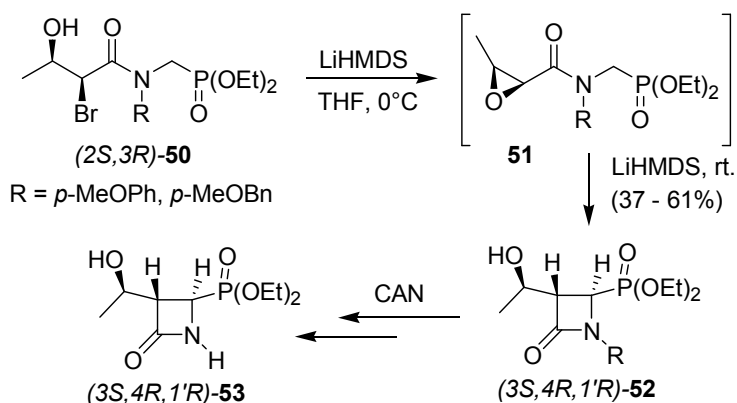
1.2 Nucleophilic phosphorylation

The apparently most obvious method to synthesize phosphonylated azaheterocycles is starting from the desired cyclic compound bearing a

suitable leaving group which is then substituted by a phosphorus reagent. However, examples of this method are rather scarce in literature.

4-Acetoxy-azetidin-2-ones are excellent substrates in substitution reactions. The C^4 carbon atom, which is connected to a nitrogen and an oxygen atom is very reactive towards nucleophilic agents due to the neighbouring group effect. The substitution by trialkyl phosphite was first explored by Clauβ and co-workers[60] and further developed by Campbell & Carruthers.[61,62] When 4-acetoxy-azetidin-2-one **54** is heated in trialkyl phosphite, phosphonylated azetidinones **55** are formed via an atypical Michaelis-Arbuzov reaction, together with the corresponding alkyl acetate. No reaction occurred with tris-(2,2,2-trichloroethyl) phosphite because of its reduced nucleophilicity. However, using methyl phosphonites instead of the corresponding trialkyl phosphites, the reaction proceeds faster and yields the 4-phosphino azetidinones in 42 to 93% yield. Performing the reaction with dialkyl phosphite anions fails due to β-lactam cleavage because of the strongly basic nature of the reagents. Later on, this methodology was also applied with toluene as a solvent,[63] with 3-substituted 4-acetoxy azetidinones[64] and with 4-acetoxy azetidines.[65]

55a R = Me (82%)
55b R = Et (90%)
55c R = Bn (46%)
55d R = CH_2CCl_3 (0%)
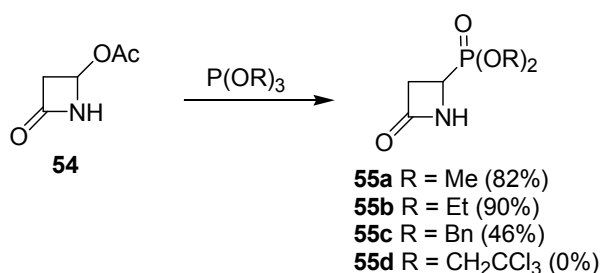
4-Sulfinyl azetidin-2-one **56** is another substrate with an appropriate leaving group for a substitution reaction with a phosphorus reagent. Treatment of **56** with diethyl trimethylsilyl phosphite (DEPTMS) in the presence of ZnI_2 at room temperature for 6 h gives the 4-phosphono azetidin-2-one **58** in 77% yield.[66] Also this reaction is not a real substitution reaction, which is indicated by the stereochemistry of the reaction. Due to the action of the Lewis acid, a reactive iminium salt **57** is formed that reacts *in situ* with the phosphorus nucleophile.
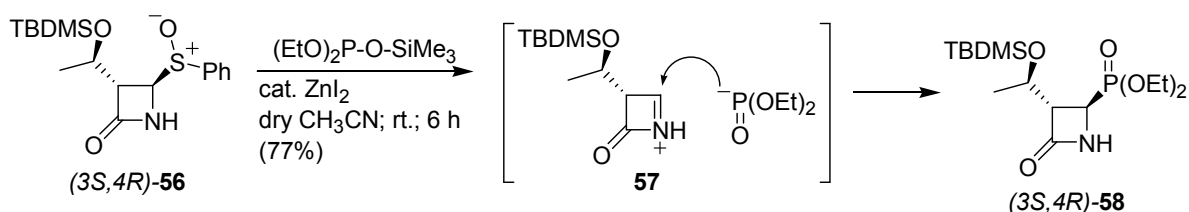
More harsh conditions are necessary for the direct substitution of the mesyl group in azetidine **59**. Only the diethyl phosphite anion is capable of performing the substitution reaction leading to 3-phosphono azetidine **60**. However, the yield is very low.[67]
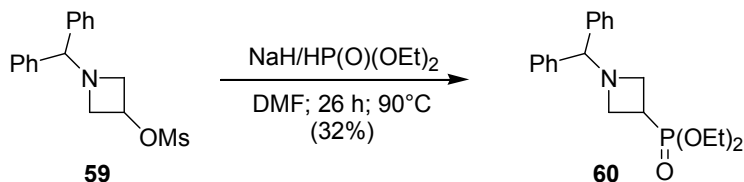
1.3 Cycloaddition

Cycloaddition is a convenient way to construct four-membered ring systems. Azetidinones are often synthesized from ketenes and imines. Ketenes bearing heteroatom substituents have been developed and successfully applied to synthesize functionalized β-lactams.[68] However, reactions with phosphono ketenes were mostly limited to some electrophilic reactions in order to prove their generation.[69,70]

Cycloaddition has been used only once for the construction of a monocyclic phosphono-β-lactam.[71] In the presence of excess benzylideneaniline **63**, ketenes **62** lead to cycloadducts **64** in 7 to 65% yield. Methyl- and chloro(diethylphosphono)ketenes **62** are generated *in situ* from the corresponding acid chlorides and triethylamine. The stereochemistry of β-lactams **64** could not be determined. However, after the reductive removal of the chlorine atom, it could be proven that the resulting azetidinones **65** are *trans* isomers.
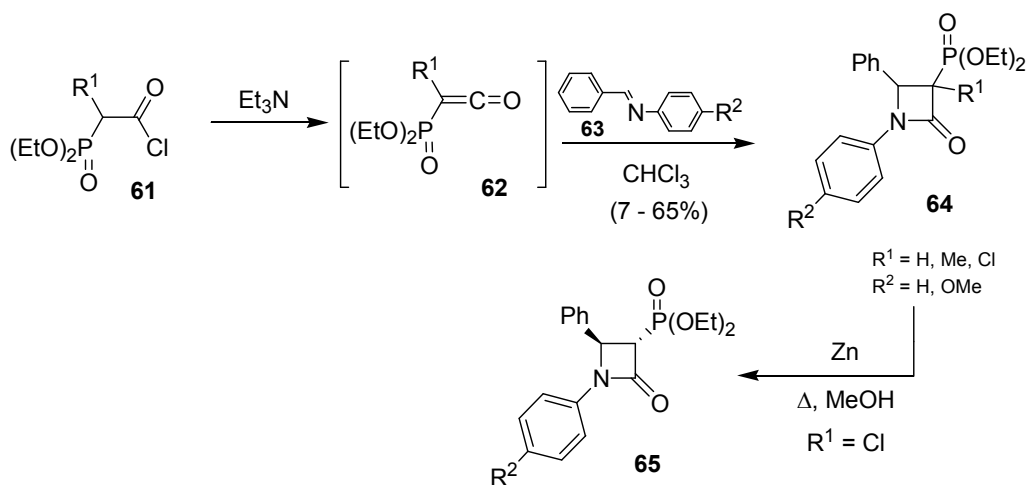
In conclusion, it is clear that cycloaddition can be a promising synthetic route to phosphono β-lactams since the reaction is stereoselective. However,

the reaction is not well explored, probably due to the instability of the phosphono ketenes leading to reaction conditions that are difficult to control.

2 Five membered rings – pyrrolidines, pyrrolines and pyrrolidinones

Five membered azaheterocycles are more widespread in organic and medicinal chemistry than the corresponding three and four membered rings. Much research has been done on the synthesis of phosphonic acid analogues of both natural and unnatural amino acids. In this chapter several methods will be discussed for the synthesis of the phosphonic acid analogue of proline (sometimes called phosphono proline). Different types of activities are associated with peptides containing phosphono proline. They are used for instance as antiviral agents because of their HIV protease inhibiting activity[72-74] or as inhibitors of dipeptidyl peptidase IV (see chapter 2, section 2.4).

Furthermore phosphono proline derivatives can be active as such. Compound **66** has bactericidal, fungicidal and herbicidal activity.[75] Recently, 3-phosphonylated pyrrolidines were found to be Edg receptor agonists, useful for treating immune mediated diseases.[76,77]
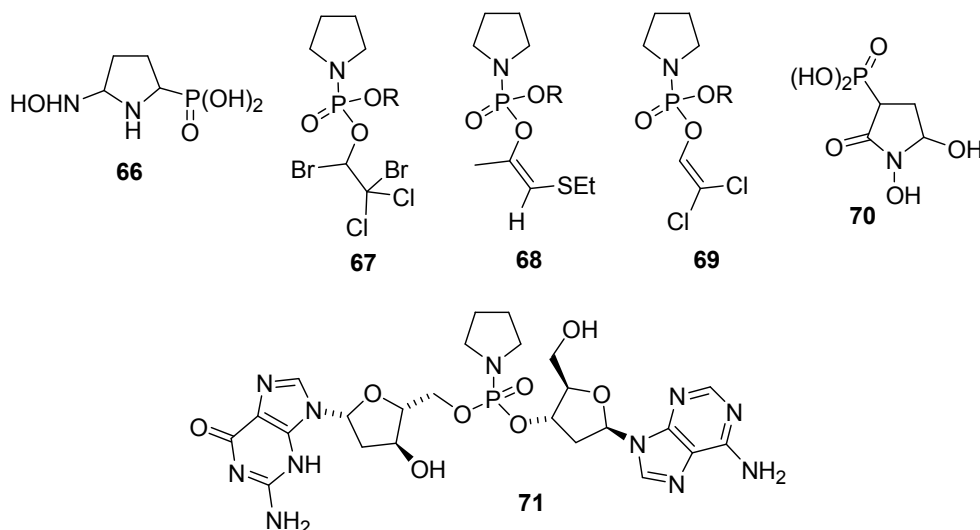
Other active 1-phosphono pyrrolidines are obtained by choosing particular alkyl side chains for the phosphoramidate. With 1,2-dibromo-2,2-dichloroethyl, vinylthio or 2,2-dichlorovinyl groups, 1-phosphono pyrrolidines **67-69** show acaricidal and insecticidal activity.[78-81] Nucleoside containing 1-phosphono pyrrolidines **71** are capable of treating hepatitis infections, particularly, hepatitis B viral infections.[82,83] Also, 3-phosphono pyrrolidinones

are of interest as lactam antibiotics. The phosphorus containing antibiotic SF-2312 **70**, produced by *Micromonospora sp.*, is active against *Pseudomonas aeruginosa* and *Proteus vulgaris*.[84]

2.1 Ring closure by nucleophilic substitution

δ-Chloro-α-aminobutane phosphonic acid **74** was formed by condensation of γ-chlorobutyraldehyde **72** with benzylcarbamate **73** and PCl$_3$, and subsequent acidic hydrolysis. The water soluble aminoalkyl phosphonic acid was then easily ring-closed to the racemic proline mimetic **75a** under basic conditions.[85] The nucleophilic amino group can also be generated by reduction of oxime **77**. The corresponding racemic diethyl phosphono proline **75b** is then obtained in slightly higher yield.[86] In both cases, an amino group was used as an internal nucleophile. However, no examples could be found in which a phosphonate stabilized carbanion was used to form the 5-membered ring.
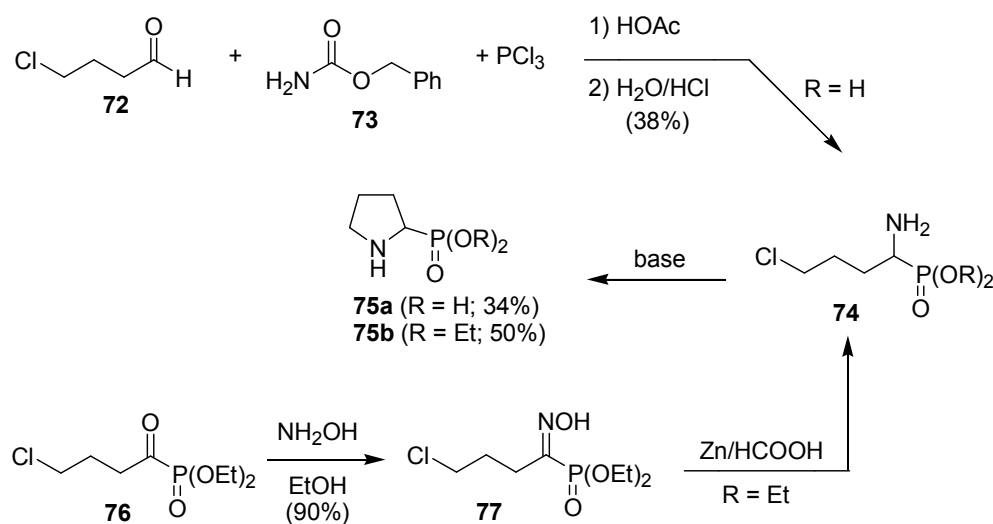
2.2 Nucleophilic phosphorylation

The benzotriazole (Bt) moiety serves as a good leaving group in α-position of a nitrogen atom and is easily eliminated in the presence of a Lewis acid to generate an iminium cation, which is subsequently attacked by a nucleophile.[87,88] Pyrrolidinone **79** can be prepared by reacting 2,5-dimethoxy-2,5-dihydrofuran (**78**) with benzotriazole and a primary amine. During this synthesis benzotriazol-1-yl (Bt^1) as well as benzotriazol-2-yl (Bt^2) pyrrolidinone is formed. However, both Bt^1 and Bt^2 are good leaving groups and give rise to the same iminium cation. Treatment of **79** in dry THF with triethyl phosphite in the presence of 1 equivalent of ZnBr$_2$ produced phosphono pyrrolidinones **80** in moderate to good yields.[89] Stereogenic

centers at the N(1)-position displayed poor control of the facial selectivity for phosphite addition onto the iminium ion, resulting in little or no diastereoselectivity at C(5).

R = HOCH₂CH₂-, p-MeOC₆H₄CH₂-, m,p-(MeO)₂C₆H₃CH₂-,
p-MeOC₆H₄CH₂CH₂-, (HOCH₂)PhCH-, (COOMe)(PhCH₂)CH-
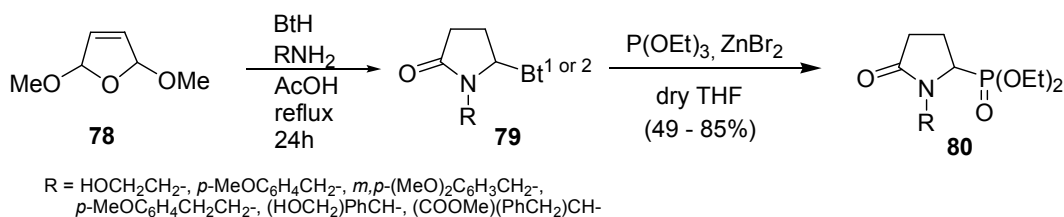
A diastereoselective version of the reaction is achieved when using the cyclic hemi-aminal **81** as substrate. Treatment of **81** with triethyl phosphite in the presence of the mild Lewis acid ZnBr₂ yields one single diastereomer in 77%. Subsequent hydrogenation gives the deprotected pyrrolidine **(-)-75b** in 63% overall yield as a single enantiomer.[90] The same method is also applicable for the synthesis of phosphono piperidines.[91] Also the other enantiomer **(+)-75b** can be prepared in the same way. After deprotonation with LDA or BuLi, this enantiomer was alkylated in the 2-position with retention of the configuration by applying the *Self-Regeneration of Stereocenters (SRS) principle*.[92] In this specific case, the SRS was believed to be caused by the special properties of the phosphorus stabilized anion (see chapter 3, section 2.4).[93]
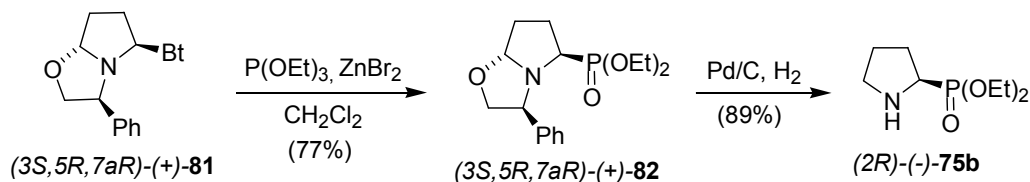
An asymmetric synthesis of 5-phosphono pyrrolidinone is based on a similar principle. Here, the hemiaminal like C-O bond is cleaved by the action of TiCl₄. The iminium ion is then trapped by trimethyl phosphite with the formation of **84** in 62% diastereomeric excess. As compared to the formation of pyrrolidine **75b**, less stereocontrol is observed during the addition reaction.[94]
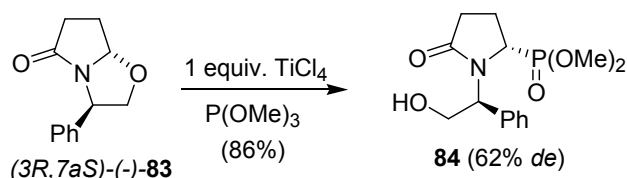
Despite the simplicity of the experiments and their often very satisfying results, electrochemistry is not a standard reaction in a synthetic lab. However, the methodology is also useful for the synthesis of functionalized azaheterocyclic compounds. The anodic oxidation of cyclic amides and

carbamates in methanol has been shown to give α-methoxylated products.[95,96] The initiation step of the oxidation involves electron transfer from the lone pair electrons of the nitrogen atom to the anode. Next an iminium salt is formed that can be trapped by the solvent (e.g. methanol). The reaction is also applicable to *N*-sulfonamides and phosphonamidates.[97] The methoxy group can be easily substituted with a phosphonate as presented before using a Lewis acid such as $TiCl_4$ or $BF_3.OEt_2$.[96,97]

X = COOMe, Ts, P(O)(OEt)$_2$
n = 1, 2

R = Me, Et
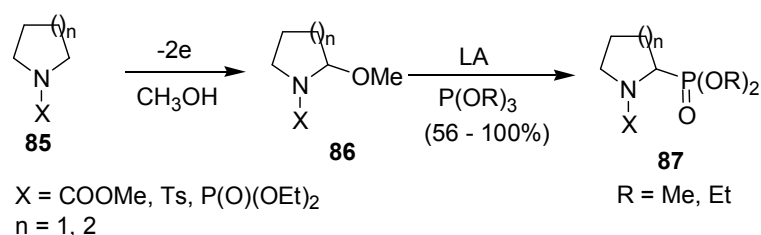
With *N*-protected 4-hydroxyproline derivatives, oxidative decarboxylation occurs during anodic oxidation. Subsequent substitution in the presence of $TiCl_4$ affords the phosphonylated pyrrolidine **90** in 96% *de*.[98]
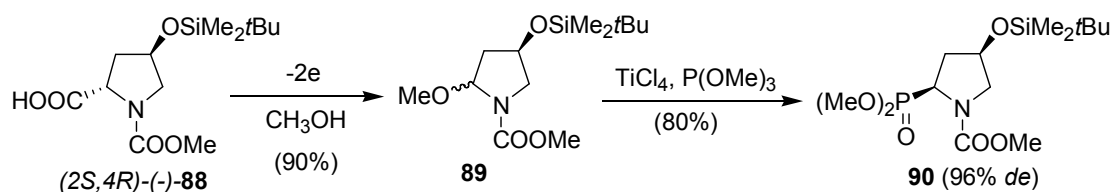
A similar oxidative decarboxylation of proline derivatives can be performed using Pb(OAc)$_4$. The obtained 2-hydroxypyrrolidines **92** are then converted to the corresponding phosphonates **93** by a reaction with trialkyl phosphite in the presence of trimethylsilyl triflate. As mentioned before, an intermediate iminium ion is formed, to which the phosphite adds.[99]
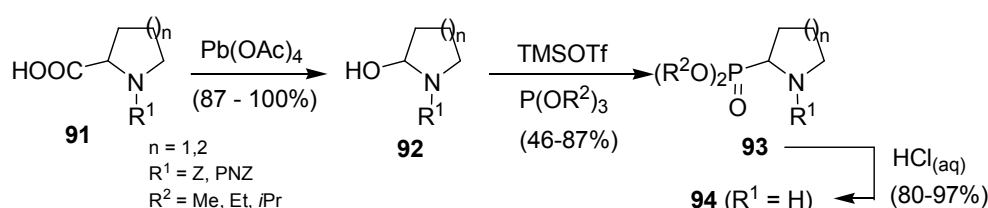
2.3 Electrophilic phosphorylation

When lactone enolates are trapped with a dialkyl chlorophosphate reagent, a vinyl phosphate is obtained that can rearrange to the α-phosphono lactone upon further treatment with base.[100] An *N*-alkyl lactam undergoes a similar rearrangement to afford an α-phosphono lactam. The enolate is made in THF by adding LDA (1.1 equivalent) followed by the chlorophosphate, together

with 1 equivalent of HMPA to facilitate the vinyl phosphate anion formation. After adding a second equivalent of LDA to initiate the rearrangement, the reaction is quenched with acetic acid in ether.[101] Similar results can be obtained when 2 equivalents of LDA are added at once in the first step (R = Me, 65%).[102]
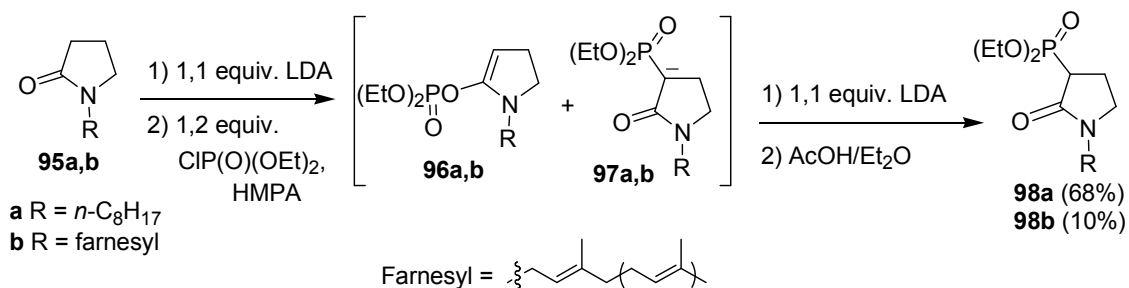
Farnesyl =

However, some side reactions occur under the strong basic conditions with the farnesyl side chain, resulting in lower yields. Using dialkyl chlorophosphite instead prevents this side reaction. The desired α-phosphono lactams **100** are then obtained by oxidation of the phosphonite using air[103,104] or hydrogen peroxide.[101] The main advantage of this P(III) method is the use of only one equivalent of base, to form the enolate anion. No further treatment with base is necessary for the rearrangement and the amount of side products is significantly reduced.[101]
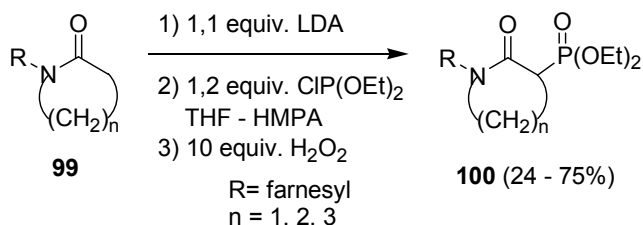
Furthermore, α-substituted α-phosphono lactams are also accessible via the P(III) reagent. The P(V) reagent fails to react, because vinyl phosphate anion formation is required for the rearrangement, which is obviously not possible in the case of pyrrolidinone **101**.
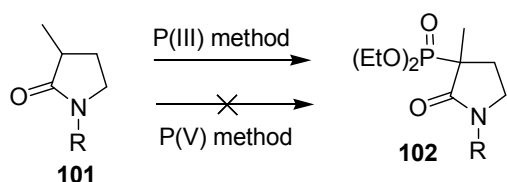
The major drawback of the P(III) method is the formation of small amounts of bisphosphonates. However, this can be used for the synthesis of bisphosphonates when the conditions are slightly modified. When 2 equivalents of base and chlorophosphite are used, the bisphosphonates **103**

are the main products next to small amounts of monophosphorylated compounds.[105]

95a n = 1; R = n-C$_8$H$_{17}$
95b n = 1; R = farnesyl
95c n = 2; R = farnesyl

103a (94%)
103b (77%)
103c (50%)
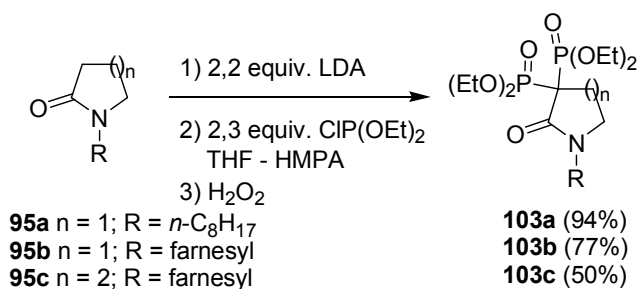
2.4 Ring closure by nucleophilic addition

Ring closure with the formation of azaheterocycles can be invoked by the attack of a nucleophilic nitrogen atom onto an electrophilic center in the same molecule. Since both functional groups have to be present in the precursor, one of them needs to be temporarily deactivated. Most of the time, non nucleophilic nitrogen groups are used which are then converted to a nucleophilic species to invoke the ring closure.

Debenzylation of an amine[106] or reduction of a cyanide[107] or nitro[108-110] functionality has been used to generate a nucleophilic amine group prior to ring closure towards phosphono pyrrolidinones. The temporarily deactivation of the amino nucleophile can also be performed by the synthesis of the corresponding imine,[111] which allows the incorporation of a chiral auxiliary.

The stereoselectivity of the Michael addition of phosphonate stabilized anions to acrylates can be mediated by camphor-like protecting groups.[112,113] Imino phosphonate **105** is formed in 66% yield with 71% *de.* The minor diastereomer was easily removed by flash chromatography on silica gel. After hydrolysis, the enantiomerically pure (*5S*)-pyroglutamic acid mimetic **106** could be isolated (*ee* ≥ 95%), while the chiral auxiliary was recovered in 60% yield. Reduction with LiBH$_4$/BF$_3$.OEt$_2$ proceeded without isomerization and resulted in the phosphonylated analogue **75b** of proline which can not be obtained by alkylation of **104** with diiodopropane and subsequent hydrolysis. When substituted acrylic esters are used, the diastereoselectivity is highly dependent on the substitution pattern.[114]

104 R=N / P(OEt)₂ / O → ZnCl₂, COOMe (66%) → MeOOC...P(OEt)₂ **105** → HOAc/H₂O (64%) → (EtO)₂P **(5S)-106** (*ee* > 95%) → LiBH₄ / BH₃.Et₂O (61%) → (EtO)₂P **(2S)-75b**

R =
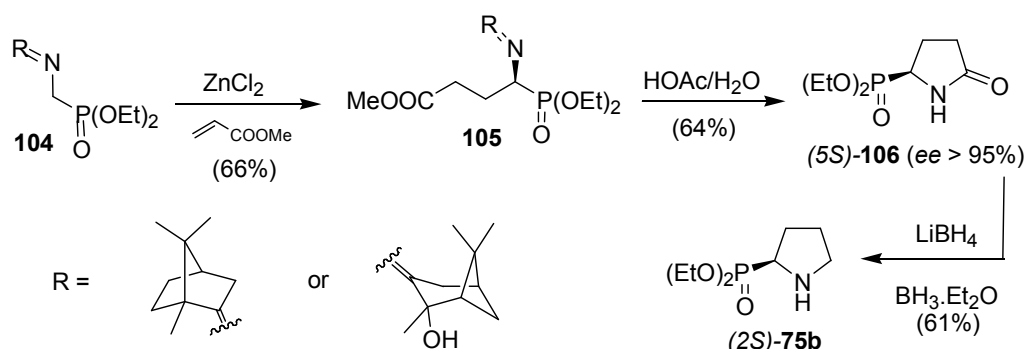
Also the electrophilic center in the precursor molecule can be masked to allow chemical transformations prior to ring closure. The carbonyl functionality in **112** for instance is protected as an acetal. Addition of lithium, sodium or potassium diethyl phosphite to the chiral sulfinimine moiety results in the corresponding aminoalkyl phosphonates **108** in high yield and high diastereomeric excess. Treatment with acid to remove the sulfinyl auxiliary and hydrolyse the acetal, results in the corresponding amino carbonyl intermediate, which immediately cyclizes to give phosphono pyrrolines **109** and tetrahydropyridine **110**.[115] NMR data suggest that azepine **111** occurs in an equilibrating mixture with its open form. Hydrogenation of the mixture gave the corresponding seven membered cyclic amino phosphonate **114** in 49% yield.

107 → M⁺PO(OEt)₂ / R¹ = H, Me, Ph / R² = Me, -CH₂CH₂⁻ / n = 1, 2, 3 → **108** 87-95% / 72-98% de → H⁺/H₂O

(*R*)-(+)-**109a**: R = H (72%)
(*R*)-(+)-**109b**: R = Me (69%)

(*R*)-(-)-**110a**: R = Me (82%)
(*R*)-(-)-**110b**: R = Ph (80%)

(*R*)-**111**

PtO₂, H₂ / EtOH

(*R*)-(-)-**75b**: R = H (72%)
(2*R*,5*S*)-(-)-**112**: R = Me (69%)

(2*R*,6*S*)-(-)-**113a**: R = Me (87%)
(2*R*,6*R*)-(-)-**113b**: R = Ph (87%)

(2*R*,7*S*)-(-)-**114** (49%)
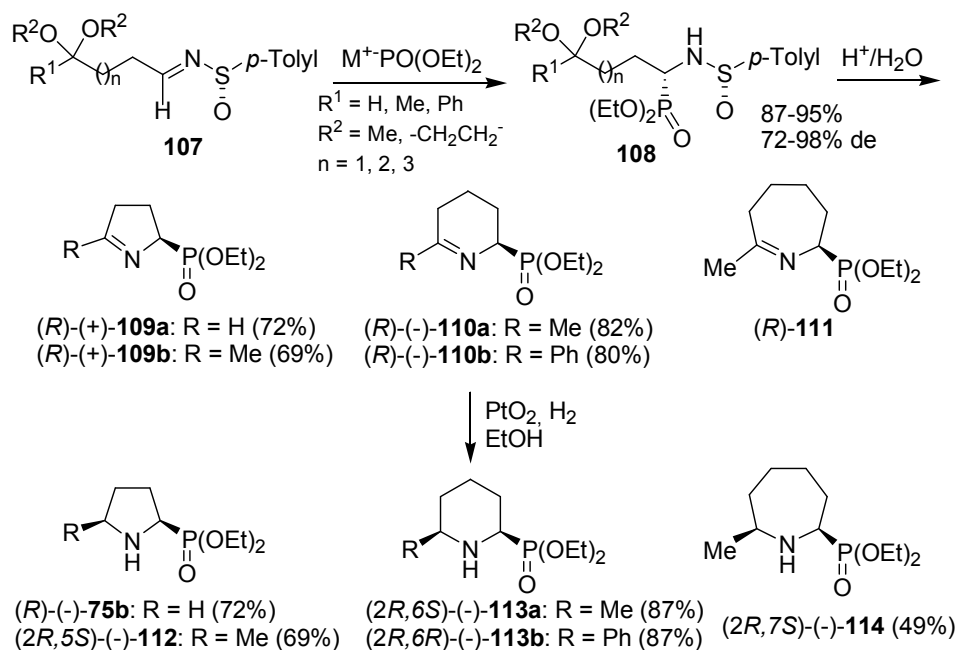
In a second example, an *N*-protected amino acid is then coupled to the free amino group of **115**. The acetal moiety is then hydrolyzed in acidic medium and the resulting mixture can be treated with several triphenyl phosphite reagents in acetic acid to give diastereomeric mixtures of the protected diphenyl phosphonates **117**. After deprotection, the free diastereomers can

be separated by column chromatography (with exception of the *L*-Pro, *L*-Ala, *L*-Ile and *L*-Arg derivatives). The real intermediate reacting with triphenyl phosphite actually remains unknown. Hydrolysis of acetal **116** followed by heating in CCl$_4$ under reflux leads to the formation of the cyclic hemiaminal **120**.[116,117]

R^1 = H, 4-OMe, 4-OAc (4-OH for 39, 40), 3-NHAc, 4-NHAc, 4-NHSO$_2$Me, 3-NHCONH$_2$, 4-(*N*-Bz-Gly-NH), 4-(*N*-Z-Gly-NH), 4-COOMe, 4-(CONHCH$_2$COOEt), 4-[CONH(CH$_2$)$_2$COOMe], 4-[CONH(CH$_2$)$_2$CH$_3$]
R = Cbz, Boc, Trt
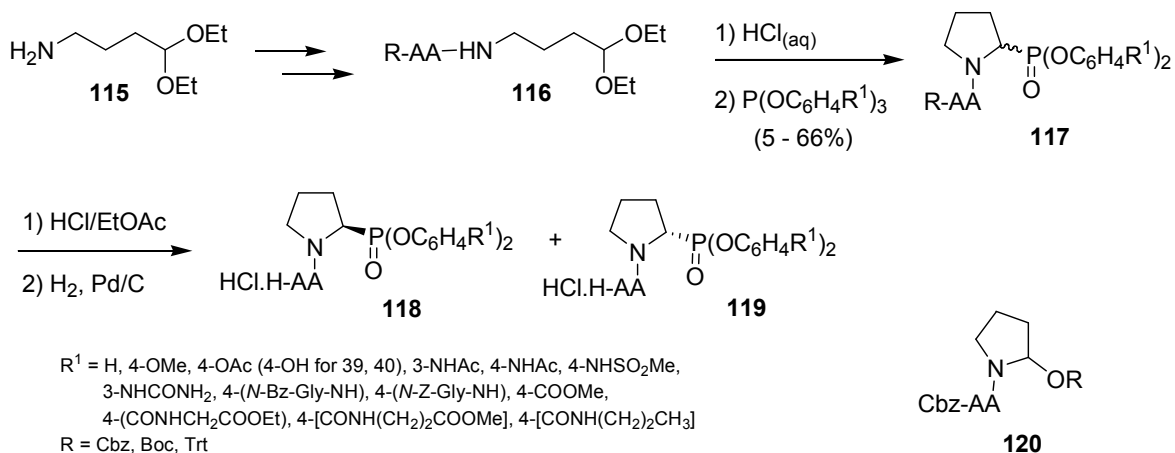
The obtained peptides, consisting of the phosphonylated analogue of proline coupled with a regular amino acid, are inhibitors of dipeptidyl peptidase IV (DPP IV). DPP IV is a post proline cleaving enzyme that has been found in a variety of mammalian cells and tissues. An extensive review about the structural properties and clinical aspects of DPP IV has been published very recently.[118] It plays a role in glucose homeostasis, through proteolytic inactivation of the incretins, and in the imune system, by influencing T-cell activity. DPP IV is also implicated in HIV-1 entry, malignant transformation and tumor invasion. Therefore, inhibitors of DPP IV may have therapeutic utility in the modulation of the rejection of transplanted tissue by the host organism and in treatment of type 2 diabetes.[119] Several other inhibitors of DPP IV are known, but unfortunately most of these are unstable in aqueous solution at neutral pH. For the diphenyl phosphonates, no cytotoxicity was observed in human peripheral blood mononuclear cells and also no acute systemic or local toxicity was seen upon single intravenous injection in rabbits. The best results are obtained with proline as amino acid and with R^1 an electron withdrawing group (e.g. AA = Proline, R^1 = 4-COOMe: IC$_{50}$ = 20 nM). However, the most potent inhibitors are also the most unstable compounds.[117] Furthermore, this class of pyrrolidine phosphonates is claimed to have inhibitory effects to a wider group of serine peptidases and proteases, e.g. prolyl oligopeptidase, dipeptidyl peptidase II, fibroblast activation protein a (FAPa) and elastase and are therefore useful as anti-inflammatory agents, anticoagulants, anti-tumor and anti-AIDS agents, and for treating vascular and autoimmune diseases.[120-122] Using the same methodology omitting the amino acid coupling reaction in step one, unprotected diphenyl pyrrolidine-2-phosphonate can be obtained, which has

been succesfully applied as a ligand in the copper-catalyzed arylation of amines.[123]

The internal nucleophile can also be generated by deprotonation. A carbanion is formed by α-deprotonation of the phosphonate **121** that attacks the carbonyl group by which it is coupled to Wang resin. Pyrrolinone **122** is then released through Dieckmann condensation leading to cleavage from the resin (81% overall yield). Tetrabutylammonium hydroxide is preferred as a base because of the more convenient work-up.[124] This method also has the advantages utilizing solid phase chemistry.
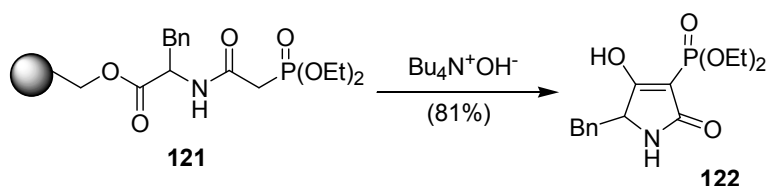
Similar to this methodology is the ring expansion of aziridines **123** that starts with an intramolecular addition reaction to generate the nitrogen nucleophile which is the active nucleophile in the ring closure. This cyclization was reported to be strongly influenced by steric hindrance and by the actual lifetime of the anion.[125]
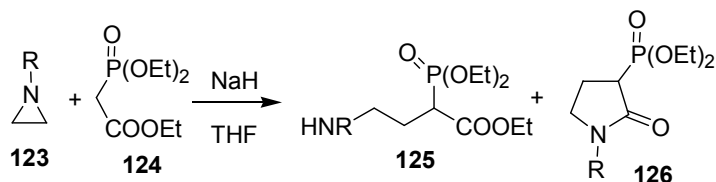
The intramolecular aminomercuration of alkenylamines is a useful approach to substituted heterocyclic amines in which the electrophilic center is generated to invoke ring closure. The starting α-amino-δ-alkenyl phosphonates **128** are synthesized by bubbling ammonia through a solution of γ-alkenylaldehydes or ketones in dialkyl phosphite. Ketones are transformed in reasonable yields (50 – 70%), however aldehydes give rather poor yields (15 – 30%). Cyclization of the α-amino-δ-alkenylphosphonates **128** is initiated by addition of Hg(OAc)$_2$ to the double bond followed by cyclization through intramolecular nucleophilic attack of the free amine. Using α-amino-ε-alkenylphosphonates it is possible to obtain the six-membered analogues in similar yields (55%). The reaction is regiospecific in most cases,[126-128] although in one case (R^1 = H; R^2 = R^3 = R^4 = Me; R^5 = Et) the formation of 3 – 7% of the six membered ring **133** is observed. Demercurization is finally achieved by a reduction with NaBH$_4$. Formation of free radicals during the reduction accounts for the formation of side products

such as dialkylmercury compounds or ring opening to the starting material **128**. The stereoselectivity of the aminomercuration depends to a large extent on the reaction conditions. When the cyclization of **128** is performed in THF/H$_2$O, the stereoselectivity is different compared to the reaction performed in acetone for the cyclization and in dichloromethane for the reduction.
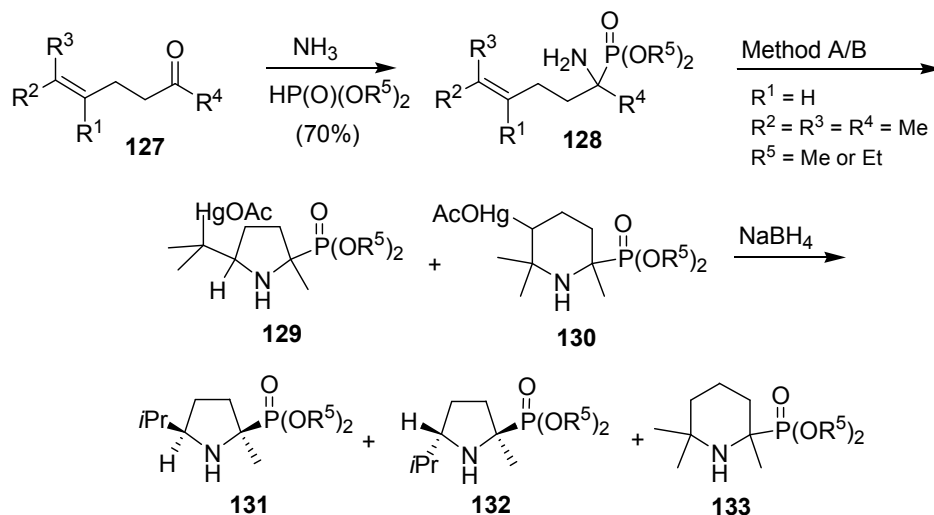
Method A: 1) Hg(OAc)$_2$; acetone - 2) NaBH$_4$; CH$_2$Cl$_2$
Method B: 1) Hg(OAc)$_2$; THF/water - 2) NaBH$_4$; THF/water

2.5 Cycloaddition

The 1,3-dipolar cycloaddition reaction is one of the most useful methods for the construction of five membered rings in a convergent and stereocontrolled manner.[129] To obtain phosphonylated azaheterocycles, a phosphonate group can be comprised in the 1,3-dipole (e.g. phosphonylated nitrile ylids and phosphonoazomethine ylids) or in the 1,3-dipolarophile (e.g. vinyl phosphonates).

The use of nitrile ylids as 1,3-dipoles in cycloadditions has received a lot of attention as a route to a variety of five-membered nitrogen containing rings. Due to the electron withdrawing effect of the phosphonate moiety, *N*-phosphonomethyl imidoyl chlorides **136** are potential precursors of phosphorylated nitrile ylids **137** via a 1,3-dehydrohalogenation process in basic medium. These imidoyl chlorides can be synthesized by a reaction of isocyanomethyl phosphonate **134** with an acid chloride. Upon treatment with triethylamine, a 1,3-dipolar species **137** is formed, which is trapped *in situ* with methyl acrylates giving a mixture of cycloadducts **138a-c** and **139a-c**. These regioisomers are difficult to separate by chromatography. When nitroalkanes are used as dipolarophiles however, 2-phosphonopyrroles

141a-d are obtained in moderate yield after elimination of nitrous acid and aromatization.[130]
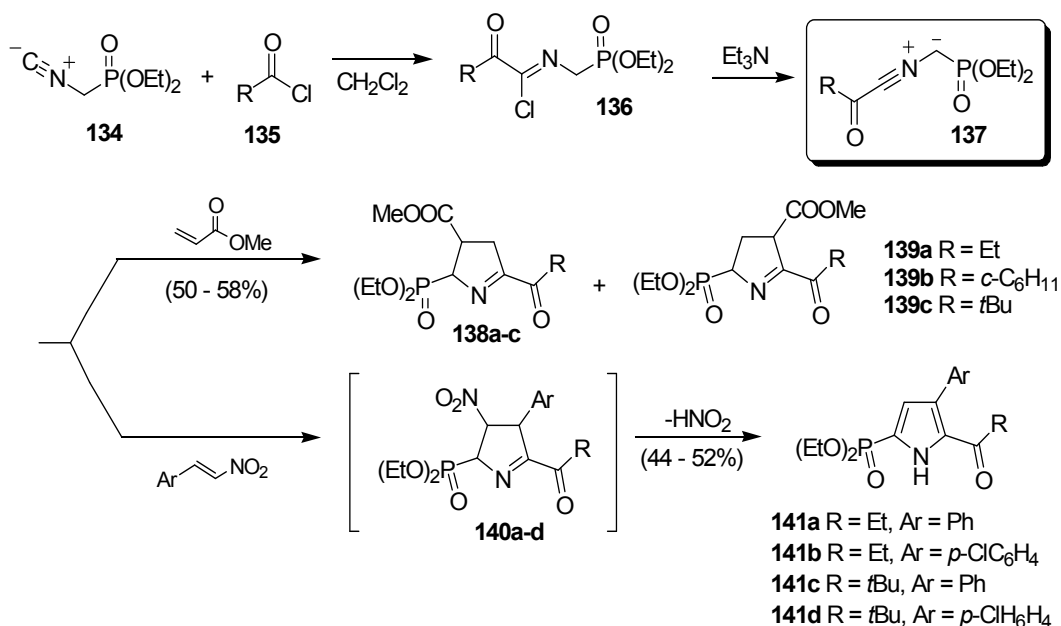
Another example of the formation of an imidoyl chloride concerns the reaction of isocyanomethyl phosphonate **134** with sulfenyl chlorides. The cycloaddition is then performed in a solid-liquid medium using a KOH/Al$_2$O$_3$ mixture in THF. With dimethyl fumarate, pyrrolines **143** are formed in 61% yield. With acetylene dicarboxylate however, aromatization occurs and 2-phosphono pyrroles **144** are isolated in moderate yields.[131] 1-Isocyanomethyl phosphonates can also be used immediately in a cycloaddition reaction under basic catalysis to yield 5-phosphono pyrrolines.[132,133]
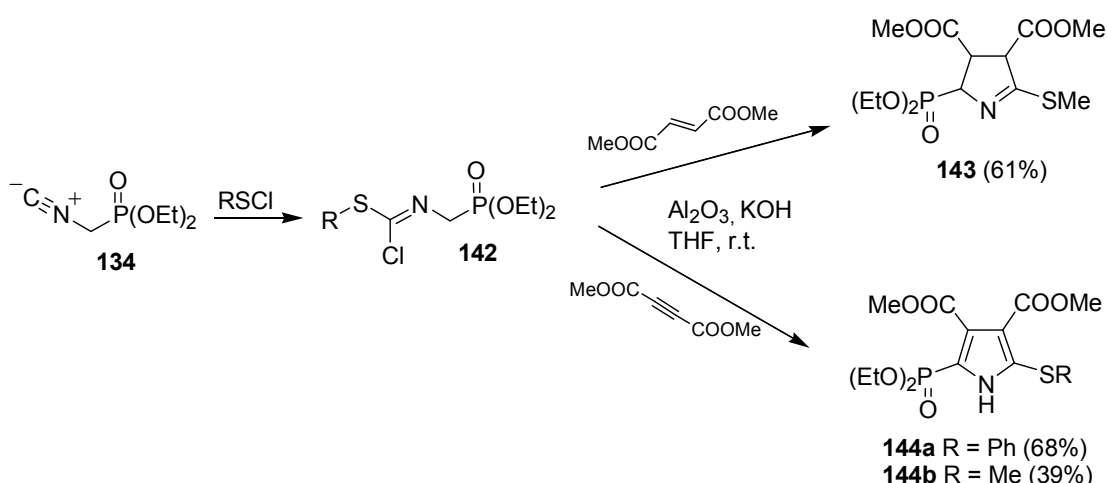
Reaction of carbanions of *N*-(phosphonomethyl) imines **145** with α,β-unsaturated esters can lead to three different products: an acyclic adduct **150** through a Michael addition, pyrroline **148** through a cycloaddition and

subsequent elimination of the diethyl phosphite anion, or pyrrolidine **149**. When sodium hydride is used as a base at room temperature, pyrrolidines **149** are formed exclusively in good yields (77–90%) due to the stereospecificity of the reaction related to the concerted mechanism. However when a lithium base is used such as butyllithium or LDA, pyrroline **148** is formed as a side product depending on the temperature profile of the reaction. In case of the lithium bases, an acyclic derivative is formed first that is then cyclized to a mixture of isomers. However, the yield is low because of the disfavoured 5-*endo-trig* mechanism.[134-136]
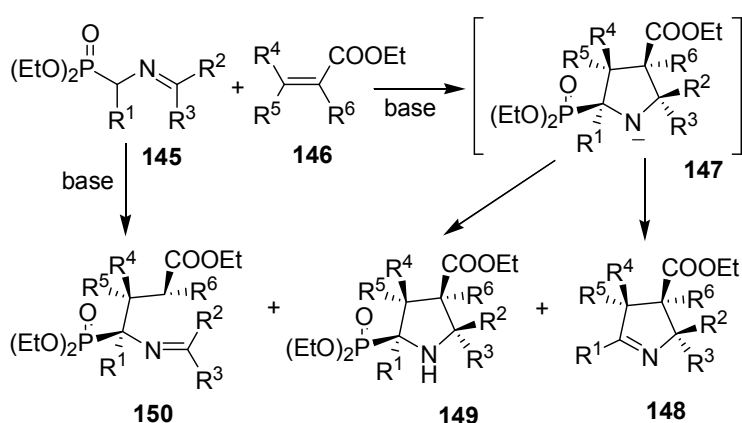
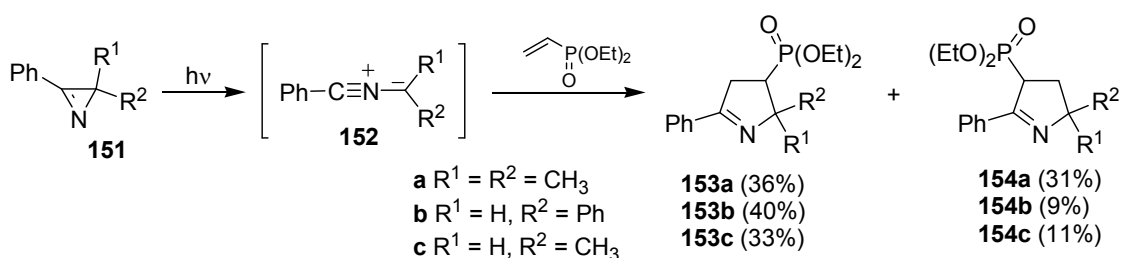The same methods with more common 1,3-dipoles are applicable towards azaheterocyclic phosphonates when vinyl phosphonates are used as dipolarophiles. When phenylazirines **152** are irradiated with UV-light, again, nitrile ylids **153** are formed which can react *in situ* with activated C=C or C=X (X = N, O, S) bonds. The P=O bond of phosphonates, however, is not active in this kind of reaction, although the phosphonate group is able to activate a C=C bond. Irradiation of azirines **152** in the presence of vinyl phosphonate yields two regioisomers **153** and **154** which can be separated by preparative GC. Both regioisomers are isolated as a mixture of the *cis* and *trans* isomers.[137]

a R^1 = R^2 = CH$_3$ **153a** (36%)   **154a** (31%)
b R^1 = H, R^2 = Ph   **153b** (40%)   **154b** (9%)
c R^1 = H, R^2 = CH$_3$ **153c** (33%)   **154c** (11%)

Cycloaddition of vinyl phosphonate with azomethine ylids instead of nitrile ylids has also been evaluated. Treatment of phenylthioglycinate **155** with NaH yields an intermediate azomethine ylid that can react with vinyl phosphonate with the formation of ethyl 4-phosphono prolinate **158**.

However, the major drawback of this approach is the formation of large amounts of 1,4-adduct **157** that causes the yield to drop to 26%.[138]
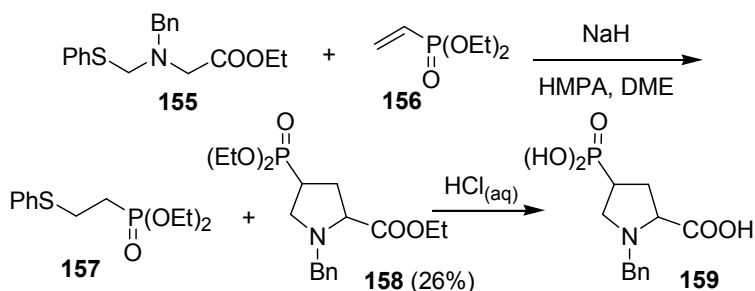
Cycloaddition of *N*-benzylidene glycinate anions appeared to be impossible under thermal conditions. However, in the presence of a catalytic amount of AgOAc as a Lewis acid, the reactions proceed in good yiel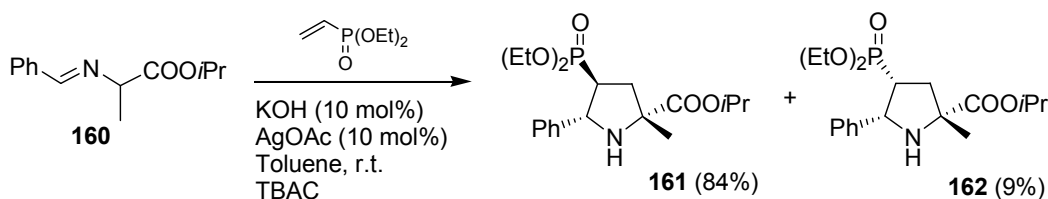ds. Tetrabutylammonium chloride (TBAC) has to be added as a phase transfer catalyst in the solid-liquid system, resulting in long reaction times. However in this case, the cycloaddition reaction is regioselective with the *trans* pyrrolidine **161** predominating.[139]

2.6   Addition to cyclic imines

Nucleophilic addition of a dialkyl phosphite to an 1,2-unsaturated azaheterocycle is one of the most direct ways to synthesize cyclic α-aminoalkyl phosphonates. For the synthesis of the phosphonate analogue of proline, pyrroline would be an interesting starting product. However, pyrroline is unstable and trimers **163a** are rapidly formed upon standing. Nevertheless, when dialkyl phosphite is added to these trimers, the desired phosphonylated pyrrolidines **75a** and **164b** are obtained in good yields by thermal depolymerization of the trimer.[140-143] The obtained pyrrolidine **75a** was then easily converted to amide **165**, which has angiotensin enzyme inhibitory activity.[144]
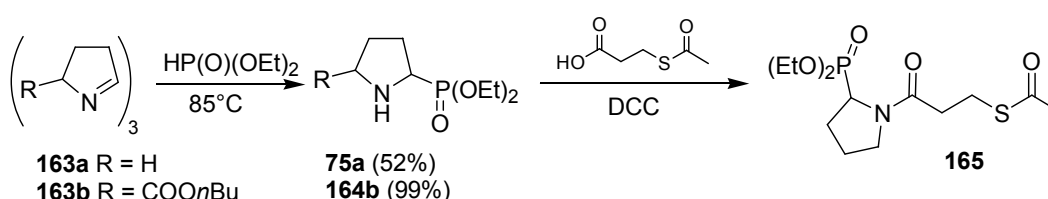
To avoid problems concerning the inherent instability of the pyrroline, it can also be generated *in situ* by oxidation of pyrrolidine,[145,146] decarboxylation of *N*-benzyl proline,[145] intramolecular hydroamination of a suitable aminoalkyne[147] or intramolecular condensation of a suitable γ-amino ketone.[148] One-pot reaction with a dialkyl phosphite then yields the corresponding phosphono proline derivatives. In contrast with unsubstituted pyrrolines, the commercially available 2-methyl-1-pyrroline is a stable compound and has been succesfully used in an addition reaction with dialkyl phosphites at room temperature.[149,150]

Compared to pyrrolines, the addition of phosphites to nitrones generally proceeds more readily. Many examples have been reported in the literature[151-157] because of the usefulness of 1-phosphoryl-pyrroline-*N*-oxides as alternatives for 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO **166**) which is one of the most widely used spin traps.[†] DMPO rapidly scavenges free radicals generating secondary radicals, so called spin adducts. The non-zero nuclear spin of the β-H on the aminoxyl spin adduct provides remarkably suitable EPR information useful for the diagnosis of the structure of the free radical addend. However, the same hydrogen atom is also responsible for the instability of the spin adducts. The stability of the adducts is greatly enhanced when a phosphonate group is incorporated. Furthermore, additional structural information can be obtained due to the non-zero nuclear spin of the phosphorus atom. The commercial diethoxyphosphoryl 5-methyl-1-pyrroline-*N*-oxide (DEPMPO **167**) exhibits unique specificity in the spin trap adduct EPR spectra with substantial improvement in stability.[159] The instability of DMPO spin adducts can also be overcome by substituting the β-H itself by a phosphorus atom, resulting in the spin trap 2-diethoxyphosphoryl 5,5-dimethyl-1-pyrroline-*N*-oxide (DEP-DMPO **168**).[152] Some nitroxides were also shown to exert a cardioprotective action that was attributed to their antioxidant action, through reduction of the hydroxyl radical formation and the tissue lipid peroxidation.[160]

**166** (DMPO)   **167** (DEPMPO)   **168** (DEP-DMPO)
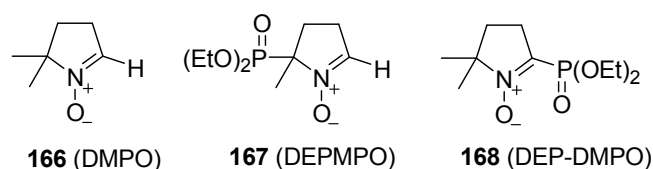
[†] Spin traps were developed in order to accumulate ("trap") highly reactive, primary radicals which cannot otherwise be observed directly. The ultimate goal in biomedical research is to detect critical bioradicals *in vivo*.[158]

2.7 Miscellaneous

The halogen atom transfer radical cyclization (HATRC) of *N*-allyl α-perchloroamides is a valuable technique for the preparation of pyrrolidinones. One of the main advantages of this rearrangement is the preservation of all carbon-halogen functions on the final skeleton which remain available for further functionalization. The reaction has also been exploited for 2-phosphono allyl derivatives **169**, yielding 4-phosphono pyrrolidinones **172** in quite reasonable yields (44 – 71%).[161] The cyclization reaction is initiated by halogen abstraction by the Cu(I)Cl catalyst. The resulting radical invokes ring closure via a *5-exo-trig* mechanism. The reaction is terminated by recombination of a chlorine atom of the catalyst with the radical **171**. The phosphonolactams could then be rearranged to the unsaturated lactams **173** upon treatment with alkoxides.
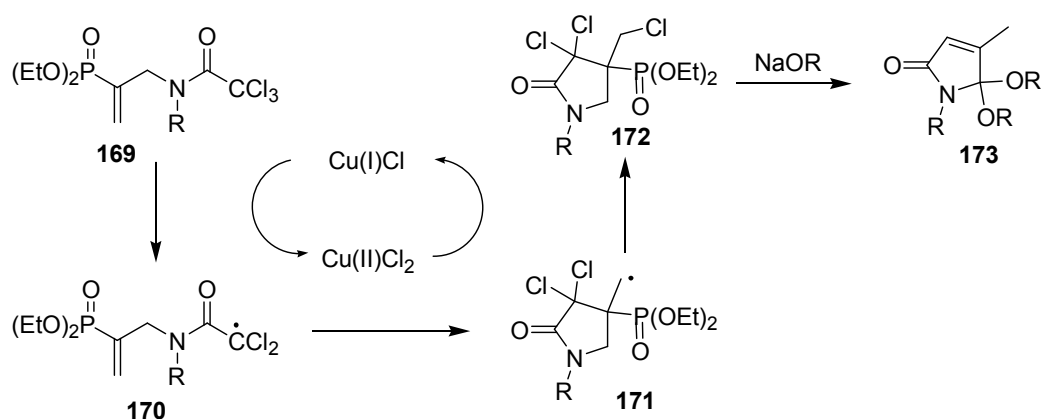
Also carbene mediated cyclizations are compatible with the phosphonate group of the substrates. The [Rh$_2$(OAc)$_4$]-catalyzed intramolecular CH-insertion of α-diazo-α-diethoxyphosphono acetamides **174** affords α-phosphono lactams **175** and **176** in high yield. The regioselectivity of the reaction is strongly determined by electronic effects and in several cases, mixtures are obtained. The phosphonate moiety not only has a stabilizing effect on the carbenoid carbon atom, it also has a profound influence on the stereoselectivity. The bulky phosphonate group appears to induce a remarkable preference for the formation of the five membered ring with stereocontrol in favour of the *trans* diastereomer.[162,163] Furthermore, the reaction can be performed in water when hydrofobic substrates are used.[164]
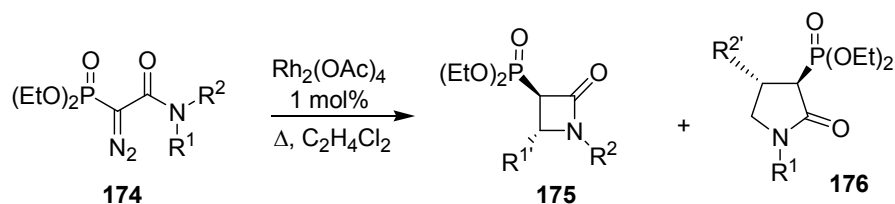
Table 1: Regioselectivity in the intramolecular C-H insertion reaction

	R¹	R²	R¹'	R²'	Yield 175	Yield 176
a	*n*Bu	*n*Bu	Pr	Et	0%	87%
b	*t*Bu	CH₂CH₂Ph	-	Ph	0%	81%
c	CH₂CH₂OMe	CH₂CH₂OMe	-	OMe	0%	89%
d	CHMePh	*n*Bu	Me, Ph	Et	18%	76%
e	Et	Et	Me	H	18%	50%

Also asymmetric carbenoid insertions have been evaluated. Using chiral dirhodium(II) catalysts and substrates **174**, the corresponding phosphonylated lactams could only be obtained in moderate *ee*.[165] However, when chiral δ-amino α-diazo β-ketophosphonates **178** were used, 3-oxopyrrolidine phosphonates **179** were formed with high stereoselectivity through intramolecular metal carbenoid NH-insertion. The corresponding phosphono proline derivatives **180** can be obtained after enolization and reduction of the keto moiety.[166]
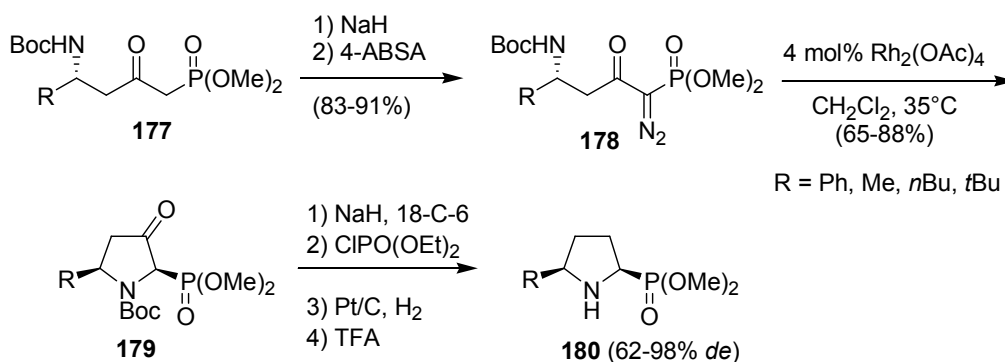
Phosphonylation of amides using Vilsmeier-type conditions has been used for the synthesis of bisphosphonates containing an amino group. When two equivalents of POCl₃ are added to a mixture of pyrrolidinone **181** and two equivalents of trialkyl phosphite, the carbonyl group is transformed into a diphosphonate moiety by consecutive addition and elimination of the phosphorus oxychloride reagents. Recently the reaction has been optimized and the bisphosphonate **182** can be obtained in 59% yield. It can be further oxidized to nitrone **183** which can be used in spin trap experiments.[167-170] Furthermore, bisphosphonate **182** is used to monitor the intracellular pH *in vivo* via non-invasive ³¹P-NMR spectroscopy and displays a 4-fold higher sensitivity than inorganic phosphate or other commonly used phosphonates.[171-173] The preparation method has also been extended to four and six membered rings, however resulting in lower yields (resp. 28% and 19%).[170]
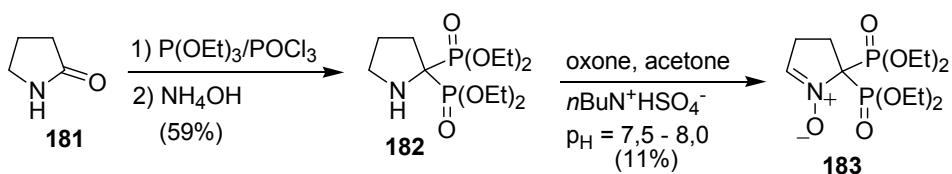
When pyrrolidinone **181** is treated with a mixture of H_3PO_3 and PCl_3, the free phosphonic acid analogue of pyrrolidine **182** is obtained together with small amounts of side products.[174] This bisphosphonic acid is useful for treating or preventing disorders of calcium and phosphate metabolism.[175] Furthermore, it is claimed to have a synergistic effect on certain neoplasm inhibitors and is therefore useful for the treatment of bone-metastasizing tumors.[176] Due to its Ca^{2+} complexing abilities it is also used as hardening retardant for gypsum[177] and as a component in anticalculus or antiplaque compositions in oral care products.[178] Finally it has proven to reduce the calcification of the rat aorta.[177]

Results and Discussion

❧❧❧❧❧❧

1   Synthesis of α-aminoalkyl phosphonates

## 1.1   Introduction

A classical method for the synthesis of α-aminoalkyl phosphonate compounds is the *Kabachnik – Fields reaction*, which was discovered in 1952 independently by Kabachnik and Medved[179] and Fields.[180] The reaction comprises a three-component condensation of a hydrophosphoryl compound, a carbonyl compound (aldehyde or ketone) and an amine. After the discovery in the late 1960's that α-aminoalkyl phosphonates possess practically useful properties, an increasing number of researchers in organic chemistry, biology and medicine have focussed their attention to their synthesis and properties. However, all this research resulted only recently in a generally accepted viewpoint on the mechanism of the Kabachnik – Fields reaction.[181]

Two pathways to the α-aminoalkyl phosphonates are applicable, since two nucleophiles are present in the reaction mixture. Condensation of the carbonyl compound and the amine involves imine formation first, followed by addition of the phosphite, which in fact is a *Pudovik‡* reaction. This reaction pathway occurs when an amine of low basicity is used, which manifests proton donor properties and forms a pre-reaction complex of the type **186** with the phosphite.

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‡ The Pudovik reaction is known as the catalysed or non-catalysed addition of hydrophosphoryl compounds to imines and was described in 1952[182] almost simultaneously with the pioneering research by Kabachnik and Medved.
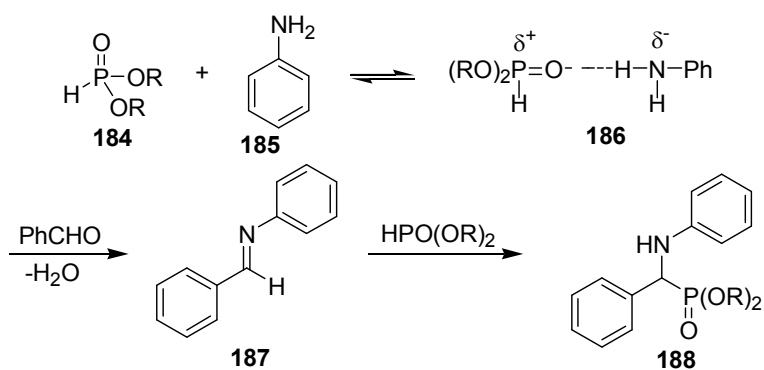
Condensation of the carbonyl compound and the phosphite gives rise to a α-hydroxyphosphonate (*Abramov reaction*) and is then followed by the replacement of the hydroxyl group by the amine to yield the corresponding α-aminoalkyl phosphonate. The *'hydroxyphosphonate'* mechanism generally operates when more basic amines are used, e.g. cyclohexylamine **189**, that show a higher tendency towards hydrogen bond formation with the phosphite hydrogen atom (pre-reaction complex **190**).
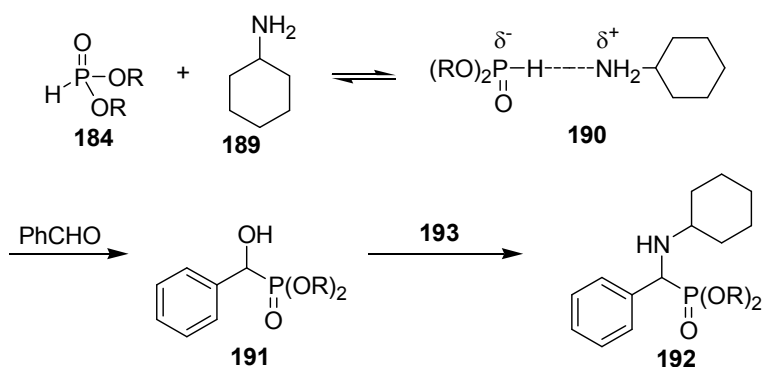
Often it is not clear which mechanism occurs under the conditions applied.[183] Furthermore, it can not be excluded that both mechanisms operate together. Therefore, the fame of the Kabachnik-Fields reaction often suffers from low yields, long reaction times and disappointing final product selectivity. In this regard, our attention should be focussed on the phosphorus nucleophile used in the reaction, to be precise, a dialkyl phosphite.

Several excellent phosphorus containing nucleophiles are known, for instance phosphines. Being a third period element, phosphorus is a large and highly polarizable atom with low electronegativity (i.e. 2.1, which is the same as for the hydrogen atom, and only modestly lower than that of carbon (2.5)). Therefore, phosphorus has enhanced nucleophilic properties compared to nitrogen, which is in the same group in the periodic table. However, in case of dialkyl phosphites, the nucleophilicty is significantly reduced due to the electron withdrawing oxygen atoms and due to the lack of a free electron

pair. Indeed, the structure of dialkyl phosphite is best represented by the tetrahedral structure **184** and therefore it is named sometimes *dialkyl H-phosphonate*. Dialkyl phosphites occur in equilibrium with their corresponding $\sigma^3\lambda^3$ form **193**. However, this equilibrium is shifted very much to the $\sigma^4\lambda^5$ *H*-phosphonate form **184** (log K = -7.2),[184] which is the only one that can be detected by ^{1}H or ^{31}P NMR. The existence of trialkyl phosphites and the unexpectedly high acidity of dialkyl phosphites however, reveal the reality of the $\sigma^3\lambda^3$ isomer **193**.

$^{1}J_{HP}$ = 692 Hz
$\delta(^{31}P)$ = 7.9 ppm

pK_a = 6.1±0.9
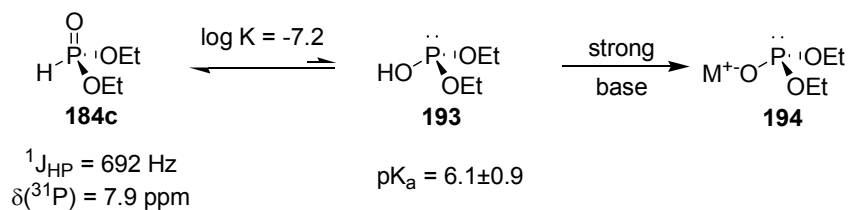
The reduced nucleophilicity of dialkyl phosphites can be conveniently overcome in principally three ways. The use of bases has been applied frequently in the synthesis of α-aminoalkyl phosphonates. With strong bases the corresponding sodium,[185] lithium[186,187] or potassium[188] salts **194** are obtained quantitatively, and are then used in a separate reaction step as the nucleophile. Weaker bases like triethylamine, tetramethylguanidine,[189] or sodium alkoxides[190] help to shift the equilibrium to the $\sigma^3\lambda^3$ phosphite form during the addition reaction, resulting in a considerable rate enhancement.

In contrast to the use of base to enhance nucleophilicity of the dialkyl phosphite, also acid catalysis has proven useful in the synthesis of α-aminoalkyl phosphonates. Addition of dialkyl phosphites to imines has been facilitated by the use of for instance Me_2AlCl,[191] BF_3,[192] $SnCl_4$[193] and $ZrCl_4$.[194] Also three component Kabachnik-Fields type reactions, involving a carbonyl compound, an amine and a dialkyl phosphite, have been reported to proceed smoothly using a variety of catalysts, such as $LiClO_4$,[195] $InCl_3$,[196] $TaCl_5$[197] or lanthanide-triflates.[198,199] Also Brønsted acids have been applied with the same purpose.[200]

A very elegant method to circumvent the drawbacks of dialkyl phosphites as nucleophiles is to convert them into the corresponding dialkyl trimethylsilyl phosphites (DAPTMS). This is easily done by adding TMSCl together with triethylamine to trap the liberated HCl. DAPTMS exists as a $\sigma^3\lambda^3$ phosphite which is confirmed by its ^{31}P chemical shift being clearly in the region of tricoordinated phosphites. Therefore, nucleophilicity is significantly increased. Furthermore, the presence of a silyl group is known to enhance nucleophilicity of the phosphorus atom, while the phosphorus increases the electrophilicity of the silicon centre.[201] The use of DAPTMS reagents in

reaction with aldimines in order to obtain α-aminoalkyl phosphonates will be evaluated and discussed in this chapter (sections 1.2 and 1.3).

$\delta(^{31}P) = 7.9$ ppm $\delta(^{31}P) = 128.0$ ppm
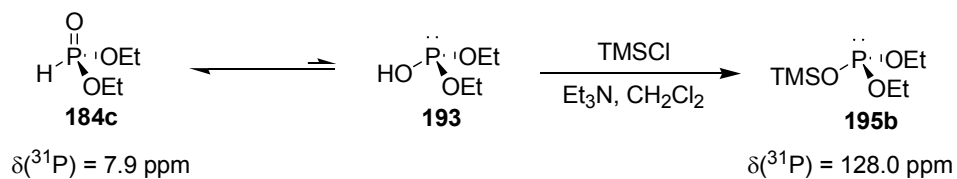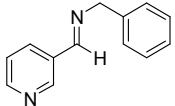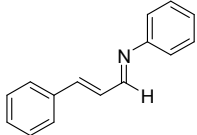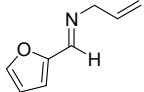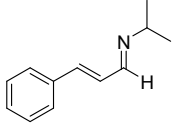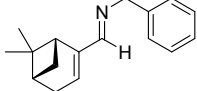
Finally, trialkyl phosphites are typical $\sigma^3\lambda^3$ phosphites and hence are expected to have good nucleophilic properties. However, upon addition of trialkyl phosphites, phosphonium salts are obtained initially, which need to be dealkylated in order to obtain the corresponding phosphonates. Therefore, additives are often used to perform or facilitate this dealkylation, e.g. AlCl₃,[202] Sc(O₃SOC₁₂H₂₅)₃,[203] TMSBr,[204,205] LiClO₄,[206,207] lanthanide triflates[198] and Me₂S·Br₂.[209]

1.2 Phosphonylation using dialkyl trimethylsilyl phosphite

To evaluate the addition reaction of DAPTMS to aldimines, the silylated reagent was freshly prepared for each batch by adding a slight excess (1,1 equivalent) of TMSCl to a cooled mixture of DAP and triethylamine in dichloromethane.[49] The formation of the $\sigma^3\lambda^3$ DAPTMS ($\delta(^{31}P)$ = 126-128 ppm) from $\sigma^4\lambda^5$ DAP ($\delta(^{31}P)$ = 7-11 ppm) was monitored easily via ^{31}P NMR. During this reaction, hydrochloric acid is deliberated which precipitates as triethylammonium chloride from the reaction mixture. After complete conversion of the DAP (usually within 30 minutes), the imine of choice was added to the reaction mixture.

Several imines were tested (Table 2), however, all giving only slow conversion at room temperature. In most cases, the reaction was stopped when side products started to build up after extended reaction periods. When the reaction was refluxed instead, faster conversion to the desired aminoalkyl phosphonate was observed. However, at these higher temperatures, also increased side product formation was found. Due to incomplete conversion and side product formation, a time consuming purification using acid/base extraction or column chromatography was required, giving rise to considerable product losses. In conclusion, the results obtained using DEPTMS as a highly nucleophilic phosphite form are not in agreement with the excellent yields reported using similar substrates.[49] Due to very long reaction times and product losses during obligatory purification, this method is less useful from a preparative point of view.

Table 2: Phosphonylation of imines with DEPTMS

| Imine	Conditions	Conversion[#]	Yield
	1 eq. DEPTMS; CH_2Cl_2, 2 weeks, rt.	67%	52% crude
	1 eq. DEPTMS; CH_2Cl_2, 48 h, Δ	85%	72% crude
	1 eq. DEPTMS; CH_2Cl_2, 14 h, Δ	98%	63%[§]
	1.1 eq. DEPTMS; CH_2Cl_2, 48 h, rt.	78%	52%[§]
	1.2 eq. DEPTMS; CH_2Cl_2, 24 h, Δ	86%	40%[§]
	1 eq. DEPTMS; CH_2Cl_2, 72 h, rt.	85%	32%[§]

[#] Measured using ^1H NMR
[§] Purification by column chromatography

1.3 Regioselectivity of dialkyl trimethylsilyl phosphite addition

In theory, a nucleophile can interact with two electrophilic centers when a carbon, carbon double bond is conjugated with an electron deficient sp^2 or sp carbon atom (as for instance in aldehydes, ketones, esters, imines and nitriles): reaction at the electrophilic carbon atom of the functional group itself (1,2-addition) or reaction via its mesomeric form with the double bond (1,4-addition). Recently, the phospha-Michael addition has been reviewed in full.[210] The regioselectivity is strongly dependent on the type of phosphorus nucleophile used, on the substrate and on the reaction conditions used (thermodynamic control vs. kinetic control).
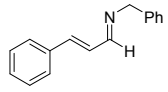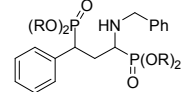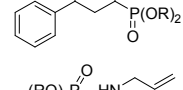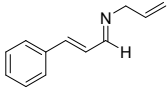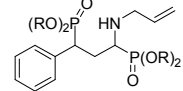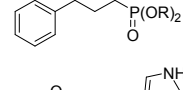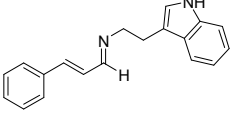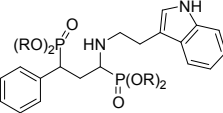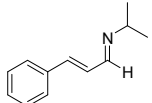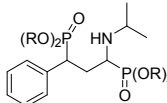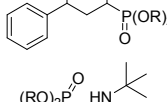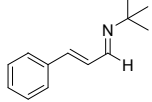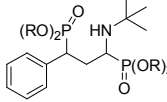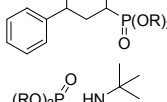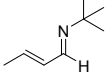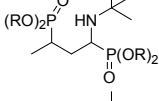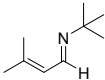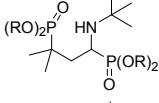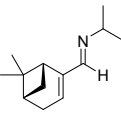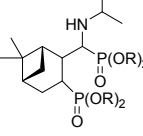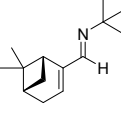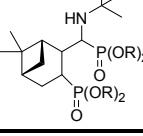
1.3.1 Addition of DAPTMS to α,β-unsaturated imines

DEPTMS is reported to add to α,β-unsaturated imines containing one or more phenyl groups with complete 1,2-regioselectivity. The corresponding α-aminoalkenyl phosphonates can be obtained in high yield and purity after column chromatography.[49,211] Therefore, the tryptamine derived imine **19f** was reacted with 1 equivalent of DEPTMS using the reported conditions. An incomplete reaction was observed even after extended reaction times and at reflux temperatures. Furthermore, increasing amounts of side products were formed during the course of the reaction (^{31}P NMR). Nevertheless, the α-aminoalkenyl phosphonate **22g** could be obtained in pure form using column chromatography (EtOAc/PE: 80/20). TLC analysis of the crude reaction mixture also revealed a second spot with a very high retention (Rf = <0.05). The corresponding products could be obtained in very small quantity from the column chromatographic purification using a more polar CH$_3$CN/EtOAc/MeOH mixture (50/47/3). The ^{31}P NMR spectrum showed 6 peaks and the ^{1}H NMR spectrum lacked alkenyl signals. MS data suggested the presence of two phosphonate groups and therefore, the reaction was repeated using 2 equivalents of DEPTMS. After three days of reflux in dichloromethane, the ^{31}P NMR spectrum consisted exclusively of the aforementioned six peaks. Similar results were obtained with other nitrogen substituents (*i*Pr and Bn). The products were finally identified as 3-phosphonyl 1-aminoalkyl phosphonates (PAP) **196g** using 1D and 2D NMR techniques.
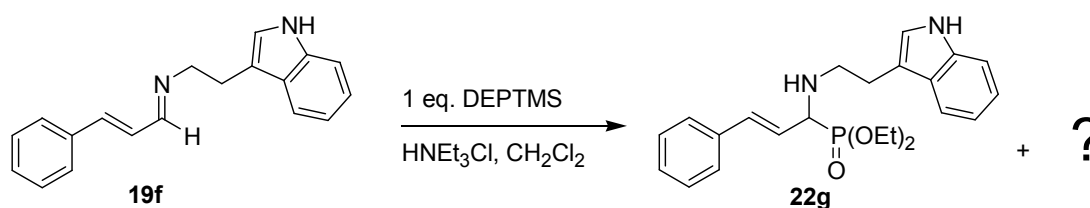
In order to evaluate this surprising reaction on other α,β-usaturated imines, DEPTMS was prepared on a large scale and subsequently purified by filtration of the triethylammonium chloride salts. The solvent was then carefully evaporated under reduced pressure (bp. DEPTMS 66°C at 15 mmHg). The residue, still containing visible amounts of ammonium salt, was then dissolved in diethyl ether and filtrated again.[†] DEPTMS was then obtained as a colourless, clear liquid with a strong smell and can be dosed more easily. Care has to be taken to avoid contact with moisture (e.g. from the air) during all handlings. DEPTMS and DMPTMS can be stored in pure form for at least two months at -32°C.

Table 3: Synthesis of PAP's **196** with DAPTMS

Imine 19	Product		Yield[#]	Diast. ratio
19b		**196c** (R = Me)	70%	19/81
		196d (R = Et)	80%	29/71
19d		**196e** (R = Me)	36%	71/29
		196f (R = Et)	40%	67/33
19f		**196g** (R = Et)	82%	29/71
19g		**196h** (R = Me)	77%	32/68
		196i (R = Et)	78%	33/67
19h		**196j** (R = Me)	82%	49/51
		196k (R = Et)	85%	36/64
19q		**196l** (R = Me)	74%	36/64
19r		**196m** (R = Me)	60%	-
19w		**196n** (R = Me)	46%	22/78
19x		**196o** (R = Me)	20%	12/88

Complete conversion was observed in all cases. Yields reported are after column chromatography or acid base extraction.

[†] Preparation of DEPTMS in diethyl ether was unsuccesful

Surprisingly, the pure DEPTMS did not react with imines at all. Several α,β-unsaturated and aromatic imines were tested without any success. Afarinkia and coworkers[49] mentioned that the excess of TMSCl used in their procedure catalyzed the reaction. However, still no reaction occurred when TMSCl was added, even when equivalent amounts were used. Then it was reasoned that chloride could be necessary to desilylate the intermediate phosphonium salt **197**. However, addition of LiCl also did not get the reaction to work (Table 4).
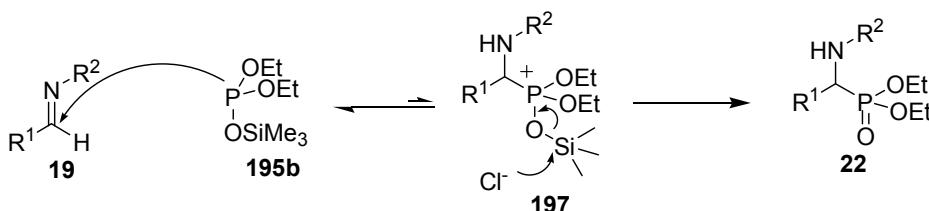
Finally, ammonium chloride was added as a readily available substitute for the *in situ* formed triethylammonium chloride in the Afarinkia procedure.[49] The same results were obtained for both salts when *N*-benzyl imine **19b** was reacted with two equivalents of DEPTMS in dichloromethane at reflux temperature. The corresponding PAP **196d** was the only reaction product after 72 hours of reflux and aqueous work-up. The reaction was easily monitored using ^{31}P NMR.[#] The imine **19b** very quickly vanished, however mostly in favour of the 1,2-addition product (α-aminoalkyl phosphonate **22c** or "AP"). The PAP **196d** was formed more slowly, while the AP disappeared again upon prolonged heating (Figure 1).[§]

Table 4: Effect of additives on the addition of DEPTMS to imine **19b**

	Additive	Temperature	Reaction time[¤]
1	None	Reflux	∞
2	TMSCl	Reflux	∞
3	LiCl	Reflux	∞
4	HNEt$_3$Cl	Reflux	72 h
5	NH$_4$Cl	Reflux	72 h
6	(NH$_4$)$_2$SO$_4$	Reflux	3 h
7	H$_2$SO$_4$	RT	30 min

[¤] Reaction time required for complete conversion at the specified temperature in dichloromethane.

[#] A small sample was taken out of the reaction mixture and centrifuged to obtain a clear NMR sample. The NMR measurement was performed without locking the signal (as no deuterated solvent was present which posed no problem given the short time scale of a ^{31}P experiment. This technique has also been used for ^1H NMR measurements.[212]

[§] PAP **196d** was easily recognized in the ^{31}P spectrum (see chapter 3, section 1.3.2 for spectroscopic characteristics). No reference data about AP **22c** were available in the literature. However, a 1,2-selective protocol was developed (chapter 3, section 1.4) which allowed to obtain AP **22c** in pure form.
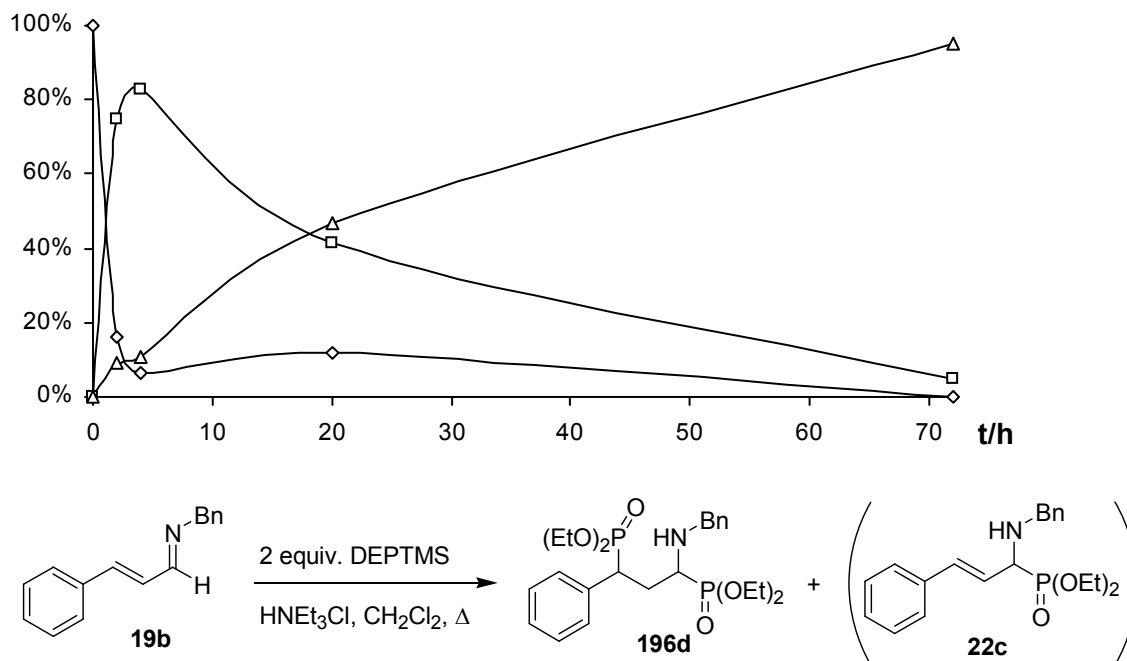
Figure 1: Composition of the reaction mixture during the reaction of **19b** with DEPTMS in the presence of HNEt₃Cl, measured by NMR. Imine **19b** (◇); AP **22c** (□); PAP **196d** (Δ).

Furthermore, an acidification of the reaction mixture was observed. This was probably due to the formation of ammonia or triethyl amine and hydrochloric acid from the corresponding salts under thermal conditions. This was observed visually by salt formation in the cooling system due to recombination of the base and acid vapours in the head space. Protons can play a crucial role in the addition reaction, in the first place to activate the imine by protonation. Secondly, as can be seen from the atom balance, a proton should be assimilated during the addition reaction. Therefore, ammonium sulphate was selected as an additive instead of the chloride salts. The sulphate is sligthly more acidic and furthermore, sulphuric acid can be formed which is far less volatile than hydrochloric acid. Indeed, a remarkable rate enhancement was observed: complete conversion to PAP **196d** took place in three hours at reflux temperature. Even more, when concentrated sulphuric acid (1 equivalent H⁺) was added at room temperature to a mixture of *N*-benzyl imine **19b** and DEPTMS in dichloromethane, the reaction mixture started to boil almost instantaneously and the PAP **196d** was formed in 30 minutes at room temperature.

No one so far has reported correctly on the regioselectivity of the DEPTMS addition to imines or on the exciting effects of acid addition to the reaction mixture. Several related substrates were evaluated in the double addition reaction (Table 3). Similar results were obtained with dimethyl trimethylsilyl phosphite (DMPTMS).[213] For all imines, a faster reaction was observed with more bulky nitrogen substituents. For imines derived from aniline, only 1,2-addition was observed.

1.3.2 Spectroscopic characteristics of PAP's 196

Spectroscopic analysis of the newly formed products was complicated by two factors. Firstly, products **196c-l,n,o** were obtained as a mixture of two diastereomer pairs. This caused most peaks to double. Secondly, the complexicity of the NMR spectra was increased due to the presence of multiple phosphorus couplings. As an example, the ^{31}P spectrum (with broadband ^{1}H-decoupling) of PAP **196j** is depicted in figure 2. The major isomer can be recognized by 2 doublets. Each doublet represents 1 phosphorus atom, with a scalar coupling over 4 bonds ($^4J_{PP}$ = 5.9 Hz). The minor isomer does not show a similar P,P coupling and appears as two singlets. The lack of a P,P coupling should be contributed to the specific conformation of this minor isomer. In some cases, little broadening of the two singlets indicated the presence of a very small coupling.# Only in the case of PAP **196l**, both couplings were resolved (Major: $^4J_{PP}$ = 5.2 Hz, minor: $^4J_{PP}$ = 2.2 Hz). The occurrence of two diastereomeric pairs of PAP **196k** was confirmed by their separation in low yield using column chromatography. Furthermore, only two doublets ($^4J_{PP}$ = 3.0 Hz) were observed for PAP **196m** with only one chiral centre.

The resolution of the applied ^{31}P experiments was 0.74 Hz at 121.66 MHz (65536 datapoints with 48.78 kHz sweep)

X : parts per Million : 31P
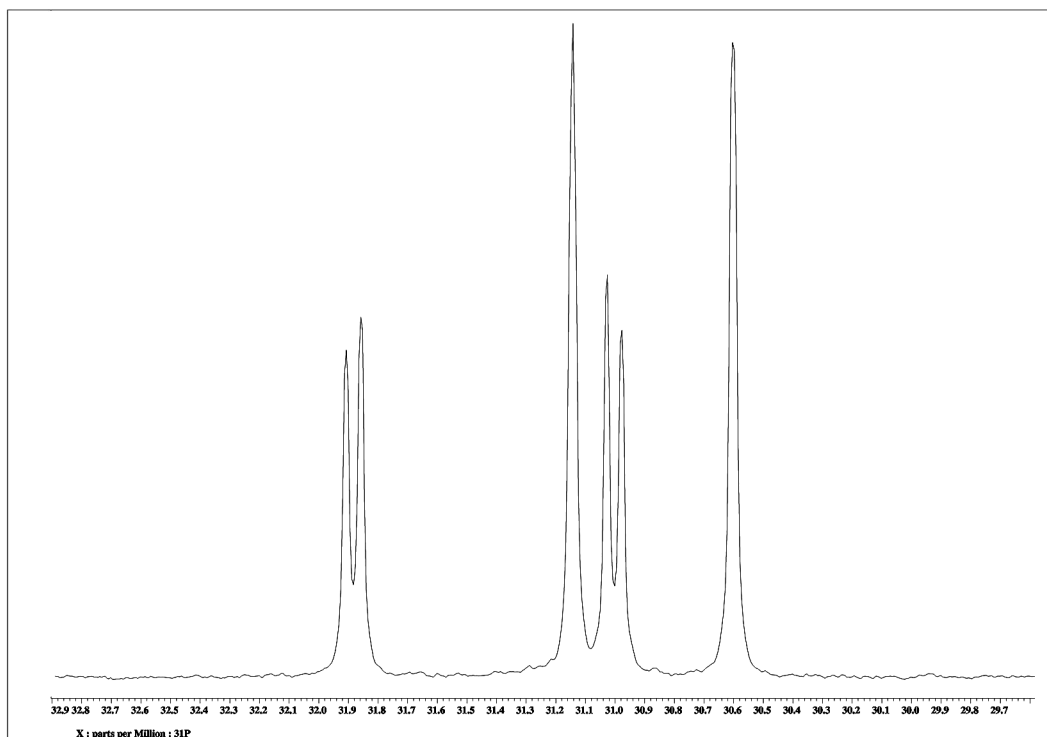
Figure 2: ³¹P NMR spectrum of PAP **196j**

Also the ¹³C NMR spectrum (with broadband ¹H-decoupling) was affected by the inherent complexicity of the PAP diastereomeric pairs. The nitrogen attached CHP was represented by 8 peaks (figure 3). Each isomer showed a large $^1J_{CP}$ coupling (151 and 160 Hz) and a smaller $^3J_{CP}$ coupling (14 and 17 Hz). Additional NMR data of PAP's **196** are collected in chapter 4, section 3.2 and appendix B.
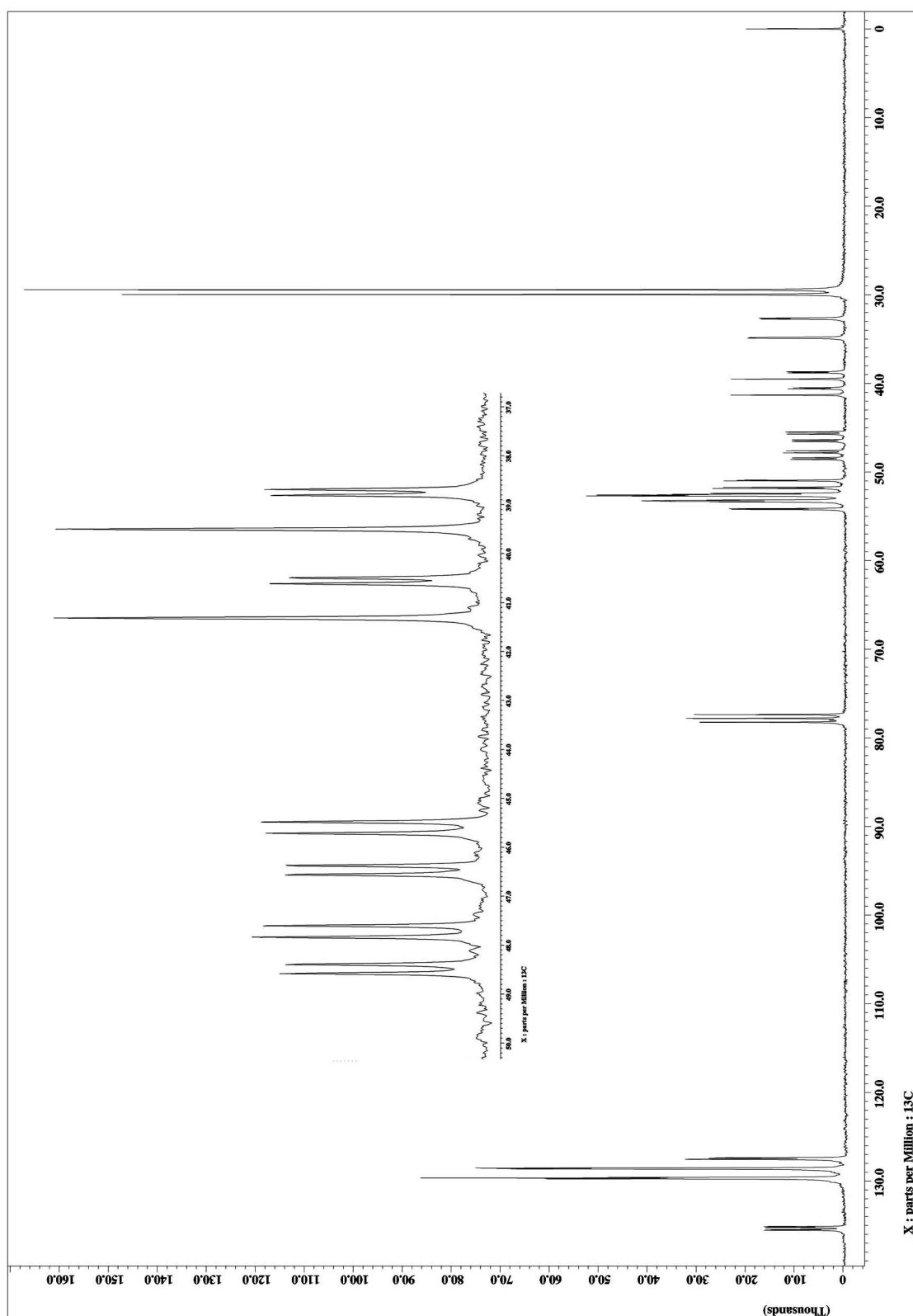
Figure 3: 13C NMR spectrum of PAP **196j**

1.3.3 Mechanistic investigation of the double DAPTMS addition to imines

Mainly three parameters influencing the reaction arise from the observations described in chapter 3, section 1.3.1. The rate of the reaction is strongly affected by the availability of protons in the reaction mixture. Even more, in the absence of protons, no reaction occurs at all. Secondly, bulky nitrogen groups greatly enhance the formation of PAP. With a sterically less demanding phenyl group, only 1,2-addition of the phosphite is observed, even after prolonged heating of the reaction mixture. Finally, monitoring the PAP formation using NMR (Figure 1) shows that the 1,2-addition product **22c** is formed during the reaction.

No observations have been made concerning the role of the nucleophile. Therefore, PCl_3 was selected as another $\sigma^3\lambda^3$ phosphorus nucleophile, however lacking the TMS group. TMSCN on the other hand, still contained the TMS group, but consisted of another nucleophilic species. However, in both cases no double addition products were obtained. TMSCN was only capable of performing a regular Strecker type 1,2-addition in high yield. This illustrates again the unique properties of silyl esters of phosphorus.[201]
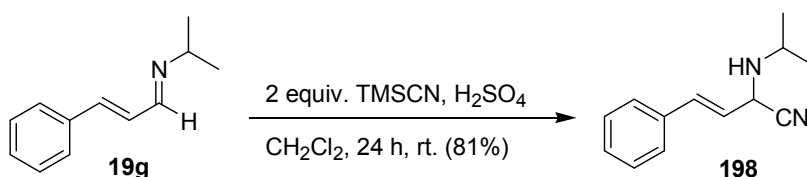
To establish the role of the acid, an experiment was set up adding different amounts of sulphuric acid to a mixture of imine **19g** and DMPTMS in dichloromethane (Table 5). Even though only partial conversion was observed after 24 h with 0.1 equivalent of sulphuric acid H^+ (entry 3), the reaction seemed to be only slowed down using subequivalent amounts of H^+.

Table 5: Role of sulphuric acid

	H_2SO_4	Reaction time	Result[#]
1	1 eq. H^+	1 h	100% PAP
2	0.5 eq. H^+	24 h	100% PAP
3	0.1 eq. H^+	24 h	32% PAP, 24% AP, 44% imine

[#] Determined with ^{1}H NMR after alkaline aqueous work-up.

From monitoring the reaction with 0.5 equivalent of sulphuric acid, it was again shown that the 1,2-adduct prevails in an early reaction stage. Therefore, it is reasonable to suggest it as an intermediate that is converted later on to enamine **202** via an S_N' type substitution (Figure 4, pathway B). However, the 1,2-addition pathway can also be considered as a dead-end

side pathway. The PAP **205** is then formed via a parallel 1,4-addition to the activated imine **199** (pathway A). However, complete conversion to the PAP via the latter pathway is only possible when the 1,2-addition is reversible.
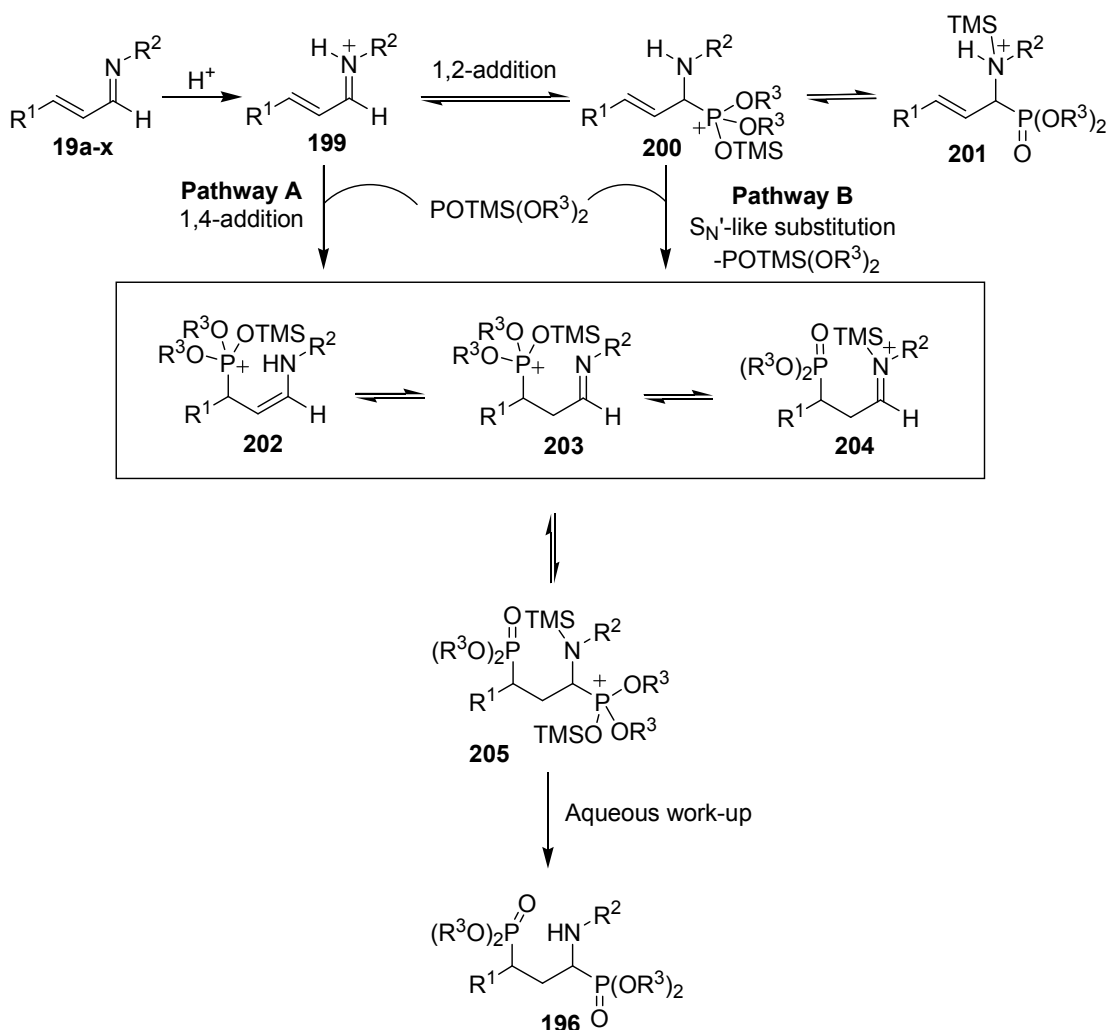
Figure 4: Proposed reaction mechanisms of the double phosphite addition

The initial equilibrium (**199** ↔ **200** ↔ **201**) was studied in a separate experiment. When dimethyl 1-amino-1-phenylmethyl phosphonate **22ad** was *N*-silylated using TMSCl and subsequently treated with a large excess of DEPTMS, mainly the diethyl phosphonate **22ae** was recovered next to small amounts of **22ad**. When the same experiment was repeated without silylation and using simply diethyl phosphite, no exchange occurred at all. This clearly demonstrated the reversibility (**200** ↔ **201**) of the reaction and the leaving group capacity of the intermediate positively charged phosphonium group. Also a tris(trimethylsilyl)phosphonium group has been reported as a leaving group before.[214]
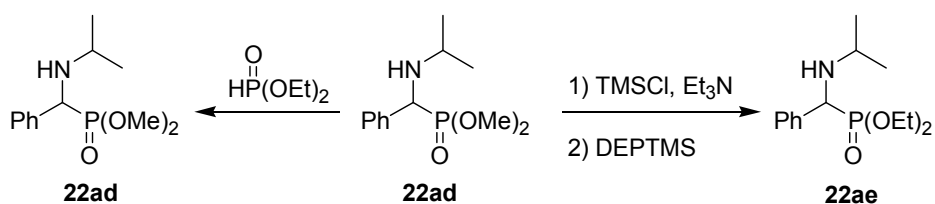
When α-aminoalkyl phosphonate **22i** was submitted to *N*-silylation and an excess of DMPTMS, a mixture of four compounds was found after aqueous work-up.
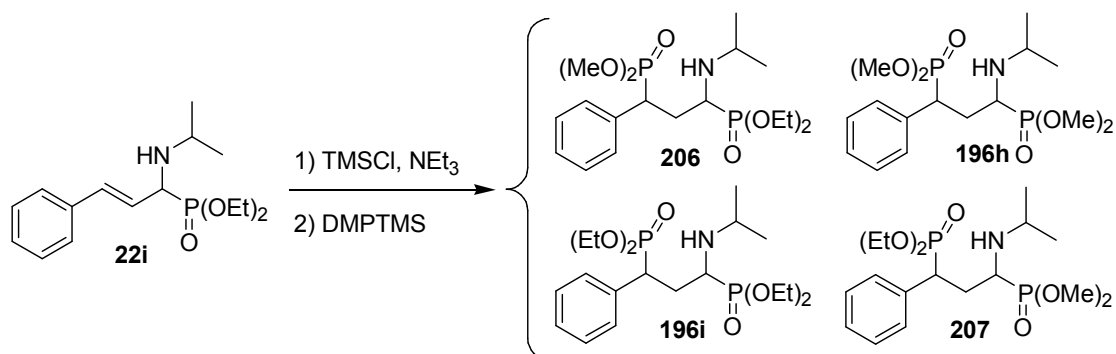
The same experiment was then repeated with PAP **196h**. However, only exchange of the phosphonate group in the neighbourhood of the nitrogen atom was observed. This indicates that phosphonate group exchange is probably nitrogen assisted. The nitrogen atom first hands over the obligate TMS group to yield a phosphonium group and then helps to kick it out by delocalisation of its lone pair.
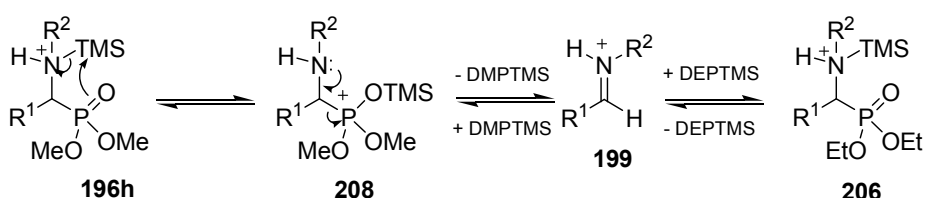
Also in the case of alkenyl phosphonate **210**, which was formed using an Arbuzov reaction with trimethyl phosphite and cinnamyl bromide, no substitution of the dimethyl phosphonate groep was observed.
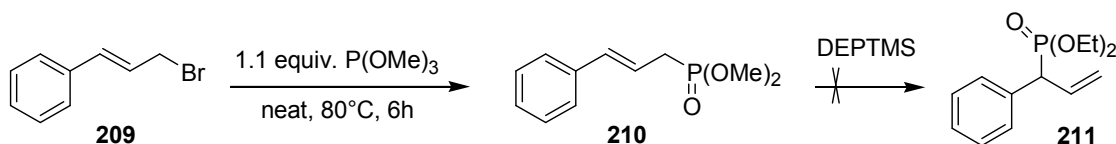
While the equilibrium (**199** ↔ **200** ↔ **201**) was now well established, the further course of the reaction however remained unclear. Both pathways A and B in Figure 4 yield the same intermediate enamine **202** which again is

expected to participate in an equilibrium with imine **203** and iminium ion **204**. However, none of these intermediates could be detected so far using NMR spectroscopy. This would require that the second phosphite addition to iminium ion **204** proceeds much faster than the NMR timescale. Furthermore, the proposed reaction mechanisms require an external proton source as one equivalent of protons is incorporated in the final product **196**. Therefore, the experiment using only 0.1 equivalent of sulphuric acid together with 2.0 equivalents of DEPTMS was repeated and monitored using NMR. Under these conditions, the reaction proceeded very sluggishly and the formation of PAP **196** was stopped completely after 3 to 4 hours. From that point on, the intermediate enamine **202** started to build up, while the rest of the imine is slowly consumed (Figure 5). After 72 hours at room temperature, water was added for work-up. However, during the work-up procedure, the composition of the mixture completely changed. The enamine **202** was completely converted to PAP **196** and part of the imine to aminoalkenyl phosphonate **22**.
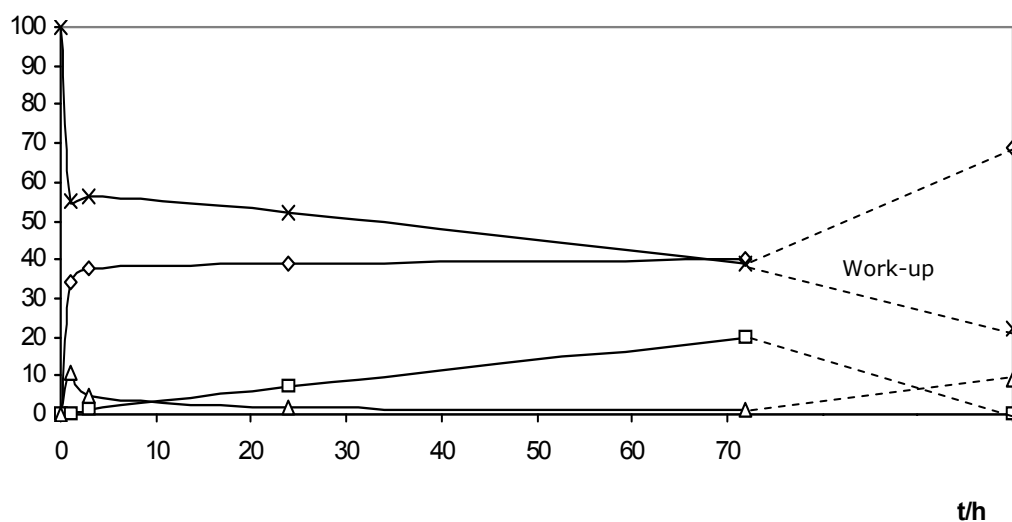
Figure 5: Composition of the reaction mixture during the reaction of **19g** with DEPTMS in the presence of 0.1 equivalent H_2SO_4 (0.2 equivalent H^+), measured by NMR. PAP **196i** ($\diamond$); Enamine **202** ($\square$); AP **22i** ($\triangle$); Imine **19g** ($\times$).

This observation displays a remarkable proton hunger of the reaction. All protons present in the reaction medium, even in bounded form (e.g. ammonium salts), are consumed very rapidly. However, when a depletion of protons occurs in the reaction mixture, it blocks. It might be reasoned that imine **19a-x** can still be activated by intermolecular silyl transfer of one of the adducts (indicated as "TMS$^+$" in Figure 6). However, Michael addition or S_N' substitution then would yield *N*-silyl enamine **215** which can not participate in the equilibrium as shown in Figure 4. Therefore, the reaction blocks at the enamine stage in the absence of protons. When protons are

added (in any form, e.g. slightly basic water during work-up), the enamine-imine tautomerization is again allowed to proceed and the remaining DAPTMS can add to the imine to form the final product (PAP).
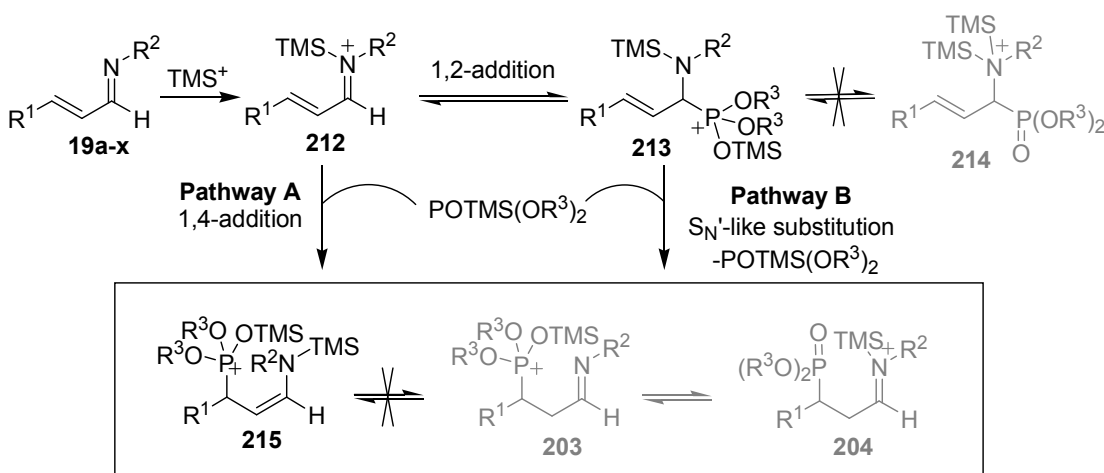
Figure 6: Possible reaction mechanism in the absence of protons

The enamine formation is clearly much slower in absence of protons. This probably demonstrates the kinetic difference between activation of the imine **19** by a proton and transfer of a large TMS group. Also 1,2-addition seems to be blocked under proton depleted conditions. Formation of adduct **214** is probably disfavoured because of sterical hindrance of the bulky TMS groups.

The occurrence of enamine **202** in the proton depletion experiment is derived from the ^{31}P and ^{1}H NMR spectra. A new peak in the ^{31}P spectrum ($\delta(^{31}P)$ = ±27 ppm in the reaction medium) is attributed to enamine **202**. This is supported by the characteristic signals in the vinylic region of the ^{1}H spectrum. To be entirely sure about the identity of the newly detected intermediate, some further experiments were performed.

Imine **19g** was reacted with 1 equivalent of AlCl$_3$ and 0.9 equivalent of DEPTMS in dry dichloromethane under a nitrogen atmosphere (experiment A). The AlCl$_3$ was supposed to act as an activator of the reaction (complexation with the imine nitrogen atom, compared to protonation of the imine by sulphuric acid), leaving no protons in the reaction medium. Only 0.9 equivalents of DEPTMS was used in order to avoid the presence of an excess of DEPTMS during the work-up. After 2 h at room temperature, the DEPTMS is completely consumed and a fast extraction using 1 M NaOH$_{(aq)}$ resulted in a large amount of 1,4-adduct next to PAP **196i**. The resulting ^{31}P-spectrum is depicted at the top in Figure 7. The PAP **196i** is recognized as two doublets and two singlets, while the large singlet at ± 28 ppm is from the

1,4-adduct in its imine form **216a** (a clear aldimine proton resonance is observed at 9,6 ppm in the ^{1}H-NMR spectrum, no vinylic protons were visible).
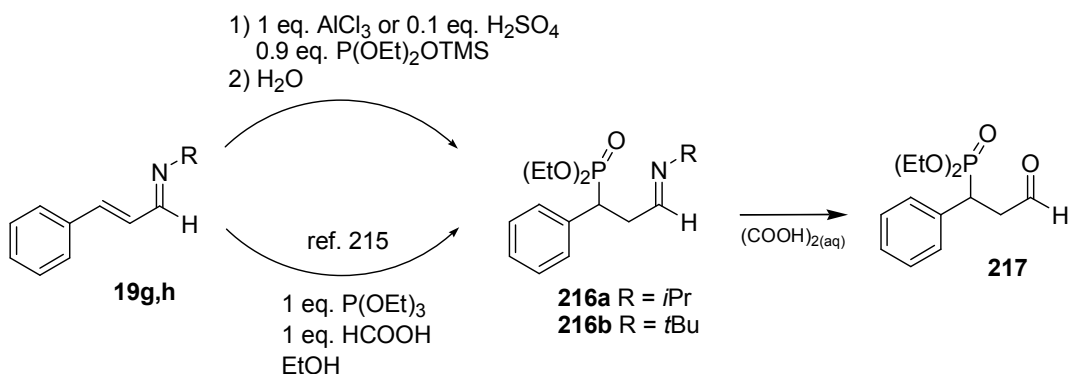
Imine **19g** was also reacted with 0.9 equivalents of DEPTMS and 0.1 equivalent of H_2SO_4 in dry dichloromethane under a nitrogen atmosphere (experiment B). As can be derived from Figure 5, a small amount of PAP would be formed very fast initially, but then the reaction would block, building up slowly the same 1,4-adduct, which could again be isolated after basic extraction (since no DEPTMS was left during extraction), giving a similar ^{31}P-spectrum (second plot in Figure 7). When neutral water was added for work-up of the reaction, also aldehyde **217** was detected at 27.6 ppm, resulting from hydrolysis of **216a** during work-up (3rd plot in Figure 7).

In order to prove the structure of the 1,4-adduct, imine **216b** was synthesized using a literature procedure. Exclusive 1,4-addition to *t*Bu imine **19h** was reported using triethyl phosphite and formic acid in ethanol.[215] Imine **216b** was suggested as the intermediate and was treated with oxalic acid in water to yield the corresponding aldehyde **217**. The intermediate imines were never isolated in the reported article and spectral data are only available for the aldehyde **217**. Therefore, imine **19g** was reacted with 0.96 eq. of triethyl phosphite and 1.04 equivalents of formic acid in ethanol (experiment C). Complete conversion took place in 1 h at room temperature. The ^{31}P-spectrum after evaporation of the ethanol is shown as the fourth plot in Figure 7 (no aqueous work-up was performed, causing a little broadening of the peaks of the 'crude' reaction mixture. Mind that traces of PAP **196i** are also formed under these conditions). This clearly shows that the intermediate is the same product in all three experiments. Upon hydrolysis using 1 M oxalic acid in water, the same aldehyde is obtained in all three experiments (δ(^{31}P) = 27.6 ppm, plot five in Figure 7).
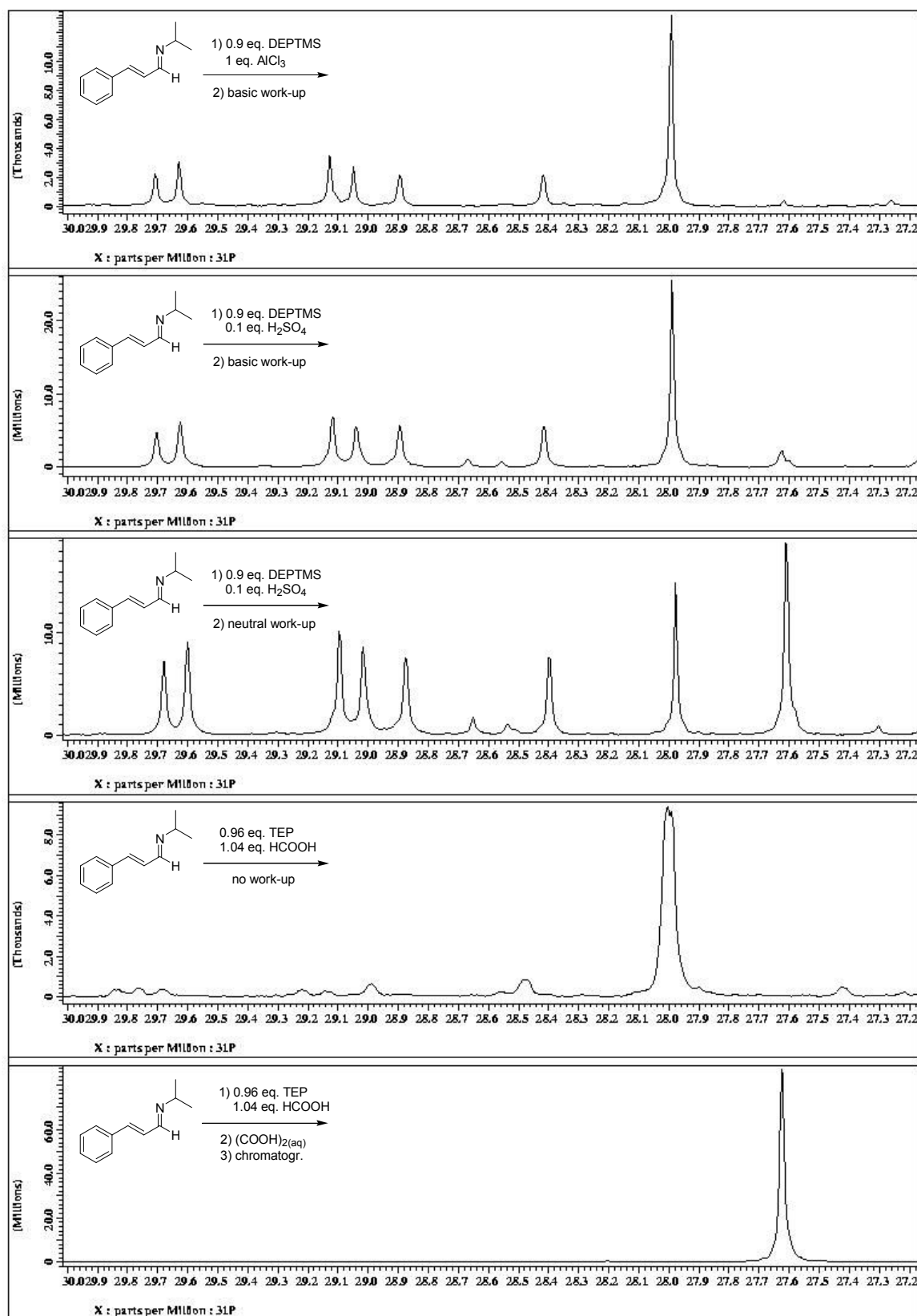
Figure 7: a) Results of experiment A after basic work-up. PAP **196i** can be clearly distinguished (28.4 – 29.8 ppm) next to imine **216a** (28 ppm). b,c) Results of experiments B after basic (b) or neutral (c) work-up. The same peaks are visible. The hydrolysis product of imine **216a** is observed at 27.6 ppm. (d) This spectrum of the

crude reaction mixture of experiment C after evaporation of the solvent shows that imine **216a** is formed almost exclusively under these conditions, next to very small amounts of PAP. (e) Spectrum of the pure aldehyde **221**.

However, the reported value for aldehyde **217** is 24.4 ppm. Also a very low chemical shift (9.0 ppm) was reported for the aldehyde proton, causing a little bit suspicion. Therefore, the experiment was repeated exactly as reported using imine **19e**. Aldehyde **217** was obtained in pure form using column chromatography. Spectral data were now in agreement with our previous results: $\delta(^{31}P) = 27.6$ ppm and the aldimine proton appears as a multiplet at 9.67 ppm in ^1H NMR. The structure was confirmed using 2D COSY and HSQC experiments.

In this way, all intermediates in the proposed reaction mechanisms (Figure 4) have been detected and identified. From the evolution of the reaction intermediates in function of the reaction time (Figure 5), it is clear that the 1,2-adduct (AP) **22** is not a real intermediate of the PAP formation. After the initial AP formation (which can also be noticed in Figure 1), also the 1,2-addition is blocked by the absence of protons, while the enamine is still formed very slowly. Furthermore, the observation of a considerable higher reaction rate for imines bearing more sterically demanding *N*-substituents, (*t*Bu>*i*Pr>Bn>>Ph) is in favour of the tandem 1,4-1,2-addition, since the 1,2-addition should be slowed down by the steric bulk. Therefore, pathway A is presented as the principal reaction mechanism of the double DAPTMS addition. In literature, one case of a double addition of ketene silyl acetals **218** to α,β-unsaturated imines can be found, also proceeding in a 1,4-1,2-tandem fashion and also requiring a proton source.[216]
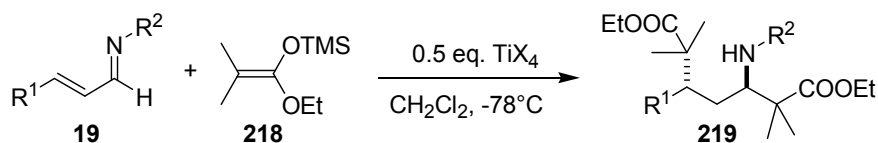
In case of the DAPTMS addition however, the mechanism is more complicated due to the parallel and reversible 1,2-addition. It can be concluded that the fast development of 1,2-adduct **22** in the reaction mixture should be a result of kinetic control, while the PAP **196** is the thermodynamic more stable final product.

In summary, the aforementioned observations lead to a new insight regarding the use of dialkyl trimethylsilyl phosphite which contradicts earlier research:[211] while it is present in its apparently most nucleophilic form, dialkyl trimethylsilyl phosphite fails to react either in a 1,2- or a 1,4-addition

in the absence of a protic acid. However, in a sufficiently acidic medium, dialkyl trimethylsilyl phosphite is able to convert α,β-unsaturated imines **19** very fast to the diphosphonates **196** in one single step via a sequential tandem 1,4-1,2-addition. A number of other synthetic pathways towards diphosphono glutamic acid analogues can be found in literature that can be subdivided in two groups. The first group uses β-phosphono aldehydes that are converted to the corresponding imines and subsequently phosphonylated.[217-219] The second group uses a Michael type addition of *N*-protected aminomethyl phosphonate anions to a vinyl phosphonate.[113,220] However these methods are far less versatile and are all comprising multiple steps.

1.3.4 What about trialkyl phosphites?

The newly discovered[221] unusual behaviour of dialkyl trimethylsilyl phosphites towards α,β-unsaturated imines prompted us to evaluate other methods presented in literature to exclusively yield 1,2- or 1,4-adducts. In particular, the resemblance of trialkyl phosphites to dialkyl trimethylsilyl phosphites, put forward these nucleophiles as potential tandem addition candidates. Nevertheless, the use of trialkyl phosphites may require special conditions in order to obtain similar results.

The addition of triethyl phosphite to α,β-unsaturated imines has been reported to proceed with complete 1,4-regioselectivity when *t*Bu groups were used on nitrogen.[215] A slight excess of formic acid was added to dealkylate the intermediate phosphonium salt **220**.
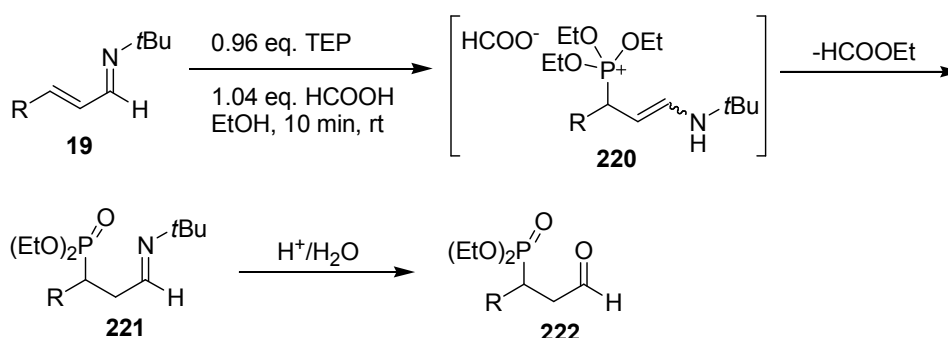
This method was used earlier in this research (chapter 3, section 1.3.3) to reveal the identity of the 1,4-adducts as intermediates in the tandem DAPTMS addition to α,β-unsaturated imines. However, the corresponding *i*Pr imine **19g** was used and small amounts of double addition products could be detected using ^{31}P NMR (see Figure 7d). Therefore, the reaction was repeated using less steric nitrogen substituents. The ratios of both products were

measured using ^{31}P NMR from the crude reaction mixtures after standard aqueous work-up.

19h R= *t*Bu
19g R = *i*Pr
19a R = Ph

1 eq. TEP
1 eq. HCOOH
EtOH
10-30 min, rt

220 + **200**

R = *t*Bu; **216b:196k** = 99 : 1
R = *i*Pr; **216a:196i** = 95 : 5
R = Ph; **216c:196b** = 9 : 91
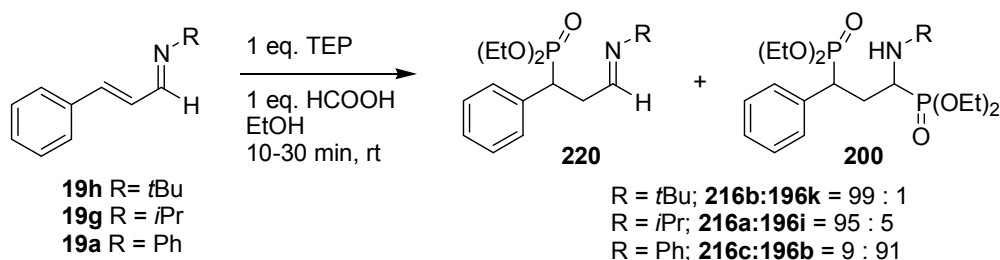
Less steric nitrogen substituents gave rise to higher conversion to the PAP's **196**. In case of imine **19a**, the PAP **196b** was the major reaction product next to residual starting material **19a**, since only 1 equivalent of the nucleophile was used. This reactivity order is opposite to the results with DAPTMS as a nucleophile; highly steric *t*Bu groups gave the best results with DAPTMS, while with imine **19a** only the 1,2-adducts could be obtained.

When two equivalents of phosphite were used together with two equivalents of formic acid, the PAP's were obtained in short times and high yields (Table 6). With *t*Bu imine **19h**, only the 1,4-adduct could be obtained. Comparable to the DAPTMS additions, the role of the acid was also essential to this reaction. The reaction proceeded violently upon addition of formic acid to a solution of the imine and TAP in ethanol (or methanol). Next to imine activation and enamine tautomerization, the acid (or its conjugated base) is also required for dealkylation of the phosphonium intermediates.

Table 6: Addition of TAP to α,β-unsaturated imines **19**

| Imine | R | TAP | Product | Time | Yield | Diast. Ratio | |
						TAP	DAPTMS[#]
19h	*t*Bu	TEP			*Exclusive 1,4-addition*		
19g	*i*Pr	TEP	**196i**	24 h	90%	38/62	33/67
19b	Bn	TEP	**196d**	30 min	78%	33/67	29/71
19d	Allyl	TEP	**196f**	30 min	70%	72/28	67/33
19a	Ph	TMP	**196a**	30 min	86%	34/66	-
19a	Ph	TEP	**196b**	30 min	86%	21/79	-

[#] From Table 3

From these experimental results it is clear that both addition reactions of TAP and DAPTMS to α,β-unsaturated imines **19** proceed very fast in acidic media, yielding the corresponding diphosphonates **196** in high yield and purity. Both reactions proceed via the tandem 1,4-1,2-addition mechanism,

which is also indicated by the similar diastereomeric ratios (Table 6). In case of TAP, the 1,4-addition is clearly favoured, causing the 1,4-adduct to be the sole reaction intermediate, or final product in case the subsequent 1,2-addition is blocked (e.g. due to steric hindrance). From the discussion in chapter 3, section 1.3.3, it became clear that the mechanism is more complicated for the DAPTMS addition. In that case, the 1,2-addition is favoured kinetically over the 1,4-addition, causing the 1,2-adducts to appear very fast in the reaction mixture. Therefore, it should be concluded that TAP is more sterically demanding in this type of reactions than DAPTMS, which is quite surprising at first sight comparing the OEt with the OTMS group.

A possible explanation for this unexpected behaviour of DAPTMS can be found in the reaction mechanism of DAPTMS additions often presented in literature.[222] In this mechanism, coordination of the imine nitrogen atom with the silicon atom is suggested, which would bring the (bulky) nucleophile in the close neighbourhood of the electrophilic center. Because of the presence of both a nucleophilic and an electrophilic center in the silylated phosphite, the subsequent transformation then occurs via a classic *'push-pull'* mechanism.[201]
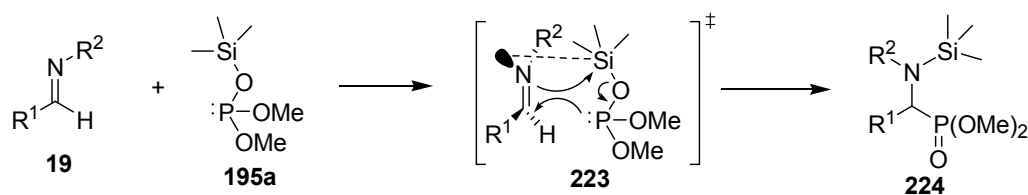
The 1,4-addition with DAPTMS on the other hand, probably proceeds similar to that with TAP, i. e. without prior coordination with nitrogen. Furthermore, the fast 1,2-addition of DAPTMS has proven to be a reversible reaction, which makes the 1,2-adduct only a transient intermediate. Therefore, only limited amounts of substrate (imine) are available for the 1,4-addition, causing it to be the rate determining step. The final 1,2-addition proceeds smoothly through nitrogen, silicon coordination. The number of reactive imine molecules is increased when the 1,2-addition is slowed down by sterically demanding nitrogen substituents, resulting in a faster 1,4-addition and subsequent PAP formation. When TAP is used, no 1,2-adduct formation is observed because of the lack of coordination. 1,4-Addition proceeds through a classical nucleophilic attack. The final 1,2-addition then is the rate determining step, which, for clear reasons, is disfavoured by the same sterically demanding nitrogen substituents. These exceptional reaction kinetics, rather than simply steric differences, may explain the opposite reactivity order for both reagents.

1.3.5 Diphosphonic acids

Since the α-amino phosphonates mostly exert their activity as amino acid analogues, most examples of active compounds comprise the free phosphonic acids rather then the corresponding esters. In contrast to carboxylic acids, the phosphonic acids are dibasic and are significantly more acidic (pK_{a1} = 2.2-3.0, pK_{a2} = 7.7-9.0).[223] A general method for dealkylation of phosphonates is the use of TMSBr.[224]

When PAP **196h** is treated with 5 equivalents of TMSBr and stirred for 1 h at room temperature in dichloromethane, the corresponding silylester **225** is obtained.§ Then water is added to hydrolyse the silylesters and the corresponding phosphonic acids are obtained as a viscous oil after evaporation of the volatiles.
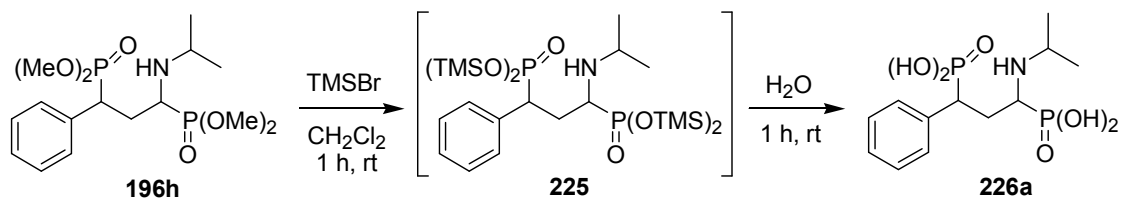
When the same conditions were used with *N*-*t*Bu PAP **196j** and *N*-Bn PAP **196c**, the corresponding diphosphonic acids **226b,c** were obtained as a solid in quantitative yields. While the oily *i*Pr-derivative **226a** was slightly soluble in water (and D_2O), the solids were insoluble in water, methanol, DMSO, acetone, chloroform, dichloromethane and benzene. Therefore, their structure could only be confirmed by mass spectroscopy with electron spray ionization and ^{31}P NMR in D_2O. No satisfying ^{1}H and ^{13}C NMR data could be recorded because of the too low solubility.

The corresponding sodium salts were expected to be more soluble. Therefore, NaOD was added to a suspension of diphosphonic acid **226b** in D_2O. This resulted in a clear solution, however with structural alterations to the product according to ^{31}P NMR. When solid $NaHCO_3$ was used as a milder base, solubility remained too low. Finally a suspension of **226b** in D_2O turned into a clear solution upon addition of an excess of triethylamine. In order to avoid the presence of free triethyl amine during product characterization, a suspension was made of the phosphonic acids in methanol. Then a large excess of triethyl amine was added and a white solid was obtained after evaporation of the volatiles. The triethylammonium salts were very soluble in D_2O and spectral data were easily collected confirming the structure of the parent diphosphonic acids.

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§ This can be easily observed by a 5 and 15 ppm drop of the ^{31}P chemical shifts.

From an atom efficiency point of view, the two step preparation of the free phosphonic acids via the corresponding ester is not favourable. Therefore, a straightforward one-pot synthesis was evaluated using tris(trimethylsilyl) phosphite as a nucleophile (P(OTMS)$_3$), which is known to show even slightly improved nucleophilicity compared to the corresponding dialkyl esters (DAPTMS).[201] The tandem 1,4-1,2-addition then should yield the corresponding bis(trimethylsilyl) phosphonates **230** which can then be hydrolyzed to the corresponding diphosphonic acids.
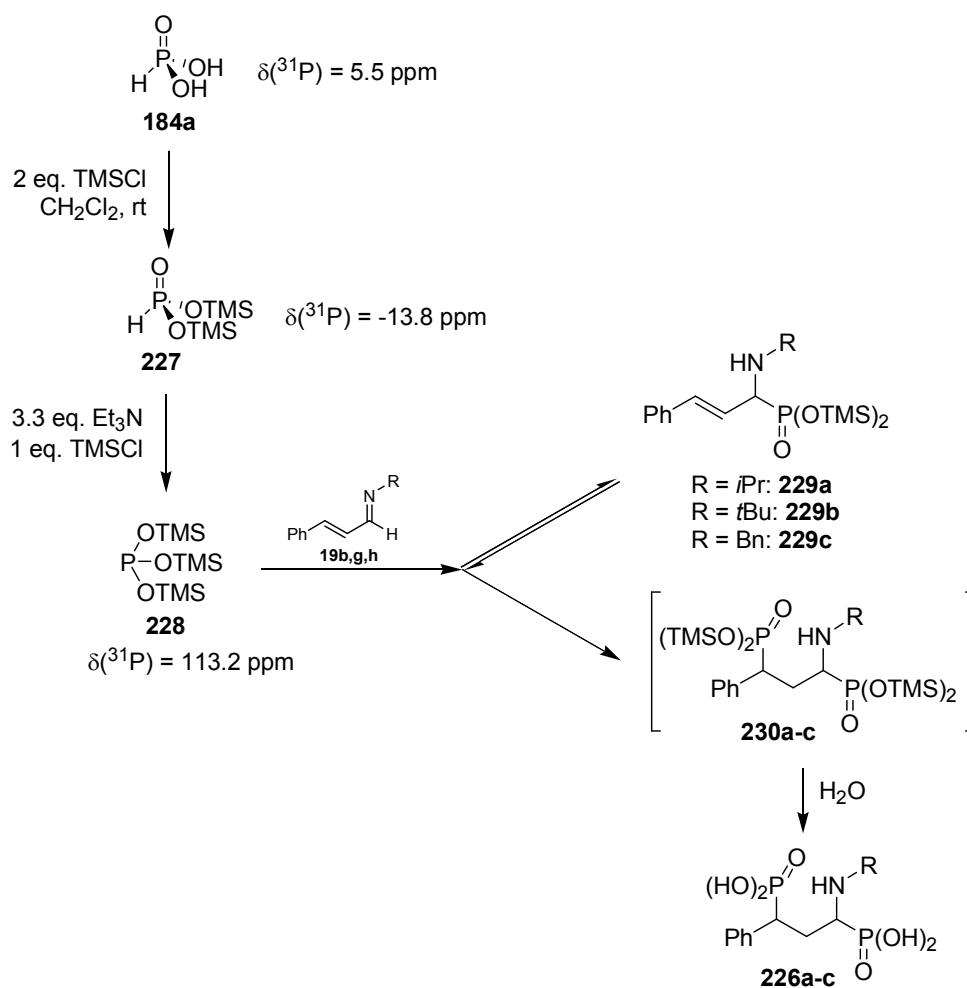
P(OTMS)$_3$ can be prepared starting from phosphoric acid **184a**. Addition of two equivalents of TMSCl smoothly results in the disilyl ester **227** and hydrochloric acid at room temperature in dichloromethane. In order to achieve complete conversion to the σ^{3}λ^3 phosphite **228**, the presence of a base is required to shift the tautomeric equilibrium. At least three equivalents of base have to be added together with the final equivalent of TMSCl in order to neutralize the liberated hydrochloric acid. The course of the reaction can be easily monitored using ^{31}P NMR. Removal of the

triethylammonium chloride salts by filtration resulted in too high degrees of hydrolysis. Therefore, the P(OTMS)$_3$ reagent was used *in situ* as a mixture with the ammonium salts.

The reaction of P(OTMS)$_3$ with imine **19h** in refluxing dichloromethane was monitored using ^{31}P NMR (Figure 8). A similar reaction course was found as can be seen in Figure 1 for the DEPTMS addition in the presence of Et$_3$NHCl. The 1,2-addition proceeds relatively fast, while the PAP is formed more slowly as the final product of the reaction. After 40 h, 1 equivalent of sulphuric acid was added which caused the reaction to speed up as could be expected. Finally, the salts were filtered of and the reaction solvent was replaced with methanol. Stirring was continued at room temperature and the free phosphonic acids precipitated during an overnight period. The use of methanol instead of water to perform the trimethylsilyl deprotection was justified because of the formation of silyl ethers that are more volatile and more easy to remove from the final reaction mixture than the corresponding silanols.
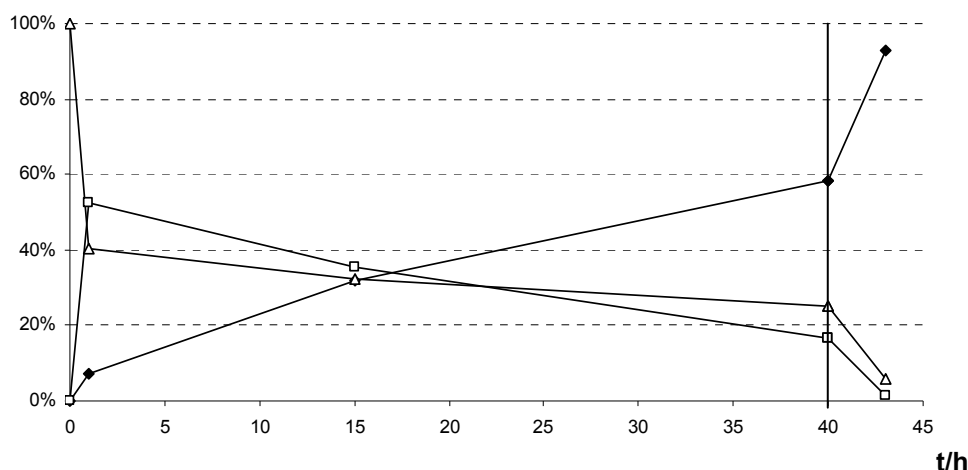
Figure 8: Course of the diphosphonylation reaction of imine **19h** (R = *t*Bu) with 2 equivalents of P(OTMS)$_3$ in the presence of HNEt$_3$Cl at 40°C. One equivalent of sulphuric acid H$^+$ was added after 40 h. PAP **230b** (◆); AP **229b** (□); P(OTMS)$_3$ **228** (Δ).

Then imines carrying other nitrogen substituents were evaluated. The same tendency in reactivity was found as with DAPTMS: more steric substituents speed up the PAP formation. Addition of sulphuric acid did result in an acceleration of the reaction, although not as enormous as was the case with DAPTMS. This may be due to the buffering capacities of the ammonium salts still present in the reaction mixture.

When sulphuric acid was added as a proton source, no precipitation occurred during the methanolysis of the silyl esters in several cases (or only in low yield). This might be contributed to the sulphate ions present in the reaction mixture, which may tend to form complexes with the PAP's preventing them to precipitate. Highly viscous, yellow oils were obtained after evaporation of the volatiles, which showed better solubility than the precipitated diphosphonic acids. Spectral data (including MS) indicated that both forms originate from the same product. Further research may be required to determine the exact properties of this kind of diphosphonic acids.
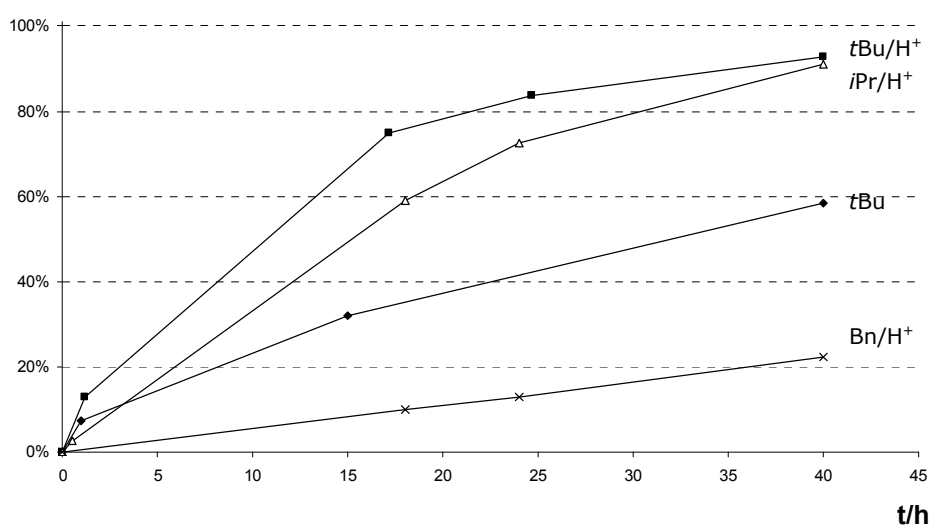
Figure 9: Course of the diphosphonylation reaction for different PAP's **226b** (R = *t*Bu (■)); **226a** (R = *i*Pr (Δ)); **226c** (R = Bn (×)) with 2 equivalents of P(OTMS)$_3$ in the presence of HNEt$_3$Cl and one equivalent of sulphuric acid at 40°C. The course of PAP **226b** (R = *t*Bu) without addition of sulphuric acid is added for reference purposes (◆).

1.3.6 Biological perspectives

The obtained diphosphonates can be of major importance because of their high similarity to glutamic acid. *(S)*-Glutamic acid (Glu) is the main excitatory neurotransmitter in the central nervous system (CNS) and operates through two main heterogeneous classes of receptors: ionotropic[225-227] (iGluR's) and metabotropic[228-231] (mGluR's) receptors. Both classes are further subdivided into several subclasses, but the number of functional receptors in the CNS is not known. Selective Glu agonists and antagonists are not only important for the characterization of different Glu receptor subtypes, but also for the treatment of CNS diseases[232] such as epilepsy, Huntington's disease, Parkinson's disease, dementia, chronic pain,...[233] Therefore, the Glu receptor field has been, and continues to be, in a state of almost explosive development.[234-236] A number of phosphonic acid Glu analogues is known as

potent selective Glu antagonists or agonists.[237] Substitution of the carboxylate group by a bioisosteric phosphonic acid group is known to increase the receptor selectivity.[233] For instance *(S)*-AP4 **231** is shown as a group III mGluR agonist, some 10-fold more potent than Glu.[238] *(S)*-AP5 **14** activates the same group III receptors, but with markedly lower potency and selectivity. *(R)*-AP5 **232** on the other hand does not interact detectively with mGluR's, but is a potent and selective competitive NMDA (iGluR) antagonist. Conformational restriction, such as in CPP **15**, is known to enhance selectivity.

(S)-AP4 (**231**)   *(R)*-CPP (**15**)   *(S)*-AP5 (**14**)

(R)-AP5 (**232**)   (**233**)
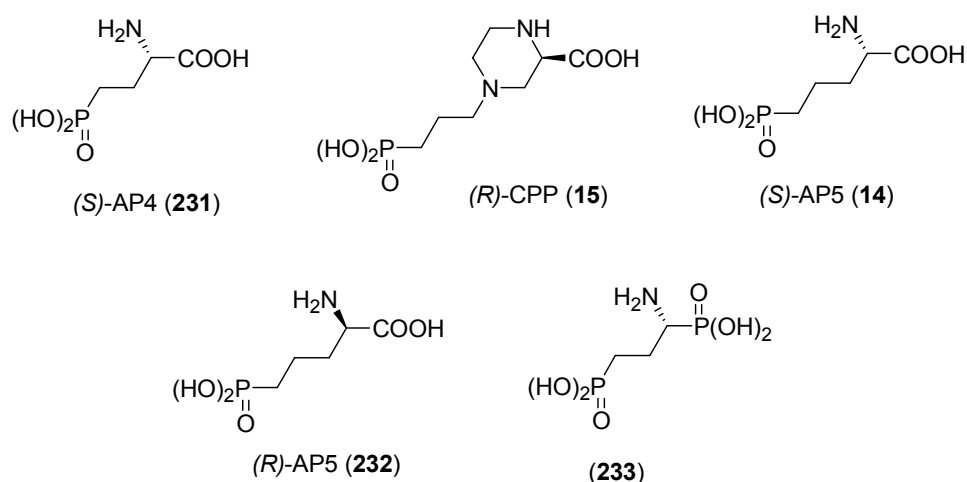
The diphosphonic acid analogue **233** ("PAP4") has been tested several times as a Glu-analogue without any activity so far.[239-243] However, further research into new bioisosteres has been indicated as a fruitful path to new subtype-selective mGluR ligands.

1.4   Direct phosphonylation of aldimines with dialkyl phosphites

The addition of dialkyl phosphites to imines, as presented by Fields[180] and Pudovik,[182] to give the corresponding α-aminoalkyl phosphonates, is an interesting reaction regarding straightforward methodology and the 100% atom efficiency. Furthermore, all expensive or toxic additives that are presented to improve the reaction yield (see chapter 3, section 1.1) are redundant. However, without additives, very high temperatures are necessary and the reaction is performed without solvent (or with a large excess of dialkyl phosphite as reagent and solvent) giving rise to highly viscous reaction mixtures and uncontrolled crystallization.[244-247] Furthermore, the reaction suffers from thermal breakdown of labile compounds.

However, while the reaction is very sluggish or non-specific in most solvents, good results were obtained when lower alcohols were used.[248] Even then, two equivalents of phosphite are necessary to get complete conversion in reasonable reaction times. Using these conditions, complete conversion is usually obtained after 2 to 3 hours of reflux. The resulting reaction mixture then consists of the desired α-aminoalkyl phosphonate and 1 equivalent of phosphite, which can be removed using a simple acid base extraction. HCl salts of some α-aminoalkyl phosphonates containing 2 phenyl rings are quite soluble in dichloromethane. Therefore, diethyl ether should be the solvent of choice for the acidic extraction step. The alcoholic solvent should be chosen in function of the phosphite ester, since some transesterification was observed at higher temperatures.
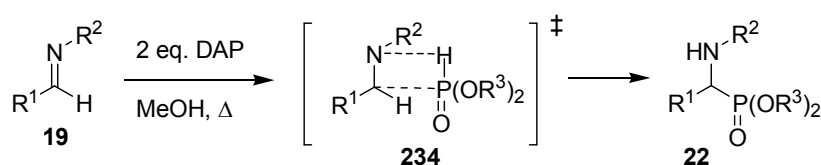
The methodology is applicable for a wide range of aldimines: aromatic and aliphatic, sterically hindered, electron poor and electron rich imines all react with the phosphite with comparable ease and yield (Table 7). Ketimines, neither hydrazones nor aldehydes showed any reaction under the same conditions. α,β-Unsaturated imines are an interesting special case in the light of the results presented in chapter 3, section 1.3. In all cases, exclusive 1,2-addition of dialkyl phosphites is observed. Several reaction mechanisms have already been presented for the formation of α-aminoalkyl phosphonates.[249] From our experiences, the reaction mechanism proposed by Sobanov and coworkers[250] is most likely. This mechanism involves H-bridge type interaction between the nitrogen atom and the phosphite proton. The transition state is presented as a four membered ring complex which finally

yields the α-aminoalkyl phosphonate through reorganisation of bonds. This kind of interactions should be more favoured in protic solvents.

Table 7: Synthesis of α-aminoalkyl phosphonates **22**

Nr	R^1	R^2	R^3	Yield(%)[#]
22b	CH=CHPh	Bn	Me	96
22c	CH=CHPh	Bn	Et	95
22d	CH=CHPh	PMB	Me	86
22e	CH=CHPh	Allyl	Me	95
22f	CH=CHPh	$CH_2C(CH_3)=CH_2$	Me	74
22h	CH=CHPh	iPr	Me	94
22i	CH=CHPh	iPr	Et	95
22j	CH=CHPh	tBu	Me	97
22k	CH=CHPh	tBu	Et	93
22l	CMe=CHPh	Allyl	Me	90
22m	C(isoamyl)=CHPh	Allyl	Me	88
22n	CCl=CHPh	Allyl	Me	54
22o	CHPh=CHMe	Allyl	Me	86
22p	CHBn=CHMe	Allyl	Me	29[§]
22q	$CH[(CH_2)_2Ph]=CHMe$	Allyl	Me	44[§]
22r	CH=CH(o-NO$_2$Ph)	Bn	Me	77[¤]
22s	CH=CH(o-NO$_2$Ph)	$CH_2C\equiv CH$	Me	58
22u	(structure)	Bn	Et	88
22v	(structure)	Allyl	Me	85
22w	(structure)	iPr	Me	39
22x	(structure)	tBu	Me	60
22y	Furyl	Bn	Me	89
22z	Furyl	Allyl	Me	89
22ab	Furyl	tBu	Me	63
22ac	Ph	Bn	Me	89
22ad	Ph	iPr	Me	94
22ae	Ph	iPr	Et	84
22af	cHex	iPr	Me	93
22ag	iPr	Bn	Me	84
22ah	iPr	iPr	Me	86

[#] Yield determined after acid/base extraction.

[§] Yield starting from the aldehyde

[¤] Isolated as the hydrochloride salt

It should be noted that no explicit nucleophilic attack of the phosphite occurs to the imine. This may explain the excellent results using a "poor" nucleophile. The absence of 1,4-adducts in the case of α,β-unsaturated imines indeed supports the four membered ring complex. In the case of a "real" nucleophilic attack of the dialkyl phosphite through its $\sigma^3\lambda^3$ tautomer, 1,4-addition should be at least a competing reaction as it is the case with similar trialkyl and dialkyl trimethylsilyl phosphites.

In conclusion an excellent high yielding, straigthforward, very mild and economic reaction pathway is presented here towards α-aminoalkyl phosphonates starting from aldimines. The exclusive 1,2-addition of dialkyl phosphites to α,β-unsaturated imines supports the mechanism involving a four-membered ring complex as a transition state. Furthermore, performing the reaction in a non-corrosive solvent makes it very well suitable for medium scale continuous production using a microreactor system.[248]

The obtained dialkyl α-aminoalkyl phosphonates **22** can be converted to the corresponding monoalkyl phosphonates **237**, which might be of interest in view of their bioavailability to living cells. Monodealkylation can be obtained using base mediated hydrolysis from the corresponding dialkyl phosphonates only under drastic experimental conditions. Potassium trimethylsilanolate (KOTMS), however, has been recently presented to afford the desired monoalkyl phosphonates with high purity and yield in anhydrous THF, diethyl ether or dichloromethane.[251] KOTMS is a common equivalent of hydroxide anion.[252] However, it has two unique advantages over hydroxide anion: (i) it has appreciable solubility in organic solvents and (ii) the oxygen silicon bond can be very often easily cleaved under mild reaction conditions.

When aminoalkyl phosphonate **22ad** was treated with 1.5 equivalent of KOTMS in anhydrous ether, the corresponding mono potassium salts **237a** precipitated after 1 h at room temperature and were easily isolated by filtration. Phosphonates **22af,z** required two days at room temperature before precipitation occurred. The selective monodealkylation can be explained by a nucleophilic attack of the silanolate anion onto the phosphonate group. A pentacoordinated intermediate **235** is formed, which returns to the more stable $\sigma^4\lambda^5$ phosphonate **236** form by elimination of methoxide. Methoxide subsequently attacks the silicon atom and the resulting methoxysilane is removed during filtration and evaporation. A second nucleophilic attack is disfavoured because of the presence of a net negative charge on the phosphonate group. It should be noted that the central, tetrahedral phosphorus atom in **237** is surrounded by four different substituents, causing it to be chiral. However, no diastereomers were observed using NMR

which can probably be explained by the existence of a mesomeric equilibrium distributing the negative charge equally over both oxygen atoms.

237a R^1 = Ph, R^2 = iPr (95%)
237b R^1 = cHex, R^2 = iPr (98%)
237c R^1 = Furyl, R^2 = allyl (63%)
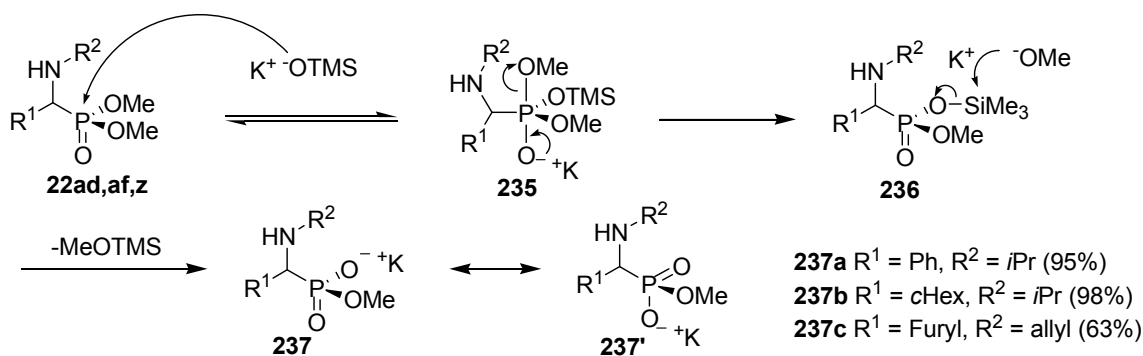
1.5 Conclusion

Because of the biological potential of α-aminoalkyl phosphonates and phosphonic acids, numerous preparation methods have been presented in literature during the last six decades involving additions of phosphorus nucleophiles to imines or three component reactions of an aldehyde or ketone, an amine and a phosphorus nucleophile. Nevertheless, not a single research group has properly addressed the regioselectivity related to the use of α,β-unsaturated imines.

Tricoordinated phosphites, such as dialkyl trimethylsilyl phosphites or trialkyl phosphites, initially react with α,β-unsaturated imines in a 1,4-fashion. However, the resulting enamine easily undergoes tautomerization yielding a β-phosphono imine, which is again susceptible to 1,2-addition by the phosphite. The results from this research reveal that the phosphite nucleophiles do not show an absolute preference to 1,4-addition. Therefore, the β-phosphono imine is further processed to the double addition product. The complex spectra of the obtained PAP's combined with the distinct properties of both phosphite reagents have caused researchers to fail to observe this particular reactivity. These special properties of DAPTMS and TAP have been discussed in chapter 3, section 1.3.3 and 1.3.4.

DAPTMS has a high tendency towards 1,2-addition to imines because of coordination between the nitrogen and the silicon atom. This caused the 1,4-addition to proceed much slower than the 1,2-addition and explains why DAPTMS was reported earlier to perform the addition with complete 1,2-regioselectivity. However, although kinetically favoured, 1,2-addition of DAPTMS is reversible causing the 1,2-adduct to disappear again from the reaction mixture in favour of the 1,4-adduct, even when only one equivalent is used. This was expressed in the initially reported results by the decreasing

yields when the bulk of the nitrogen substituents was increased. Furthermore, neither 1,2-adition, nor 1,4-addition occurs at all in the absence of protons.

TAP on the other hand shows a high tendency towards 1,4-addition to imines, probably because of the softness and steric bulk of the nucleophile. The enamine and β-phosphono imine are easily formed but the 1,2-addition is slowed down. This caused Teulade and Savignac[215] to report exclusive 1,4-addition of TAP to *t*Bu-imines, while imines with less sterically demanding nitrogen substituents probably gave mixtures of "unidentifiable" products.

Dialkyl phosphite, finally, has been reported as a poor nucleophile, requiring some type of activation in order to perform nucleophilic additions. DAP was reported to add to imines only under harsh conditions using no solvent and high temperatures. This may not be suitable for labile products and may cause difficulties regarding mixing of the reaction and isolation of the end products. This was easily overcome in this research by performing the reaction in a protic solvent (alcohols) with 2 equivalents of DAP. Imines smoothly react with DAP under these conditions at moderate temperatures. The products are conveniently isolated by acid/base extraction, which allows large scale preparations. Furthermore, complete 1,2-regioselectivity can be observed in case of α,β-unsaturated imines, indicating that a third mechanism is operating during the reaction: a four membered transition state complex is formed through *H*-bridge type interactions yielding exclusively the 1,2-addition products through reorganization of bounds.

In conclusion, a new light has been thrown on the phosphite additions to imines. Large differences have been established between three types of phosphorus nucleophiles. Furthermore, also the reaction conditions are critical for the final result of the reaction. Nevertheless, 1,2-, 1,4- and 1,2/1,4-adducts are accessible using the methods developed in this section.

2   Synthesis of 4-phosphono β-lactams

2.1   Introduction

Since the advent of the antibiotic era with sulfonamides in the 1930's, medical science has witnessed the successful therapeutic application of numerous classes of antibiotics, targeting different units of the bacterial cell (Figure 10). From these classes, compounds targeting the bacterial cell wall are of special interest. The bacterial cell wall is a macromolecular structure consisting of peptidoglycan that is essential to all bacteria and has general functional and structural features that are highly conserved across multiple pathogens. Most importantly, it is not present in mammalian cells and therefore, antibiotics targeting the bacterial cell wall have a low incidence of mechanism-based toxicity.[253]
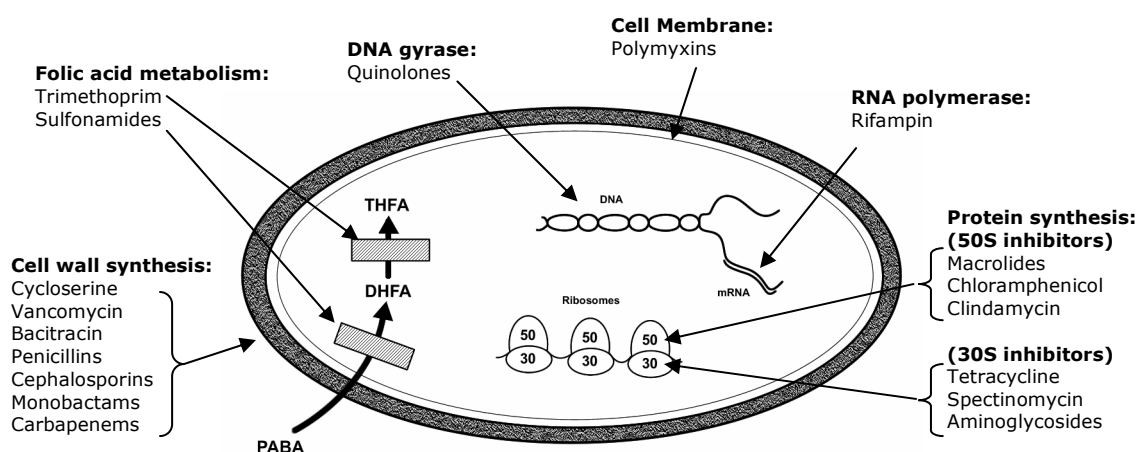

Figure 10: Sites of action of various antimicrobial agents (adaptation from ref. 254). PABA, *p*-aminobenzoic acid; DHFA, dihydrofolic acid; THFA, tetrahydrofolic acid.

Peptidoglycan consists of linear glycan chains of alternating *N*-acetylglucosamine and *N*-acetylmuramic acid units connected by $\beta(1\rightarrow4)$ linkages. These chains are interlinked by short peptides (transpeptidation) to form a rigid, polymeric material, which main functions are to preserve cell integrity by withstanding the internal osmotic pressure, to maintain a well defined cell shape and to participate in the cell division process.[255] A group of enzymes that belong to a protein family collectively known as *"penicillin binding proteins (PBP)"* are responsible for the transpeptidation reaction. PBP transpeptidases bind to the D-Ala-D-Ala residues of a 'donor' peptidoglycan strand and the terminal D-Ala residue is cut off. An acyl-enzyme intermediate is formed between the carbonyl of the penultimate D-Ala and an active site serine of the PBP, which reacts with the amine of an 'acceptor'

peptidoglycan strand to form a cross-link between the strands. PBP carboxypeptidases on the other hand moderate the degree of cross-linking by removing the terminal D-Ala of the peptidoglycan, hence preempting the possibility of cross-linking.[256]

The activity of β-lactams drugs such as penicillin and cephalosporin, comes from their ability to mimic the D-Ala-D-Ala moiety of peptidoglycan. When the PBP-enzymes are submitted to these substrate mimetics, the initial acylation reaction remains enabled (with opening of the β-lactam), but the capacity for deacylation is abolished causing the enzyme to fail to complete its catalytic cycle.[257] The loss of these enzymatic activities yields a cell wall unable to withstand osmotic forces. Bacteriolysis is accelerated by the action of autolysins destroying the existing cell wall.[258]

Penicillin (238)
"Penam"
(1929)

Cephalosporin (239)
"Cephem"
(1945)
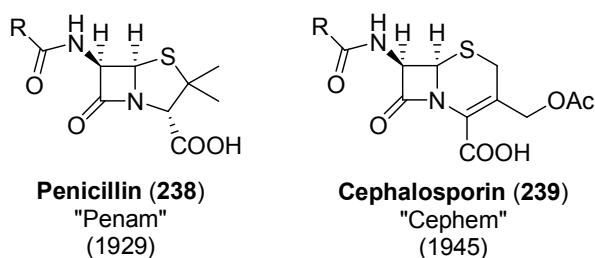
The introduction of antibiotics helped drop the death rates from infectuous diseases from 797 per hundred thousand in 1900 to 36 per hundred thousand in 1980, a 20-fold improvement.[259] However, antibiotics select for those very rare bacteria in a population that are less susceptible and allow them to become dominant in the population as susceptible bacteria die off. This process has already resulted in some fully resistant pathogens.[254,260] β-Lactams in particular have been exposed to serious resistance problems. For example, clinically significant antibiotic resistance to penicillin V has ensued from introduction into human therapeutic use after only one year.[259] The underlying mechanisms of this resistance are (i) alterations (mutations) in the PBP transpeptidases, (ii) the occurrence of β-lactam hydrolytic deactivating enzymes (β-lactamases), (iii) reduced permeability of the antibiotics (because of porin deficiency in the outer membrane of Gram negative organisms or modification of the cell wall) and (iv) acquisition and activation of efflux exporter proteins.[257,261]

Of these resistance mechanisms, the occurrence of β-lactamases is clinically the most important. These enzymes have in common with the PBP's to undergo acylation at an active site serine by β-lactam antibiotics. However, in β-lactamases the acyl-enzyme complex is easily hydrolysed, regenerating the active enzyme together with the ring-opened inactive antibiotic. The number of known β-lactamase enzymes is currently approaching 500.[262] They are

subdivided into 4 classes: class A, C and D are constituted active site serine enzymes and class B consists of Zn^{2+} requiring enzymes.[257,261,263] Intriguingly, class A and C β-lactamases are believed to have evolved from the PBP's by acquiring a catalytic hydrolytic step and reduced peptidoglycan recognition.[264-266]

Two main therapeutic strategies have been adopted to counteract bacterial resistance to β-lactam antibiotics. One involves the design of new antibiotics which are not susceptible to β-lactamase catalysed hydrolysis. The other is to use an inhibitor of the β-lactamase together with a normal β-lactam antibiotic.

An historic overview of the development of new β-lactam antibiotics can be found in many review articles.[258,267] Initially, new antibiotic derivaties were obtained by altering the side chains present on the bicyclic β-lactam core in penicillin or cephalosporin. This resulted in enhanced or broadend activity and improved pharmakinetic properties. However, it was only with the introduction of the methoxy group directly on the four membered azetidinone ring in Temocillin **240** that an important break-through was achieved in terms of β-lactamase stability.

Next to side chain and substitution pattern alteration, also structural modifications to the bicyclic cephem and penam unit have been made. The oxacephem Latamoxef **241** is very active against Gram-negative aerobes and anaerobes. Carbapenems (e.g. imipenem **242**) on the other hand have the broadest spectrum of activity of all β-lactam antibiotics and great β-lactamase stability (resulting from the *trans*-configured 6-hydroxyethyl group).[268-270]

240 (Temocillin)
"Penam"

241 (Latamoxef)
"Oxacephem"

242 (Imipenem)
"Carbapenem"
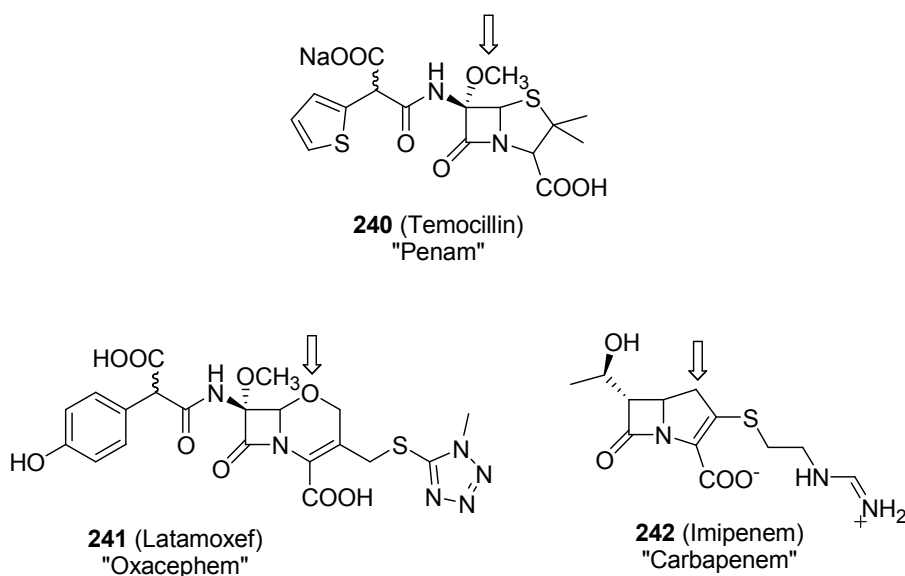
Also certain monocyclic β-lactams have been found to possess excellent antibiotic activities. The first members of this class were nocardicins, which however do not have any clinical importance.[271,272] The only clinical used monocyclic β-lactam is Azthreonam, which is a semisynthetic member of the monobactam family. Monobactams (or Sulfazecines as they were called in early publications) were isolated in 1981 by two research groups independently from bacterial media and are characterized by a sulfonic acid substituent on nitrogen.[273,274]

243 (Nocardicin A)

244a (R = H)
244b (R = Me)

245 (Sulfazecin)

246 (Azthreonam)
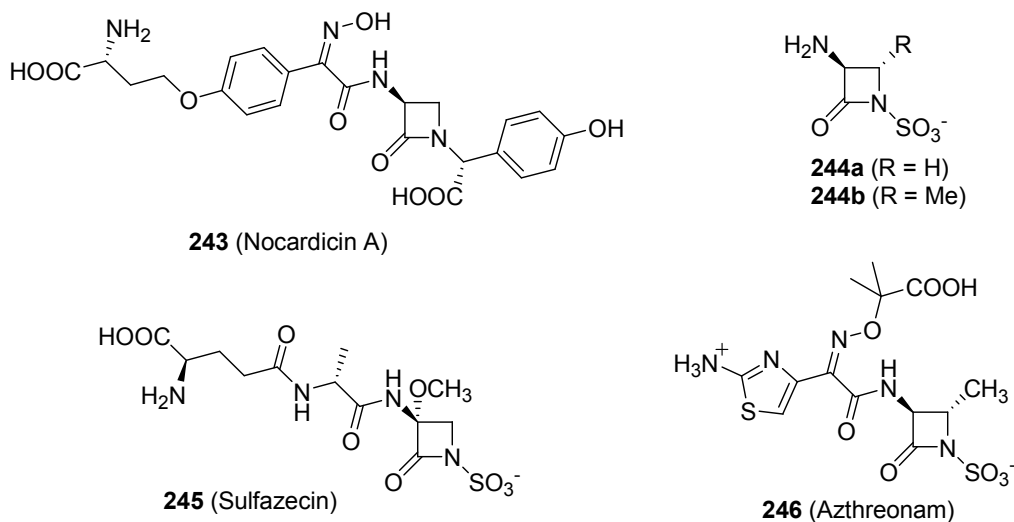
However, isolation from fermentation broths was not a valuable technique, since mixtures of monobactams were obtained. In order to improve the activity against Gram-negative bacteria, (semi)synthetic pathways to the 3-monobactam building block **244a** were developed from natural penam[275] and cephem[276,277] nuclei. The total synthesis starting from threonin presented by the Squibb group[278] led to the 3-amino 4-methyl sulfonylated azetidinone building block **244b**, which was the basis for further functionalization to Azthreonam **246**. Because of the 4-methyl substituent, it is highly resistent to β-lactamases.[279] Furthermore, it shows low toxicity and excellent pharmacologic properties.

Further structural modification of the monobactam core as a lead structure resulted in other classes of antibacterial monocyclic β-lactams such as *N*-sulphato lactams, *N*-phosphato lactams, phosphams and oxamazins.[267,280,281] Phosphams, carrying a monoalkyl phosphonate group on the nitrogen atom, offer increased β-lactamase stability at the expense of lower antibacterial activity.[279,282] Recent research has shown that monocyclic β-lactams, which do not show the typical anionic center, can possess potent antibacterial activity, indicating that the mechanism of action for these lactams is totally different from all previous classes. Examples are *N*-thiolated 2-azetidinones,[283,284] *N*-aryl 3,3-dichloro-4-aryl-2-azetidinones,[285] *N*-aryl 3,3-

diphenyl-4-aryl-2-azetidinones[286] and *N*-thiazolyl 3-chloro-4-aryl-2-azetidinones.[287] Although the perceived failure of new technologies to create another golden era of new antibacterial classes has led many large pharmaceutical companies to prioritise other areas of research,[288,289] continuing efforts towards old and new targets[290-292] have resulted in several antibacterial agents currently at or beyond phase 1 clinical trials (e.g. 2 carbapenems and 3 cephalosporins).[280,293,294]

As already mentioned, a second strategy to counteract bacterial resistance to β-lactam antibiotics through the action of β-lactamases, is the development of β-lactamase inhibitors.[295] These compounds may not show antibacterial activity on themselves, but are used in preparates with (older) β-lactam antibiotics to ensure their proper functioning. Two clinical important groups are clavulanic acid **247** and the penicillanic acid sulphones (sulbactam **248** and tazobactam **249**).[258,296] Also monocyclic β-lactams have been found with good inhibitory activity towards β-lactamases.[297]
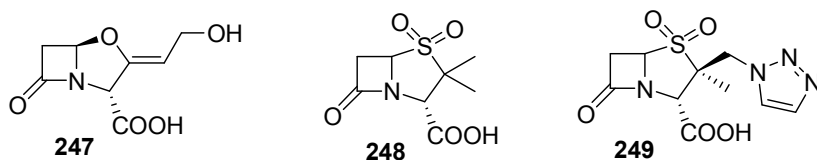

Phosphonates have been studied as potential transition state analog inhibitors of β-lactamases. Acyclic phosphonate monoesters **250** are inhibitors of class C and A β-lactamases with increasing activity correlated to the leaving group capacity of the phenol group. The mechanism is based on phosphorylation of the active site serine residue.[298-301] Also phosphonamidates **251** which bear a simple resemblance to penicillin type structures have been found active as active site phosphorylation agents in class C β-lactamases.[302] Their activity is pH dependent as the nitrogen atom has to be protonated in order to become a good leaving group. Their mechanism for phosphyl group transfer involves a pentacoordinate intermediate with trigonal bipyramidal geometry. The difference between class A and C can be found in the amino acids that are participating in the proton transfer steps. As a consequence of this difference, the deacylation of the enzyme is the rate determining step in class C β-lactamases.

The mechanism based inactivators which have been used against the serine enzymes are generally ineffective against this class of enzymes. Class B lactamases are inhibited by several thiol derivatives because of their ability to coordinate at the zinc active site.[262,303]

pH independent:

250a (X = COO⁻, Y = H)
250b (X = H, Y = NO₂)

pH dependent

**251**   **252**   **253**   **254**
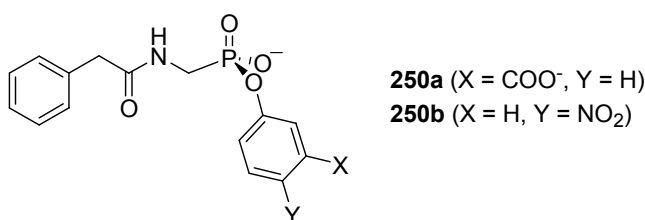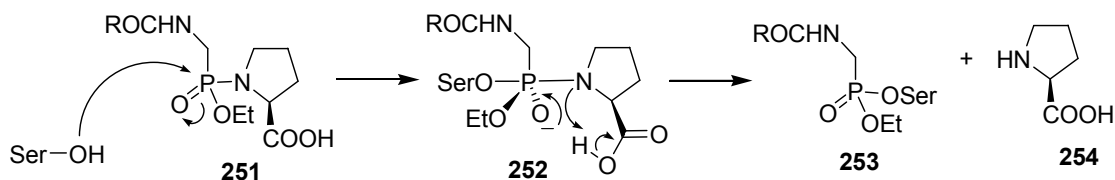
In recent years, β-lactam compounds have also found utility as inhibitors of other 'serine' enzymes and, in particular the family of serine proteases. These enzymes are involved in numerous important physiological processes including protein tunrover, digestion, blood coagulation, wound healing,... Therefore, protease inhibitors have considerable potential utitlity for therapeutic intervention in a variety of disease states such as cancer, viral infections, inflammation, Alzheimer's disease, etc...[304] Inhibition of these enzymes by β-lactams is also believed to originate from the inability of the acyl-enzyme complexes, formed by nucleophilic attack of the active site serine residue on the β-lactam ring, to undergo efficient deacylation. For this reason, several compounds that were known as β-lactamase inhibitors, were also found to inhibit certain serine proteases.[305,306]

Also monocyclic azetidinones are suitbale serine protease inhibitors, provided that they are adequately functionalized with substituents raising specific enzyme recognition and chemical activation towards nucleophilic attack. Monocyclic azetidinones have been found that inhibit elastase (HLE and PPE),[307-309] HCMV protease,[310-312] thrombin[313] and human chymase.[314] Irreversible acylation of the enzyme is often obtained by having leaving groups in the 3-, 4- or 1-position of the 4-membered ring or by activating a second functional group through ring-opening of the β-lactam that can react with another amino acid residue in the active center of the enzyme (the so-called *double hit* or *suicide mechanism*).[307,315]

The widespread biological potential of the azetidinone ring has stimulated a tremendous amount of investigations, including the development of synthetic pathways to basic azetidinone skeletons.[45] However, only a limited number of synthetic patways towards phosphono β-lactams have been presented in literature so far (see chapter 2, section 1). [2+2] Cycloadition between a

ketene and an imine, which is probably the most exploited reaction in the stereospecific synthesis of β-lactams, has not proven useful yet in the synthesis of phosphonylated lactams. While the formation of the β-lactam ring via C^3-C^4 ring closure is less well known, it represents however a valuable alternative for the synthesis of 4-phosphono lactams **23**. *N*-chloroacetyl 1-aminoalkyl phosphonates **21** would be appropriate substrates for ring closure via an intramolecular alkylation reaction of a phosphorus stabilized anion. These *N*-chloroacetyl 1-aminoalkyl phosphonates **21** can be prepared via two related pathways: (i) acylation of a suitable 1-aminoalkyl phosphonate **22**, or (ii) one-pot phosphonylation of an *in situ* generated *N*-acyliminium ion **20**.
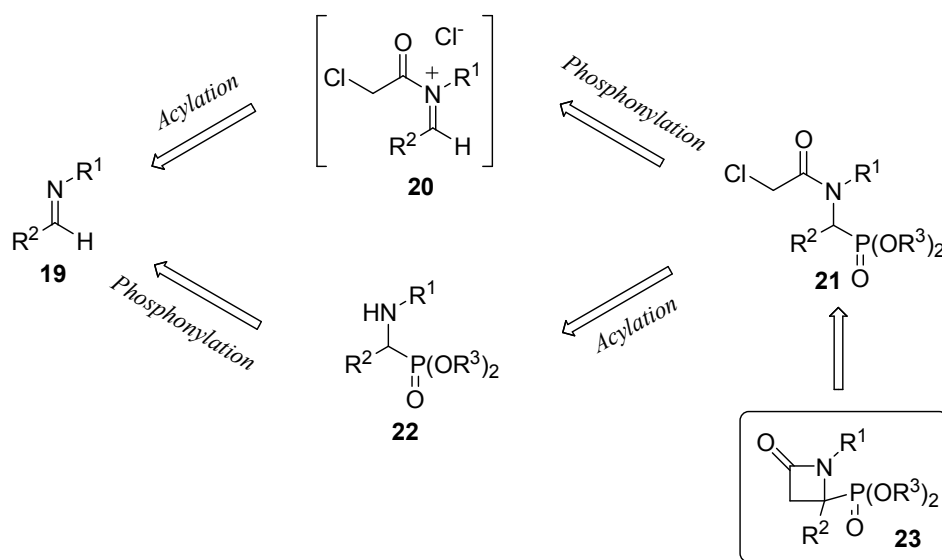
2.2 Preparation of *N*-chloroacetyl 1-aminoalkyl phosphonates

2.2.1 Acylation of 1-aminoalkyl phosphonates

Acylation of the 1-aminoalkyl phosphonates obtained in chapter 3, section 1.4 can be performed using acid chlorides. THF was selected as the best solvent after some initial experiments. The reactivity of the 1-aminoalkyl phosphonates was strongly dependent on the substrate properties. 1-Furyl methyl phosphonates reacted violently with the acid chloride simply using triethyl amine to scavenge the liberated hydrochloric acid (Table 8, entry 1-2). Complete conversion took place in typically 30 minutes at room temperature. When 1-(2-phenylethenyl) phosphonates were used as substrates, an excess of pyridine relative to the acid chloride (entry 9 vs. 11) was required as a nucleophilic catalyst in order to obtain a clean and complete conversion to the acylated products after stirring the reaction mixture for 2 h at room temperature (entry 9-16). The excess of acid chloride is easily removed by washing the reaction mixture with a saturated $NaHCO_{3(aq)}$ solution, while pyridine and any residual starting material were removed by subsequent washing with 0.5 M $HCl_{(aq)}$.
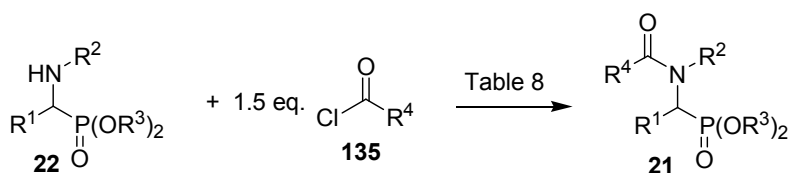
With 1-phenyl or 1-alkyl methylphosphonates, acylation proceeded sluggishly producing many side products (entry 20-27). The strongest acylation conditions proved to be refluxing in THF using pyridine as a base and 0.2 equivalent of DMAP as a nucleophilic catalyst. Nevertheless, in many cases, the desired products could not even be obtained in satisfying purity after column chromatography. Furthermore, substrates with bulky nitrogen substituents (*t*Bu) or sterically hindered acid chlorides (e.g. pivaloyl chloride) failed to react in all cases. Also PAP's **196** have been used as a substrate in the acylation reaction, although without any success. Regardless of their use as a precursor of 4-phosphono β-lactams, related *N*-chloroacetyl 1-aminoalkyl phosphonates may also have some biological significance. *N*-acylated 1-aminoalkyl phosphonates are known to be well transported through biological membranes.[316]

Table 8: Acylation of 1-aminoalkyl phosphonates

| Entry	R^1	R^2	R^3	R^4	Product	Conditions	Result
1	Furyl	Allyl	Et	CH$_2$Cl	**21j**	1.5 eq. Et$_3$N, CH$_2$Cl$_2$, 30 min., rt	99%
2	Furyl	Allyl	Me	CH$_2$Cl	**21i**	1.5 eq. Et$_3$N, CH$_2$Cl$_2$, 30 min., rt	99%
3	Furyl	Allyl	Me	tBu		1.5 eq. Et$_3$N, CH$_2$Cl$_2$, 30 min., rt	¤
4	Furyl	Allyl	Et	tBu		1.5 eq. pyridine, CH$_2$Cl$_2$, 24 h, Δ	¤
5	Furyl	Allyl	Me	tBu		2 eq. pyridine, 0.2 eq. DMAP, THF, rt., 24 h	¤
6	Furyl	Bn	Me	CH$_2$Cl	**21h**	2 eq. pyridine, THF, 1 h, rt	99%
7	Furyl	Bn	Me	(CH$_2$)$_3$Cl	**25c**	2 eq. pyridine, THF, 1.5 h, rt	92%
8	Furyl	tBu	Me	CH$_2$Cl		2 eq. pyridine, 0.2 eq. DMAP, THF, rt., 24 h	¤
9	PhCH=CH	Allyl	Me	CH$_2$Cl	**21e**	1.5 eq. pyridine, THF, 1 h, rt	30%
10	PhCH=CH	Allyl	Me	(CH$_2$)$_3$Cl	**25b**	1.5 eq. pyridine, THF, 1 h, rt	71%
11	PhCH=CH	Allyl	Me	CH$_2$Cl	**21e**	2 eq. pyridine, THF, 1 h, rt	96%
12	PhCH=CH	Allyl	Me	(CH$_2$)$_3$Cl	**25b**	2 eq. pyridine, THF, 1 h, rt	98%
13	PhCH=CH	Allyl	Me	CH$_3$	**255a**	2 eq. pyridine, 0.2 eq. DMAP, THF, 1 h, rt, 1 h, Δ	78%
14	PhCH=CH	Bn	Me	CH$_2$Cl	**21b**	2 eq. pyridine, THF, 1 h, rt	97%
15	PhCH=CH	PMB	Me	CH$_2$Cl	**21d**	2 eq. pyridine, THF, 3 h, rt	91%
16	PhCH=CH	iPr	Me	CH$_2$Cl	**21f**	2 eq. pyridine, THF, 1 h, rt	97%
17	PhCH=CH	tBu	Me	CH$_2$Cl		2 eq. pyridine, 0.2 eq. DMAP, THF, 1 h, rt	¤
18	o-NO$_2$PhCh=CH	iPr	Me	CH$_2$Cl		2 eq. pyridine, 0.2 eq. DMAP, THF, 1 h, rt	¤
19	MeCH=CH	tBu	Me	CH$_2$Cl		2 eq. pyridine, THF, 2 h, rt	¤
20	Ph	iPr	Me	CH$_2$Cl	**21l**	2 eq. pyridine, THF, 2 h, rt	64%[#]
21	Ph	iPr	Me	(CH$_2$)$_3$Cl	**25e**	2 eq. pyridine, THF, 2 h, rt	33%[#]
22	Ph	iPr	Me	CH$_2$Cl	**21m**	1.5 eq. pyridine, 0.2 eq. DMAP, 2 h, rt.	70%[#]
23	Ph	iPr	Me	CH$_2$Cl		1.5 eq. Et$_3$N, 1.5 eq. Me$_3$N.HCl, THF, 19 h, rt	¤
24	cHex	iPr	Me	CH$_2$Cl	**21n**	2 eq. pyridine, THF, 2 h, rt	68%[#]
25	cHex	iPr	Me	CH$_2$Cl		2 eq. pyridine, THF, 2 h, Δ	¤
26	iPr	iPr	Me	CH$_2$Cl	**21o**	2 eq. pyridine, THF, 14 h, rt	40%[#]
27	iPr	Bn	Me	CH$_2$Cl		2 eq. pyridine, 0.2 eq. DMAP, THF, 5 h, rt	¤

[#] Containing unidentifiable side products

¤ Complex mixture

### 2.2.2 One-pot phosphonylation of *N*-acyliminium ions

N-acyliminium ions **20** are well known to have highly versatile reaction characteristics, which is reflected in an impressive number of synthetic applications.[317,318] Being related to the Mannich reagents **259**, their imino carbon atom is even more electron-poor because of the presence of an electron withdrawing carbonyl group. Due to this strongly electrophilic nature, they are readily attacked by nucleophiles, e.g. phosphorus nucleophiles, which has been extensively exemplified for the synthesis of azaheterocyclic phosphonates in chapter 2. Because of their limited stability and high reactivity, acyliminium ions are almost always generated *in situ*. *N*-acyliminium ions can be generated for instance by heterolysis of amides bearing a leaving group on the α-carbon (see chapter 2, sections 1.2 and 2.2 for relevant examples), by oxidation of amides or by *N*-acylation of imines.
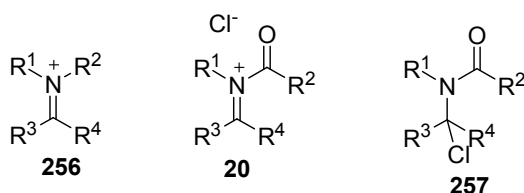
When an aromatic imine **19** was treated with 1.1 equivalent of chloroacetyl chloride in toluene at –40°C, acyliminium salt **20** was formed.[46,47] The structure of this species is often presented as **257** in which a covalent bond exists between the chlorine and the imine carbon atom. Due to their hydroscopic nature, the acyliminium intermediates **20** could not be isolated from the reaction mixture for structural characterization. Nevertheless, the reaction can be followed visually by the precipitation of the salts in toluene, which clearly points to the ionic nature of these species. It should be noted that from both proposed structures **20** and **257** the same reactivity can be expected and therefore, the acyliminium adducts will be presented in their ionic form in the rest of this manuscript.

Reaction of the acyliminium intermediates **20** with 1.1 equivalent of trialkyl phosphite was then evaluated. Trialkyl phosphites were selected in this case because of their enhanced nucleophilic properties compared to dialkyl phosphites and because of the possibility of dealkylation of the intermediate phosphonium adducts **258** by chloride ions present in the reaction medium. High temperatures are normally required for this Arbuzov type dealkylation reaction and alkyl halides are deliberated from the reaction mixture. The *N*-chloroacetyl aminoalkyl phosphonates **21** should then be obtained after simply evaporating the solvent (Table 9).

Table 9: Initial results for the one-pot synthesis of *N*-chloroacetyl aminoalkyl phosphonates **21**.
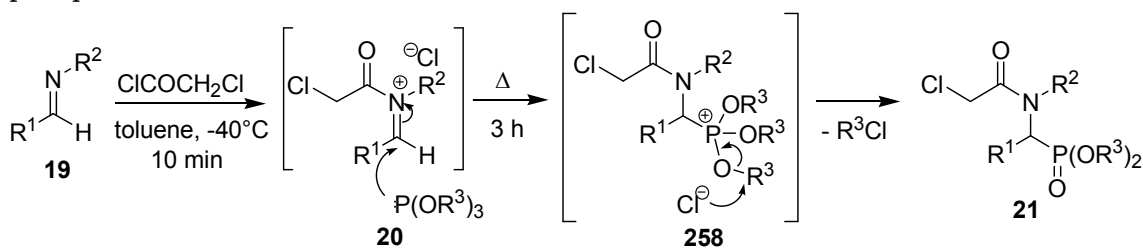
SM	R^1	R^2	R^3	Product	Yield 21 (%)§
19b	Phenylethenyl	Bn	Et	**21c**	26
19b	Phenylethenyl	Bn	Me	**21b**	35
19z	Furyl	Bn	Me	**21h**	32
19y	Furyl	Ph	Me	**21g**	24

§ Yield determined after column chromatography

However, using these very convenient reaction conditions, the *N*-chloroacetyl aminoalkyl phosphonates **21** could be only obtained in satisfying purity after column chromatography. The best results were obtained with trimethyl and triethyl phosphite, while triisopropyl phosphite is probably to steric for the addition reaction. Yields were generally low due to the formation of a major side product which was easily observed in ^{31}P NMR spectra as two doublets (dimethyl ester: δ = 10.1 and –3.9 ppm, J_{PP} = 25.5 Hz; diethyl ester: δ = 7.3 and -6.3 ppm, J_{PP} = 26.7 Hz). However, this side product was never recovered during column chromatographic purifications. The occurrence of two doublets in ^{31}P NMR implicated the presence of two phosphorus atoms in one molecule, which was finally identified as 1-phosphono vinyl phosphate **259**. To confirm the proposed structure **259**, it was synthesized according to a literature procedure from chloroacetyl chloride and trialkyl phosphite.[319] The mechanism of this reaction involves a Perkow and an Arbuzov type reaction.

259a (R = Me; 63%)
259b (R = Et; 55%)
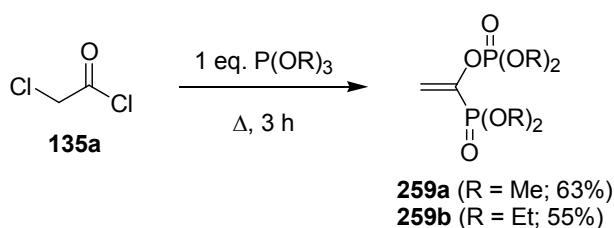
The side product can thus be generated from unreacted chloroacetyl chloride present in the reaction medium and trialkyl phosphite. However, the same side product **259** was found when only 1.0 equivalent of chloroacetyl chloride was used or when a small amount of iminium salt **20** is separated from the reaction medium through filtration under an inert atmosphere and treated with the trialkyl phosphite. Therefore, vinyl phosphate **259** is probably formed via two concurrent pathways to give the same intermediate **260**: non-

regiospecific attack of the phosphite on the carbonyl group of the acyliminium ion (pathway B) or reaction with unreacted chloroacetyl chloride (pathway C).
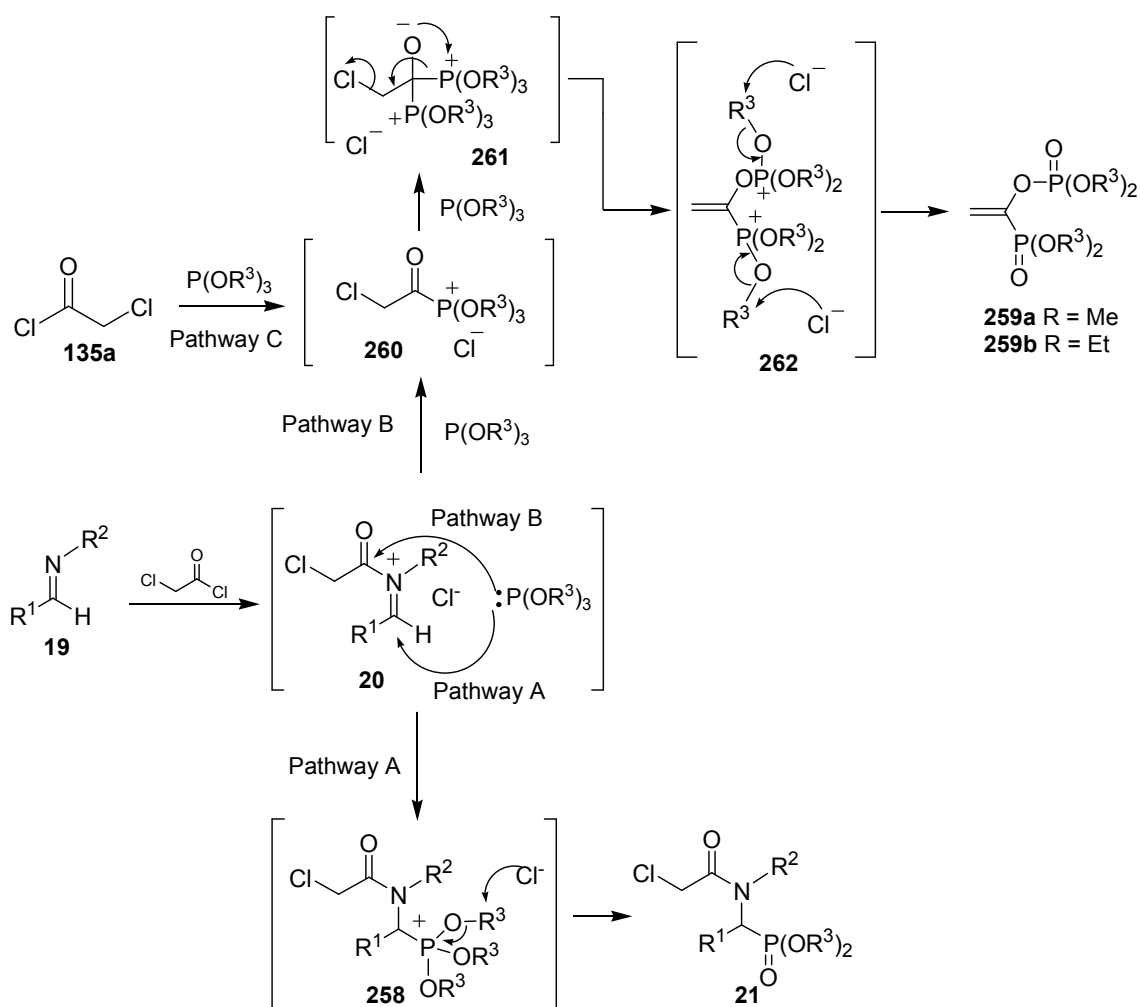

These results clearly indicate that the reaction conditions applied so far were not optimal. In order to influence the regioselectivity of the phosphite addition, DEPTMS was evaluated as phosphonylation agent. However, incomplete conversion and side product formation were observed. When bromoacetyl chloride was used to acylate the imine, even more vinyl phosphate **259** was formed during the phosphonylation step, as could be expected from the known increasing reactivity of Cl>Br>I in the Perkow reaction.[320] With trichloroacetyl chloride, complex mixtures were obtained.

Using the initial reaction conditions (1.1 equivalent of chloroacetyl chloride was added to a solution of imine **19b** in dry toluene under a nitrogen atmosphere), precipitation of the iminium salts **20** occurred within 10 minutes at -40°C. Triethyl phosphite was then added and the mixture was refluxed for 2 hours. After evaporation of the solvent under reduced pressure,

the ratio of pathway A versus pathway B/C ratio was determined to be 1.6 using ^{31}P NMR (Table 10, entry 1) and also the ^{1}H NMR spectrum showed a lot of impurities. From this mixture, the desired *N*-chloroacetyl 1-aminoalkyl phosphonate **21c** could be obtained in pure form by column chromatography in 26% yield.

Table 10: Effect of different reaction parameters to the formation of *N*-chloroacetyl aminoalkyl phosphonate **21c**
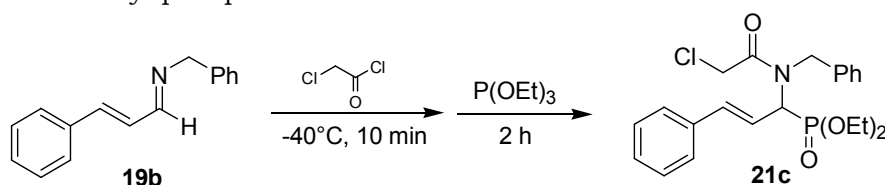
Entry	ClCH$_2$COCl	P(OEt)$_3$	Ratio 21c/259b[#]
1	1.1 eq., toluene	1.1 eq., 2h, Δ	1.6
2	1.0 eq., toluene	1.1 eq., 2h, Δ	2.8
3	1.0 eq., acetonitrile	1.1 eq., 2h, Δ	-
4	1.0 eq., THF	1.1 eq., 2h, Δ	6.1
5	1.0 eq., toluene	1.1 eq., 2h, 66°C	2.1
6	1.0 eq, THF	1.1 eq., 2h, Δ, passive air cooling	8.3
7	1.0 eq., THF	1.0 eq., 2h, Δ, passive air cooling	13.7

[#] Ratio **21c:259b** (pathway A to pathway B/C) determined by ^{31}P NMR. Vinyl phosphate **259b** is the major side product and can be recognized by two doublets around 10.1 and -3.9 ppm for the methyl esters **259a** and 7.3 and -6.3 ppm for the ethyl esters **259b** with a coupling constant of 25.5 Hz and 26.7 Hz, respectively.

To minimize the effect of pathway C, a limiting amount of chloroacetyl chloride was used in a second experiment for comparison, giving a higher, more favourable ratio (entry 2). The precipitation of the intermediate acyliminium salt **20** from the reaction mixture will affect the addition step. Therefore, more polar solvents compared to toluene were selected. The reaction failed using the very polar acetonitrile (entry 3) but when THF was used, a strong beneficial effect could be observed (entry 4). This could be explained by the lack of precipitation of the intermediate salts, together with an enhanced stabilization of the positively charged transition state of the phosphite addition. This positive effect was not due to a temperature effect (bp. THF = 66°C; bp. toluene = 110°C), since the results of entry 5 are similar to those of entry 2. The conditions of entry 4 were then repeated using passive air cooling instead of intensive cooling with a double jacket water cooler (entry 6). Again, the result of the reaction was improved, probably because of the enhanced removal of ethyl chloride (bp. 12°C) from the reaction atmosphere.

Since we showed before that phosphite is able to attack at the carbonyl group of the acyliminium salts, the excess of phosphite was also omitted, causing the A/B ratio to rise up to a level where side product determination via NMR-measurements became almost impossible. Using these optimal conditions, the desired *N*-chloroacetyl 1-aminoalkyl phosphonate **21c** was obtained in quite pure form (purity >90% from the ^{1}H NMR spectrum) after evaporation of the solvent. Even though subsequent column chromatography resulted in great losses, the yield almost doubled (46%) compared to the initial procedure. Furthermore, the obtained reaction mixture had a much higher purity and therefore could be used immediately in the next step, as will be discussed below (chapter 3, section 2.3).

Using the obtained optimal conditions, the method was extended to other imines.[321] The yields mentioned in Table 11 are isolated yields after column chromatography. This purification step always caused great losses, probably due to the high affinity of the products towards silicagel. However, for imines **19a,b,d,z** and **19aa**, the products can be obtained from the reaction mixture in high yields and in quite pure form (purity > 90%) after evaporation of the solvent. Surprisingly, the reaction did not work well for imines derived from benzaldehyde. Several reaction conditions were tested, but in all cases, incomplete conversion of the imines was observed with ^{1}H NMR.

Table 11: Yields of *N*-chloroacetyl 1-aminoalkyl phosphonates **21**

| SM	R^1	R^2	R^3	Product	Yield 21 (%)[§]
19b	Phenylethenyl	Bn	Et	**21c**	46
19b	Phenylethenyl	Bn	Me	**21b**	55
19d	Phenylethenyl	Allyl	Me	**21e**	41
19g	Phenylethenyl	*i*Pr	Me	**21f**	27[#]
19h	Phenylethenyl	*t*Bu	Me		Complex
19a	Phenylethenyl	Ph	Me	**21a**	43
19s	*o*-Nitro-phenylethenyl	Bn	Me		Complex
19ad	Ph	Bn	Et	**21k**	(39)[¤]
19ac	Ph	Ph	Et		0
19aa	Furyl	Allyl	Me	**21i**	43
19z	Furyl	Bn	Me	**21h**	57
19y	Furyl	Ph	Me	**21g**	35
19ah	*i*Pr	Bn	Me		0
19u		Bn	Me		0

§ Yield determined after column chromatography
# 27% of the 1,2-adduct was isolated next to 7% of the 1,4-adduct
¤ Yield estimated by ^{1}H NMR without isolation of the product

An important requirement for the reaction to minimize side product formation is to work under strictly dry conditions. Chlorinated amides **263** are found in the final reaction mixture due to hydrolysis of the iminium

cation when traces of water were present. Furthermore, the reaction is not suitable for alifatic imines, since an α-proton in the iminium salt is easily eliminated with the formation of the corresponding enamides upon heating, even in the presence of the nucleophilic phosphite. Therefore, elimination should occur much faster than nucleophilic attack. Imine **19u** derived from (-)-myrtenal was selected as a non-aromatic aldehyde without α-proton to study the stereochemistry of the reaction. Several reaction conditions were evaluated, but the desired product could never be isolated. The resulting mixture consisted mainly of vinyl phosphate **259a**, diene **266**, formed by elimination of the γ-proton, and a small amount of 1-aminoalkyl phosphonate **22t**, probably formed by phosphite addition after deacylation of the iminium salt.
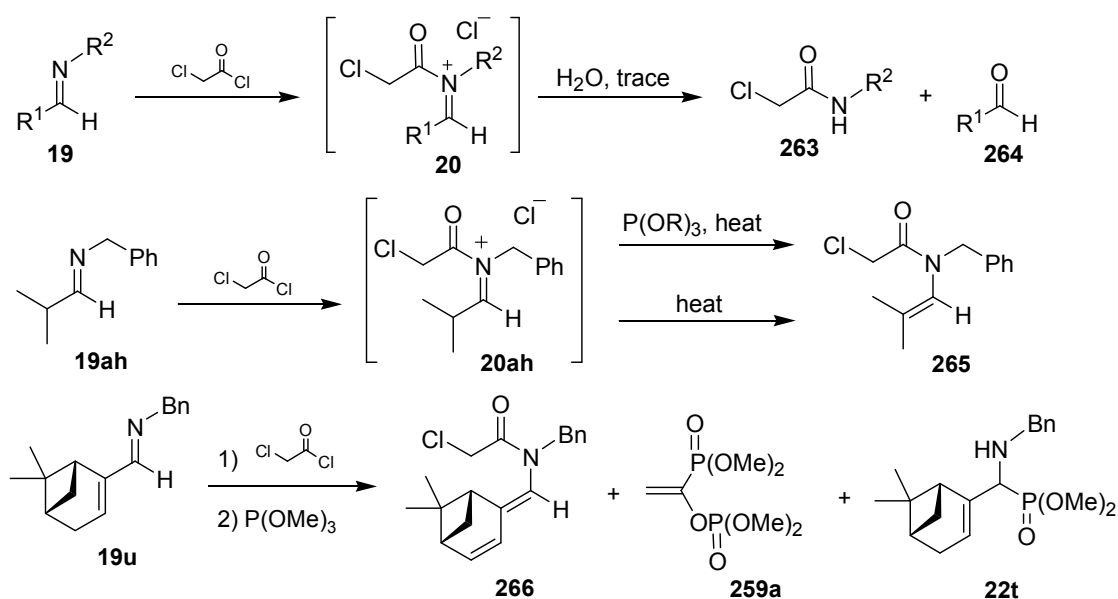
When α,β-unsaturated acyliminium salts **20** were treated with trialkyl phosphite, 1,4-regioselectivity could be expected similar to previous research of Savignac and Teulade.[215] A side product could be observed in the crude ^{1}H NMR spectrum of 1-aminoalkenyl phosphonates **21b,c,e,f**. However, only with a bulky *iso*-propyl group on nitrogen, the product could be isolated in 7% yield. Complete 2D spectral analysis of the products obtained from the reaction with *iso*-propyl imine **19g**, revealed their identities: the 1,2-addition product **21f** was formed next to the corresponding 1,4-product (ratio 3:1). When the more steric demanding triethyl phosphite was used, this ratio is slightly higher in favour of the 1,4-product. However, ^{1}H NMR chemical shifts and multiplicities substantially differed from those seen for similar products derived from imines **19b,d** (1,4-adducts were only present in minor quantities in the crude reaction mixture and could not be isolated). In order

to confirm the structure of the 1,4-adducts derived from imines **19b,d,g**, another pathway towards these enamides was evaluated.[**]

β-Phosphono aldehyde **217** was synthesized according to a literature procedure.[215] Using the specified conditions, a very fast and regioselective addition of triethyl phosphite occurred to imine **19h** and the corresponding aldehyde could be obtained after acid hydrolysis. Subsequent careful distillation resulted in considerable product losses due to break down. The β-phosphono aldehyde **217** was then easily converted to the corresponding imines, which were then treated with chloroacetyl chloride in the next step. Because of the presence of α-protons in the resulting acyliminium salt, HCl is easily eliminated upon refluxing for 2 h (*vide supra*). However, when triethylamine was added as a proton acceptor, the desired enamides **267b-d** were obtained smoothly in higher purity after 1 h at room temperature. Finally, the enamides **267b-d** were obtained in pure form using column chromatography. Only the (*E*)-isomers were observed.
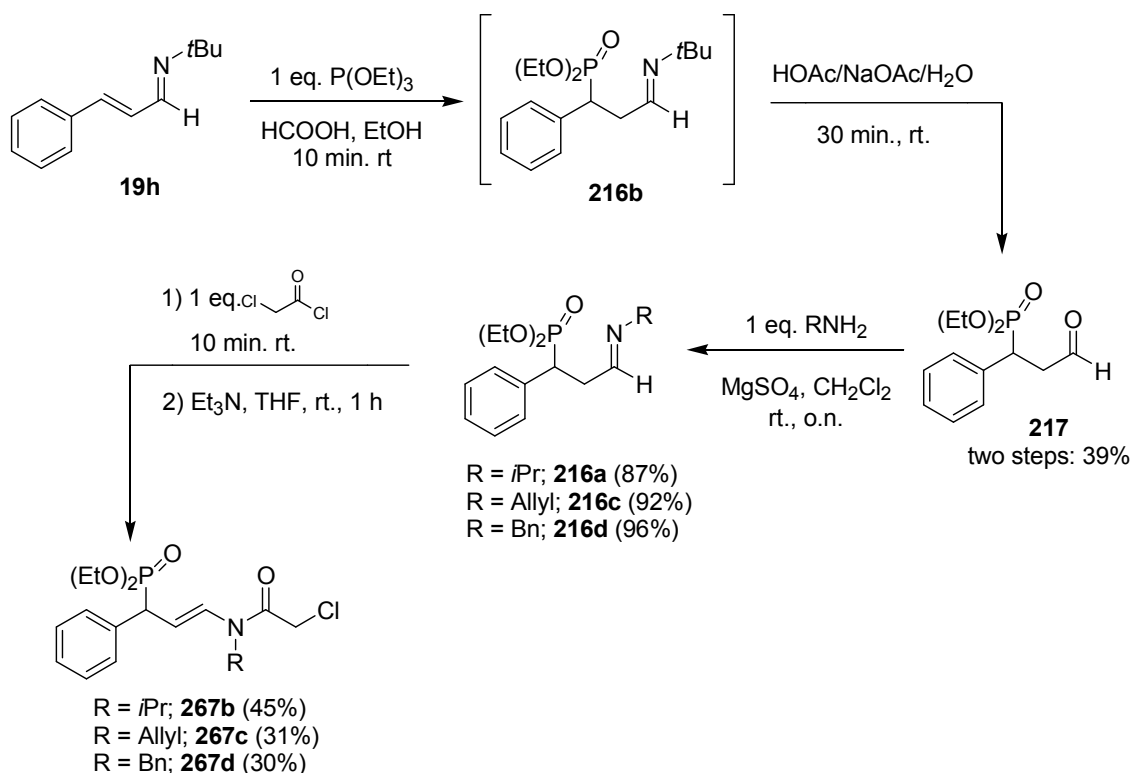
Comparison of the spectral data unambiguously revealed the identity of the 1,4-addition side products in the acyliminium/phosphite reaction. In all cases, 1,4-adducts were present in the reaction mixture (Table 12) when α,β-unsaturated imines were used. This incomplete regioselectivity significantly

[**] The structure of the 1,2-adducts was comfirmed by comparison with the results obtained in chapter 3, section 2.2.1.

lowered the yield of the desired *N*-chloroacetyl 1-aminoalkenyl phosphonates **21**, especially when bulky nitrogen substituents are used. However, when *t*Bu-imine **19h** was selected in order to facilitate the 1,4-addition, it failed to react with the chloroacetyl chloride, probably due to steric hindrance, leading to complex reaction mixtures after the phosphite addition. Also, when an electron withdrawing nitro group was introduced on the phenyl ring, the reaction failed (imine **19s**).

Table 12: Ratio of 1,4- vs. 1,2-addition of TAP to α,β-unsaturated acyliminium salts

Imine	R	Phosphite	1,4:1,2[#]
19a	Ph	TMP	0:100
19b	Bn	TEP	24:76
19b	Bn	TMP	22:78
19d	Allyl	TMP	18:82
19g	*i*Pr	TEP	33:67
19g	*i*Pr	TMP	29:71

[#] Determined by ^{1}H NMR integration measurements

Finally, the reaction was evaluated with various related acid chlorides (Table 13). This resulted mostly in complex reaction mixtures. Only with chlorobutyryl chloride, the corresponding *N*-acyl aminoalkyl phosphonates could be obtained in moderate yields.

Table 13: Evaluation of different acid chlorides

Imine	R^1	R^2	R^3	Product	Result
19b	CH=CHPh	Bn	CCl$_3$		Complex mixture
19b	CH=CHPh	Bn	CH$_2$CH$_2$CH$_2$Cl	**25a**	38% (31:69)[#]
19d	CH=CHPh	Allyl	CH$_2$CH$_2$CH$_2$Cl	**25b**	45% (11:89)[#]
19b	CH=CHPh	Bn	C(CH$_3$)=CH$_2$		Complex mixture
19aa	Furyl	Allyl	C(CH$_3$)$_3$		Complex mixture

[#] Yield of the 1,2-adduct after column chromatography. Ratio 1,4:1,2 phosphite addition given in parentheses (from ^{1}H NMR integration measurements).

2.2.3 Conclusion
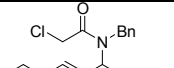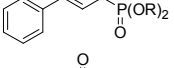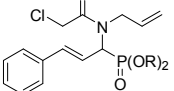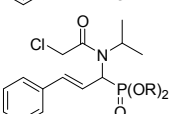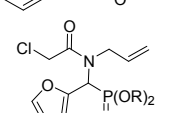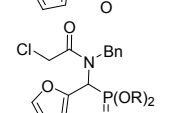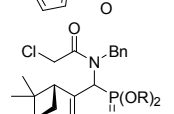
The best results for the synthesis of the *N*-chloroacetyl aminoalkyl phosphonates **21** were obtained using the two step phosphonylation-acylation sequence with overall yields from 88 to 92% for furyl or

phenylethenyl derivatives (Table 14). Mixtures of low purity and difficult purification, were obtained from phenyl and alkyl derivatives, because of the difficulties encountered during the acylation step.

The one-pot acylation/phosphonylation could be advantageous when comparing the ease and time consumption of the reaction. However, the methodology was not useful at all for alkyl imines. Furthermore, competitive 1,4-addition was observed in the case of α,β-unsaturated imines, causing the yields to drop. Finally, the obtained reaction mixtures were less pure, requiring an additional chromatographic purification step in order to obtain the *N*-chloroacetyl aminoalkyl phosphonates **21** in pure form.

Table 14: Comparison of the synthesis of *N*-chloroacetyl aminoalkyl phosphonates **21** via the two step phosphonylation/acylation (see chapter 3, sections 2.2.1 and 1.4) and via the one step acylation/phosphonylation (see chapter 3, section 2.2.2)

Product			2 steps	1 step
	R = Me	**21b**	92%	55%
	R = Et	**21c**	90%	46%
	R = Me	**21e**	91%	41%
	R = Me	**21f**	91%	27%
	R = Me	**21i**	88%	43%
	R = Me	**21k**	88%	57%
	R = Et	**21p**	76%	0%

2.3 Ring closure towards 4-phosphono β-lactams

The classical methods for the formation of the β-lactam ring can be classified as (i) Staudinger's ketene-imine reaction, an overall [2+2] cycloaddition, (ii) cyclization reactions of β-amino acids and esters and (iii) carbene insertion. However, the obtained *N*-chloroacetyl 1-aminoalkyl phosphonates **21** appeared to be excellent substrates for ring closure to 4-phosphono-β-lactams **23**, through an unusual C^3-C^4 bound formation. When treated with sodium hydride, a phosphorus stabilized carbanion was formed, which led to the four membered heterocycle upon refluxing for two or three hours in THF. No side products were formed during this procedure and the 4-phosphono β-lactams **23** were obtained in excellent yields. When ether was used as a solvent, longer reaction times were required, indicating the need for some heating to form the highly strained 4-membered heterocycle. When LiHMDS was used as a base instead of NaH, the reaction proceeded smoothly at room temperature yielding the products in the same purity and yield after typically 1 h. Only when the *p*-methoxy benzyl derivative **21d** was used, extended reaction times were required to obtain complete conversion (up to 6 h of reflux in THF using NaH as a base). In case of *N*-chloroacetyl aminoalkenyl phosphonates **21a-f** (R^1 = phenylethenyl) an ambident allyl anion is formed upon deprotonation. However, ring closure proceeds with exclusive 4-membered ring formation. The origin of this particular selectivity will be investigated in chapter 3, section 2.4.

Table 15: Synthesis of 4-phosphono β-lactams **23**
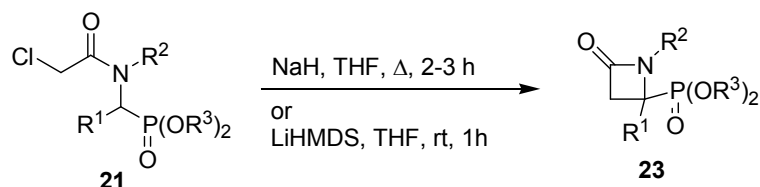
SM	R^1	R^2	R^3	Product	Yield (%)[#]
21a	2-Phenylethenyl	Ph	Me	**23a**	90
21b	2-Phenylethenyl	Bn	Me	**23b**	75
21c	2-Phenylethenyl	Bn	Et	**23c**	92
21d	2-Phenylethenyl	PMB	Me	**23d**	39
21e	2-Phenylethenyl	Allyl	Me	**23e**	62
21f	2-Phenylethenyl	*i*Pr	Me	**23f**	85
21g	Furyl	Ph	Me	**23g**	89
21h	Furyl	Bn	Me	**23h**	99
21i	Furyl	Allyl	Me	**23i**	55
21k	Phenyl	Bn	Me	**23j**	92

[#] The 4-phosphono β-lactams **23** are obtained in high purity (>98%) after simple aqueous work-up on condition that purified *N*-chloroacetyl aminoalkyl phosphonates **21** are used as starting material.

The C3-C4 ring closure has already been evaluated for similar carboxylates.[322] However, for the carboxylates, longer reaction times are necessary (one to several days at room temperature) and the yields are lower, indicating a difference between the stabilizing effect of the carboxylate and phosphonate group towards the anion. This can also be illustrated by the use of LiHMDS as a base; 4-phosphono β-lactams **23** are formed in typically 1 h at room temperature while the 4-alkoxycarbonyl β-lactams are not formed at all under these conditions: in this case an amide enolate is formed more readily yielding pyrrolinones via a Dieckmann type condensation.[323]
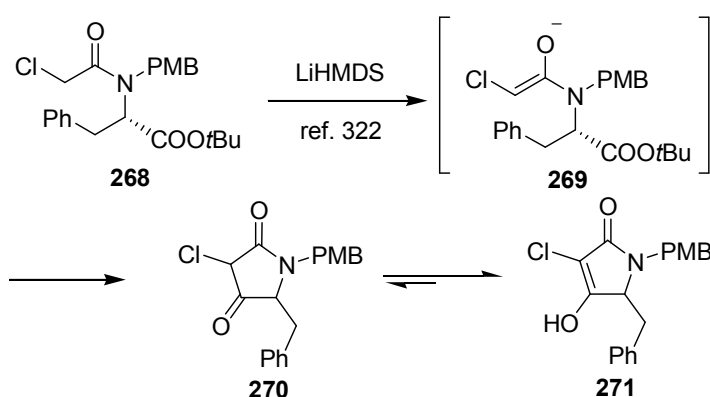
Given the good yields of the final ring closure step, we were now able to synthesize 4-phosphono β-lactams **23** in a three or four step sequence. However, the intermediate purification of the *N*-chloroacetyl 1-aminoalkyl phosphonates **21** constituted a major drawback for the synthesis pathway, seriously lowering the overall yield. Therefore, we succesfully attempted to use the *N*-chloroacetyl 1-aminoalkyl phosphonates **21**, obtained via the acyliminium addition method, directly in the ring closing reaction without prior chromatographic purification. The desired β-lactams **23** were obtained in reasonable purity (>90%) and with good overall yields after a simple aqueous work-up of the final reaction mixture. Furthermore, they could be obtained in pure form by a final chromatographic step with much smaller losses than the *N*-chloroacetyl 1-aminoalkyl phosphonates **21** because of their lower affinity for silicagel. Both yields are mentioned in parentheses in the scheme below.
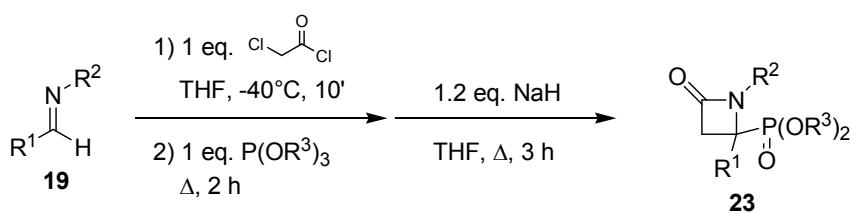
R¹ = PhCH=CH; R² = Bn; R³ = Et (92%, 60%)
R¹ = PhCH=CH; R² = Allyl; R³ = Me (85%, 40%)
R¹ = PhCH=CH; R² = iPr; R³ = Me (81%, 51%)
R¹ = Furyl; R² = Allyl; R³ = Me (62%, 25%)

In an attempt to introduce more diverse substituents on the lactam nitrogen atom, *N*-deprotection was evaluated first. Treatment of *N*-benzyl lactam **23c** with Pd/C under 4 bar H₂-atmosphere only resulted in hydrogenation of the double bond. Treatment with HCl in ether or *p*-toluene sulphonic acid in toluene at reflux temperatures did not offer the desired deprotection either. Oxidative removal of the *p*-methoxybenzyl group of lactam **23d** using CAN resulted in a complex mixture. When *N*-allyl lactam **23e** was refluxed in EtOH in the presence of Pd/C for 4 days, no reaction occurred.
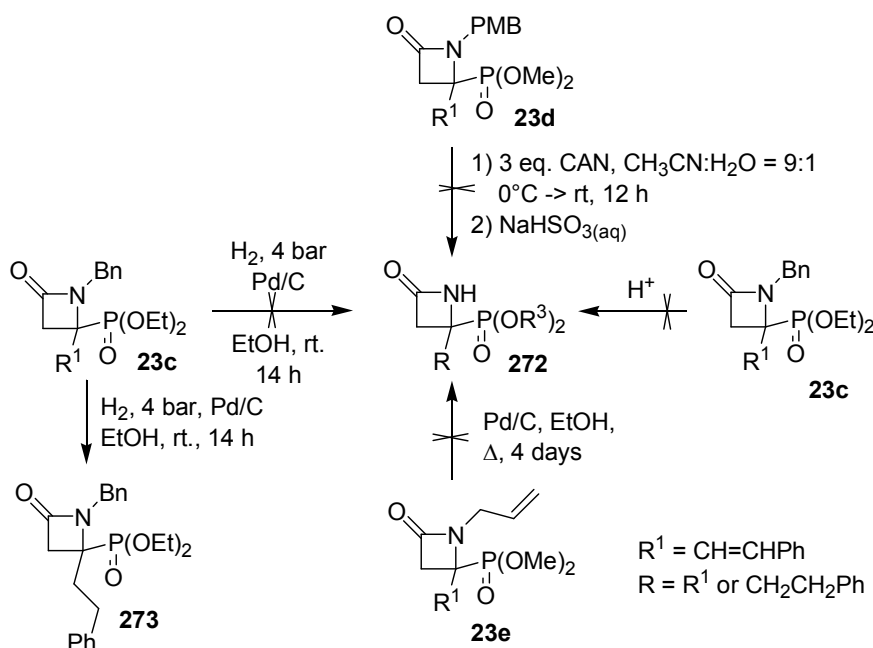
Also the deprotection of the phosphonate ester groups was problematic. Refluxing in 6 M aqueous HCl resulted only in starting material. Conversion of the alkyl esters to silyl esters followed by methanolysis resulted in complex mixtures. Also partial deprotection using KOTMS (see chapter 3, section 1.4) resulted in complex mixtures.
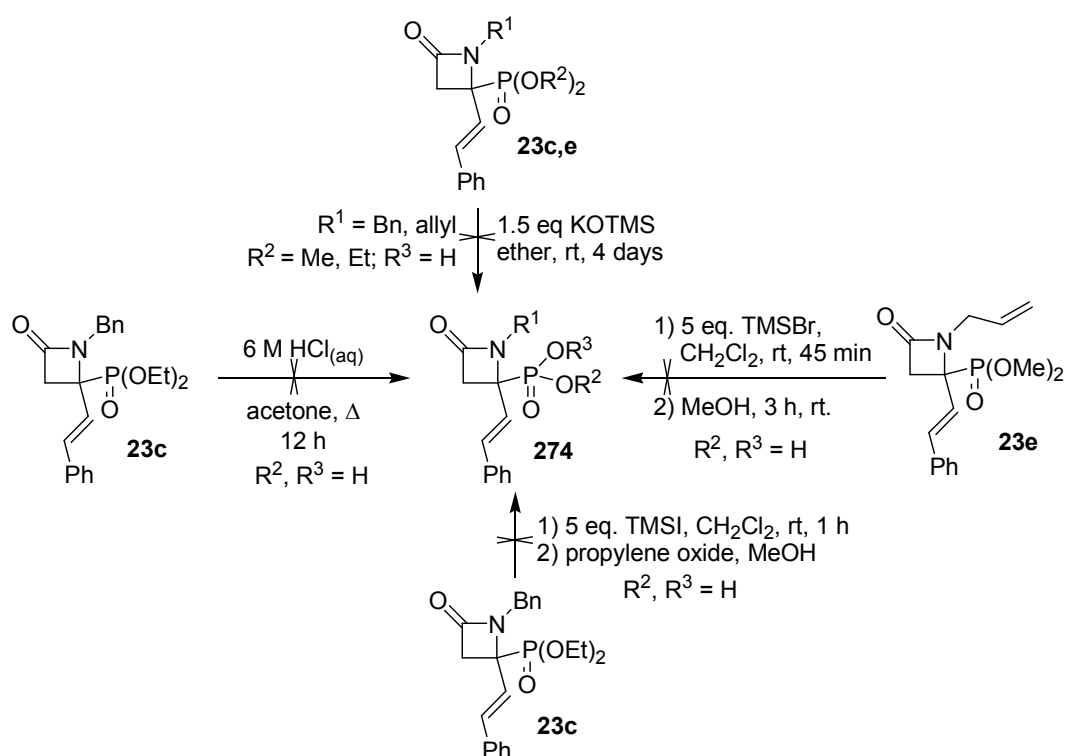
Finally, the ring closure was also evaluated for *N*-chlorobutyryl aminoalkyl phosphonates **25** in order to obtain six-membered lactams **24**. Sodium hydride and LiHMDS were used as a base under the same conditions used for the preparation of the β-lactams. However, complex mixtures were obtained in all cases (Table 16). Then the temperature was lowered to -78°C during base addition to avoid lithium-halogen exchange and afterwards stirring was continued for 2 h at room temperature. From this reaction, lactam **24** could be obtained in 15% yield using column chromatography. Using the same conditions, the furyl derivative **25f** resulted again in a complex mixture. Therefore, no further research has been performed. The difficulties encountered during the formation of these six-membered rings are somewhat surprising, since the four-membered rings are formed so easily.

Table 16: Preparation of 6-phosphono δ-lactams **24**.
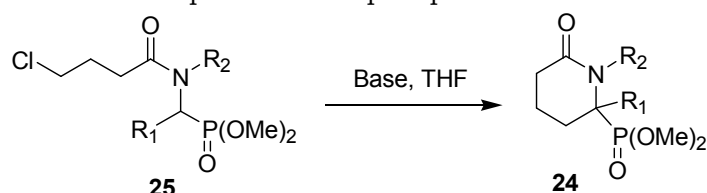
SM	R^1	R^2	Base	Temp.	Result
25a	CH=CHPh	Bn	NaH	Reflux	Complex mixture
25b	CH=CHPh	Allyl	NaH	Reflux	Complex mixture
25a	CH=CHPh	Bn	LiHMDS	rt	Complex mixture
25b	CH=CHPh	Allyl	LiHMDS	rt	Complex mixture
25b	CH=CHPh	Allyl	LiHMDS	-78 → 0°C	15%
25c	Furyl	Bn	LiHMDS	-78 → 0°C	Complex mixture

2.4 Origin of regioselectivity towards four-membered phosphono lactams

Allyl anions are stabilized by resonance and are considerably more stable than the corresponding alkane anions. Allyllithium, for instance, has a stabilization energy of -65.8 kJ/mol, wheras that of *n*-propyllithium has been calculated to be +16.7 kJ/mol.[324] Considerable further stabilization can arise when an allylic anion contains one or two heterosubstituents, as is the case in *N*-chloroacetyl aminoalkenyl phosphonates **21a-f**. Furthermore, the unsymmetrically substituted allyl anion is an ambident anion, which can react with electrophiles at two sites, conveniently visualized below by the two mesomeric resonance contributors **26** and **27**.
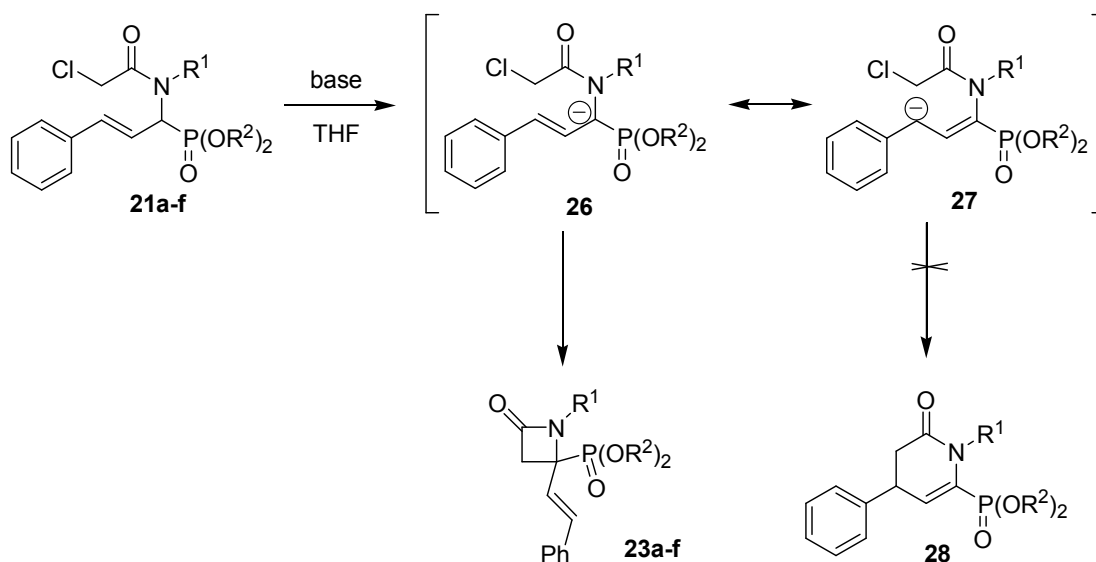
With *N*-chloroacetyl aminoalkenyl phosphonates **21a-f**, only cyclization to the highly strained four-membered ring is observed, while formation of a six-membered ring is generally accepted to proceed more smoothly. A similar result with an amide stabilizing group instead of a phosphonate has been presented in literature without any further comments on the nature of this unexpected selectivity.[325,326] The proposed 4-phosphono β-lactam structure was confirmed upon further spectroscopic investigation. The very high infrared absorption of the carbonyl (> 1750 cm^{-1}) is typical for highly strained rings. Furthermore, the ring $CH_2(3)$ appears as a second order spin system at 3.2 ppm in the ^{1}H NMR spectrum (Figure 11), involving a geminal coupling constant of 14.6 - 15.3 Hz and also quite large ^{31}P couplings (5.5 - 5.8 Hz), indicating the near presence of the phosphorus atom. According to the integrals of the signals in the region of 6 - 7 ppm in the proton spectrum, two alkenyl protons are present in the molecule. An (*E*)-coupling of 16.2 Hz was found for all five products, next to smaller ^{31}P couplings. All aforementioned

phosphorus couplings disappeared when the proton spectrum was run with selective ^{31}P decoupling. All ^{13}C peaks could be attributed to the appropriate carbon in the azetidinones using 2D techniques (HSQC and HMBC) together with DEPT spectra. The quaternary carbon atom bearing the phosphonate group is expressed as a doublet (J = 166.7 - 168.5 Hz) in the ^{13}C spectrum, with a chemical shift clearly within the aliphatic region (58.06 - 59.82 ppm). From this carbon, a clear HMBC coupling was observed with the $CH_2(3)$ of the four-membered ring.
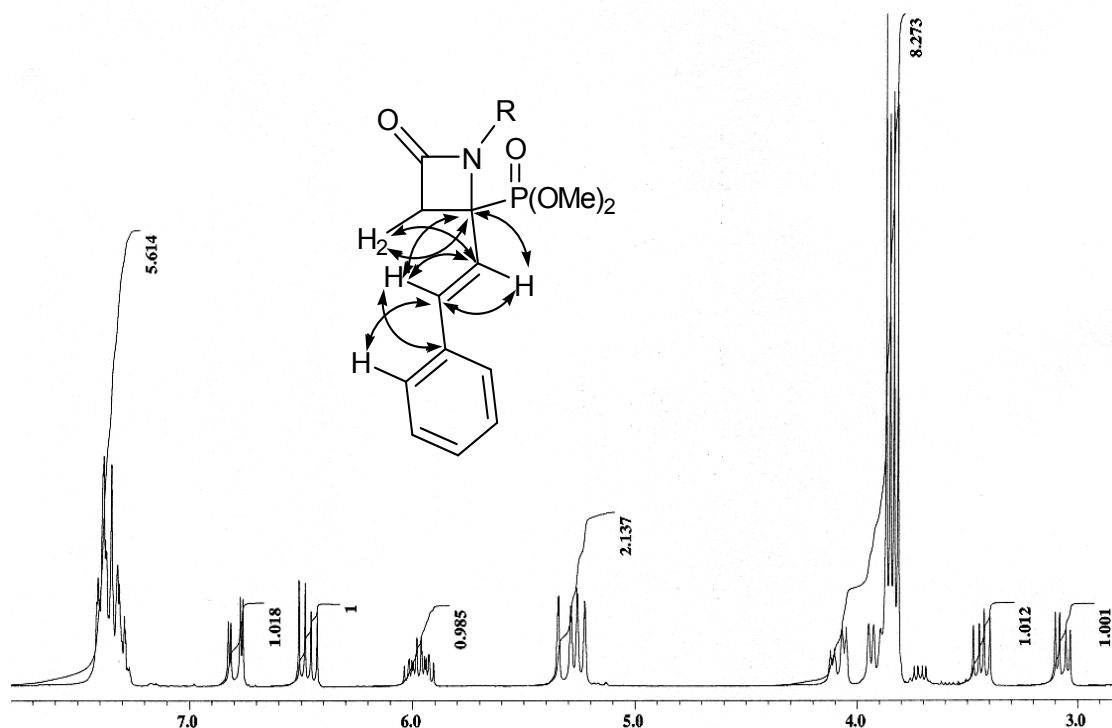
Figure 11: ^1H NMR spectrum of lactam **23e** (R = allyl). HMBC couplings that are common for all 4-alkenyl 4-phosphono β-lactams **23a-f** are indicated in the diagramma.

An overview of the regioselectivity of intermolecular reactions between heteroatom-stabilized allyl anions and electrophiles has been presented by Katritzky and coworkers.[324] However, no general conclusion could be drawn from this extensive work. Nevertheless, some important directing factors could be identified such as the nature of the electrophile, steric characteristics of the anion and the electrophile, coordination between the electrophile and the substrate prior to bond formation, nature of the counterion, reaction conditions, etc... An influence of the reaction conditions or the counterion can be excluded on the basis of the results reported in chapter 3, section 2.3. The same four-membered ring preference was observed in diethyl ether or in THF, at 20°C or at 66°C, with sodium as a counterion or with lithium.

The phosphonate group itself is found to behave mainly like a huge hydrogen-like atom, having a low electronegativity, being highly ionic inside, and therefore polarising the adjacent carbon frame.[327] Its influence is relatively poor on neutral organic groups, but is impressive through electrostatic interactions on a negative charge in α-position, especially when anion delocalisation is possible into the carbon skeleton.[328] Because of their importance in olefination reactions, some experimental and theoretical research has already been devoted to these phosphonate stabilized carbanions.[329,330] The main conclusions for allyl phosphonic diamides **275** can be summarized as follows:[331]

275
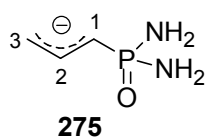
- The carbanion is planar (sp^2). However, according to the bond lengths, the structure appears to be midway between a vinyl substituted planar carbanion and a typical allyl anion.
- Charge stabilization is primarily coulombic. No valence type bonding to phosphorus d orbitals is observed. The P-C^1 bond is considerably shortened, becoming almost ylidic in character.
- The localization of electronic charge remains heavily in the region of the allyl unit and is equally distributed over C^1 and C^3.

However, the high number of functionalities in substrate **21a-f** compared to the simple allyl phosphonic diamide model, calls for an in depth investigation of this reaction. Furthermore, the intramolecular reaction under investigation involves complications compared to the intermolecular reactions, such as anion geometry and substrate conformation.

The following aspects have been taken into consideration and will be discussed below: (i) structural properties of the substrate, (ii) Hard-Soft, Acid-Base (HSAB) considerations, (iii) geometry of the allyl anion, (iv) transition state conformation.

2.4.1 Structural properties of the substrate

In order to investigate the role of the phenyl group in substrates **21a-f**, the preparation of analogous N-chloroacetyl aminoalkenyl phosphonate **21q** was evaluated. Starting from crotonaldehyde **276**, the corresponding benzylimine could not be obtained via condensation in the presence of $MgSO_4$ or $TiCl_4$, probably because of its thermal instability. With solid potassium hydroxide as a dehydrating agent, the reaction proceeded fast at 0°C to yield imine **19o**

together with degradation products. Kugelrohr distillation yielded the unstable imine **19o** in maximum 30% yield. It could be stored several days at -32°C, but was better used immediately in the next reaction. Reaction with DEPTMS resulted in PAP formation. No efforts were made however to isolate the product **196p** from the unpure reaction mixture. A fast reaction of imine **19o** with chloroacetyl chloride and triethyl phosphite yielded the corresponding *N*-chloroacetyl aminoalkenyl phosphonate **21q** in only 9% yield after column chromatography, next to 5% of the 1,4-adduct **277** (mixture of *E* and *Z* isomers). Treatment of **21q** with sodium hydride in THF resulted in complex mixtures.
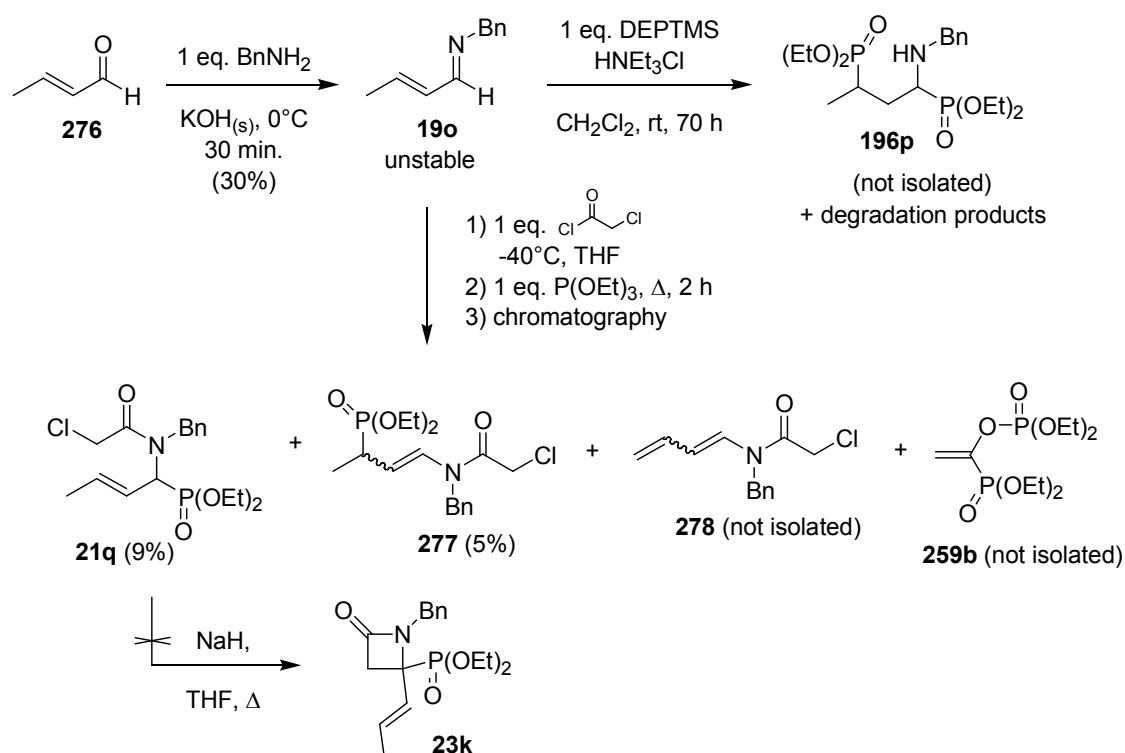
Then (-)-myrtenal **279** was selected from the chiral pool as a stable α,β-unsaturated aldehyde and to evaluate the stereochemistry of the final ring closure. Condensation with benzylamine quantitatively yielded the stable imine **19u**. One-pot phosphonylation of the acyliminium salt with triethyl phosphite had already proven not to be suitable for imine **19u** (see chatper 3, section 2.2.2). α-Aminoalkyl phosphonate **22u** could be obtained using DEPTMS or DEP. Almost no chiral induction coming from the chiral auxiliary was observed since both diastereomers were present in almost equal amounts. Acylation proceeded smoothly with triethyl amine as a base in THF. In this case, both diastereomers could be separated using column chromatography. No absolute attribution of the stereochemistry was performed, since treatment of a pure isomer of **21p** with sodium hydride resulted in a racemic β-lactam **231**: no memory of chirality[332] was observed as was the case for similar carboxylates.[323]

The ring closure reaction was hampered due to the more steric substitution pattern of the allyl anion, resulting in longer reaction times and lower purity of the final reaction mixture. After three hours of reflux in THF, no starting material was present anymore (^{31}P NMR). Using column chromatography, the racemic β-lactam **231** could be separated from the reaction mixture together with another product in low purity. A phosphonate substituted quaternairy carbon (J_{CP} = 216 Hz) was clearly visible in the alkene region of the ^{13}C spectrum. According to the DEPT spectrum, one CH is missing to be in accordance with the structure of the six-membered ring **280**. All spectroscopic observations pointed to **281**, which was formed by protonation of the unreacted anion during work-up (see chapter 3, section 2.4.2). Furthermore, the mass spectrum was clearly indicating the presence of a chlorine atom. In conclusion, this result clearly showed that substituents on the double bond have no impact on the regioselectivity of the ring closure reaction.
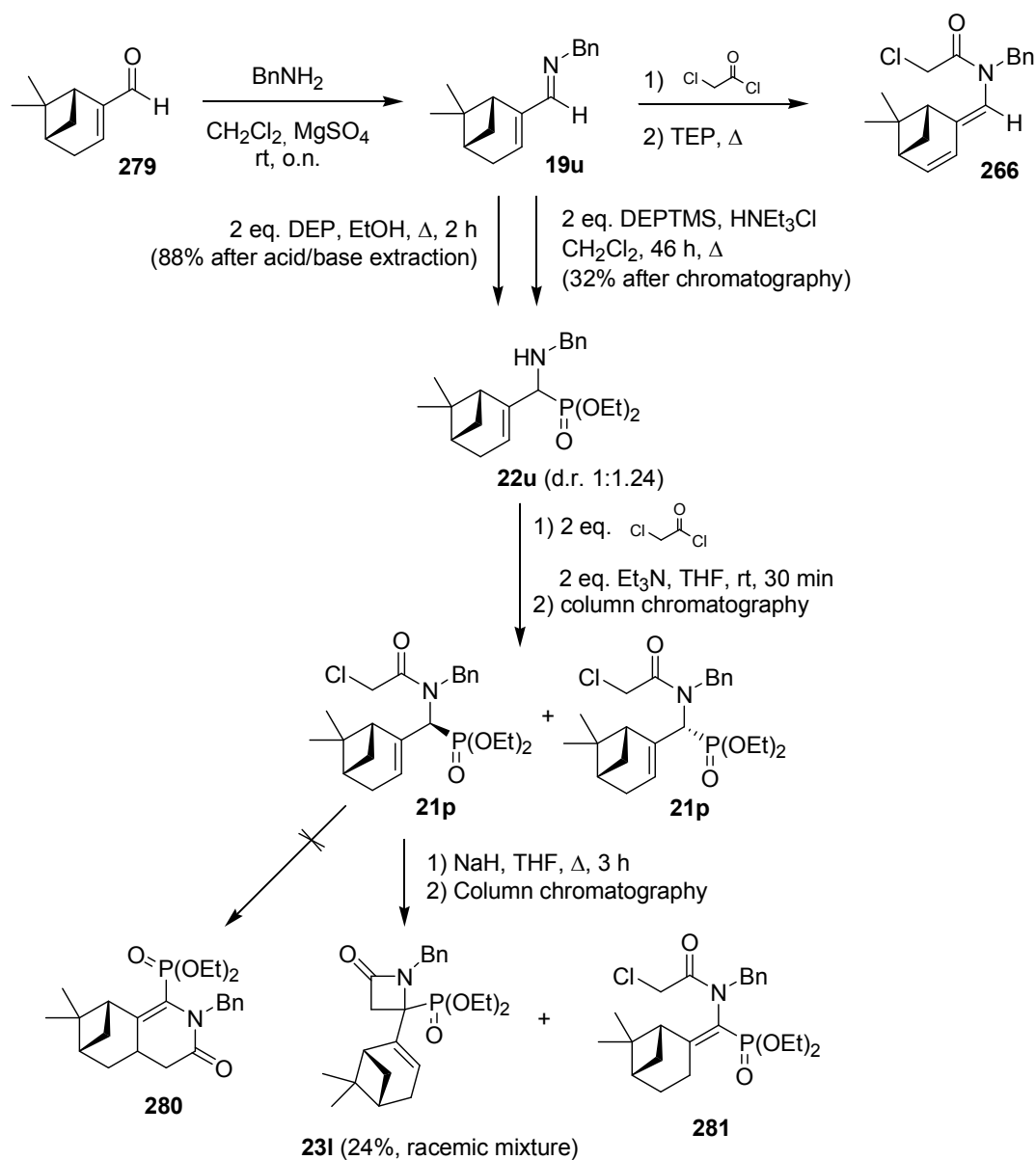
Finally, an electron withdrawing substituent was introduced on the aromatic ring in order to investigate the electronic effects of the reaction. The nitro substituent in **283** was believed to stabilize the anion to a greater extent in the γ-position, possibly leading to six-membered ring formation. The electron withdrawing effect was illustrated by the downfield shift of the =CHPh in the ^{13}C spectrum of **22r**. However, the desired *N*-chloroacetyl aminoalkyl phosphonate **283** could not be obtained either through the one-pot acylation-phosphonylation, neither through the two step phosphonylation-acylation.
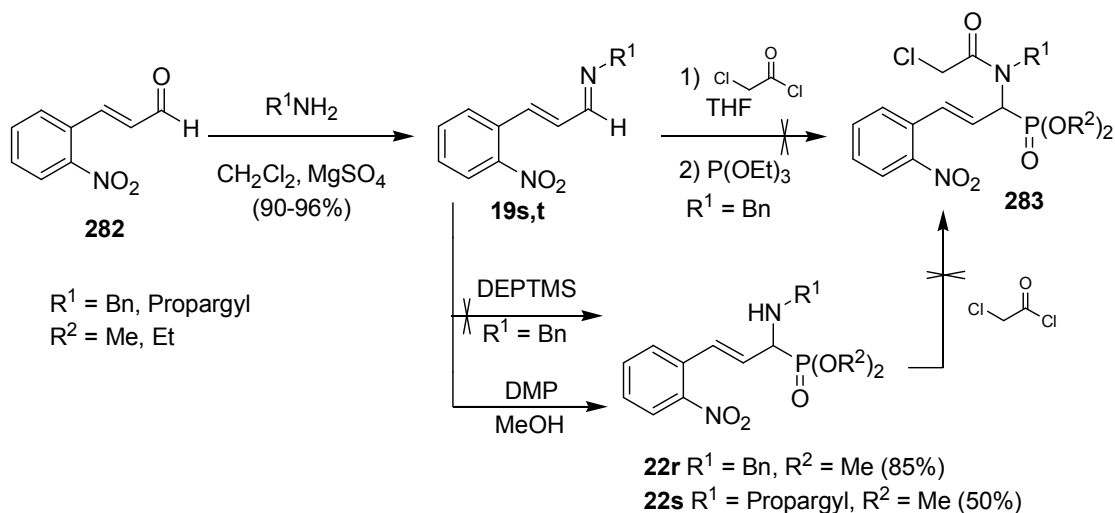
2.4.2 HSAB considerations

In the past, the regioselectivity of intermolecular reactions of allyl anions have sometimes been explained using the HSAB theory.[324] In the present intramolecular case, a soft electrophile is used (an alkyl chloride) in the alkylation reaction. However, it is not straightforward to predict the softest center of the allyl anion **284**. Even more, it may be reasonable to suggest that the hard/soft properties of both nucleophilic centers in allyl anion **284** are very similar.
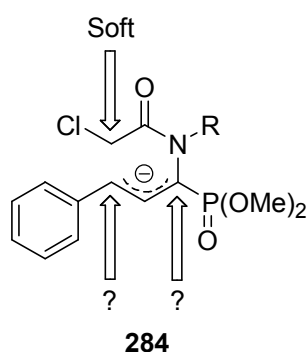
In order to investigate these properties experimentally, the synthesis of *N*-acetyl aminoalkenyl phosphonate **255b** was started. This substrate has

similar steric and electronic properties as the corresponding *N*-chloroacetyl derivatives, but is not prone to intramolecular reactions because of the lack of a leaving group. Therefore, it would be a suitable model for the ring closure substrates. The synthesis is very similar to the corresponding chloroacetyl derivatives. However, some problems were encountered in the acetylation of aminoalkenyl phosphonate **22h**. Using the strongest acylation conditions obtained before (see chapter 3, section 2.2.1), only 20% conversion was obtained. Altering these conditions finally led to 100% conversion and 66% yield of the crystalline *N*-acetyl aminoalkenyl phosphonate **255b** after a final washing step with 0.5 M HCl$_{(aq)}$ to remove any residual pyridine.
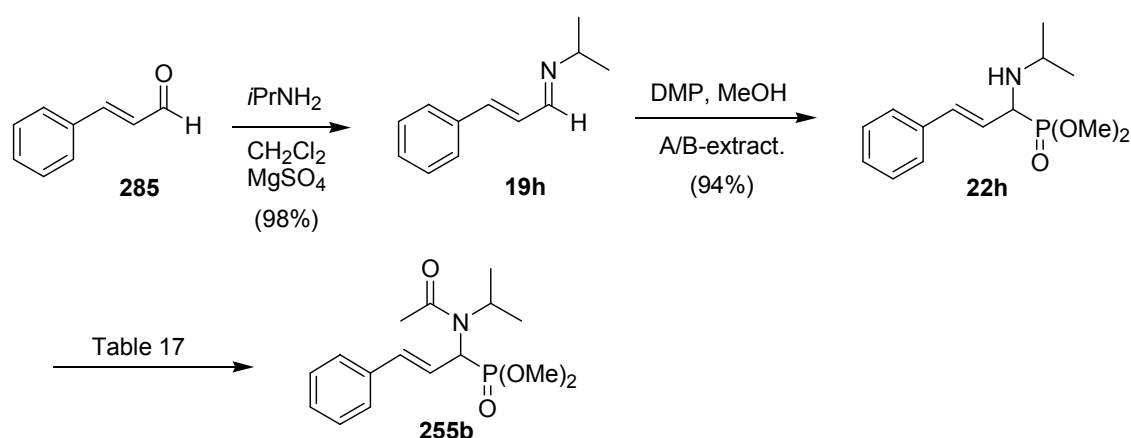
Table 17: Acetylation conditions

	Conditions	Conversion[#]	Yield (255b)
1	1) 1,1 eq. AcCl; 2 eq. Pyridine; 0,2 eq. DMAP; THF;rt., 1 h 2) 1 N HCl$_{(aq)}$	20%	-
2	1) 1,5 eq. AcCl; 2 eq. Pyridine; 0,2 eq. DMAP; THF;rt., 2 h 2) NaHCO$_{3(aq)}$	30%	-
3	1) 1,5 eq. AcCl; 2 eq. Et$_3$N; 0,2 eq. DMAP; THF;rt., 19 h 2) NaHCO$_{3(aq)}$	10%	-
4	1) 1,5 eq. AcCl; 2 eq. Pyridine; 0,2 eq. DMAP; THF;rt., 1 h; Δ, 1 h 2) NaHCO$_{3(aq)}$	100%	66%

[#] Measured using ^{1}H NMR after washing the reaction mixture with an aqueous, saturated NaHCO$_3$ solution.

The obtained substrate analogue **255b** was then submitted to deprotonation with LiHMDS at -78°C. An intense red-brown color indicated the formation of the anion. An excess of MeI was then added and the reaction mixture was allowed to warm up to room temperature. However, this procedure resulted in a complex mixture of reaction products. MeI was selected as a soft

electrophile, mimicking the ring closure. A second attempt was then made, adding deuterium oxide after initial anion formation, providing hard deuterons to the anion. This procedure resulted in the recovery of 12% of deuterated starting material next to two novel compounds, which appeared in a 1:1 ratio. However, structure characterization using NMR was not possible at this stage. Therefore, water was added in a third experiment instead of deuterium oxide. The same products were obtained in similar proportions. However, no successful structure elucidation was performed due to great product losses during aqueous work-up and failure to separate both products using column chromatography.
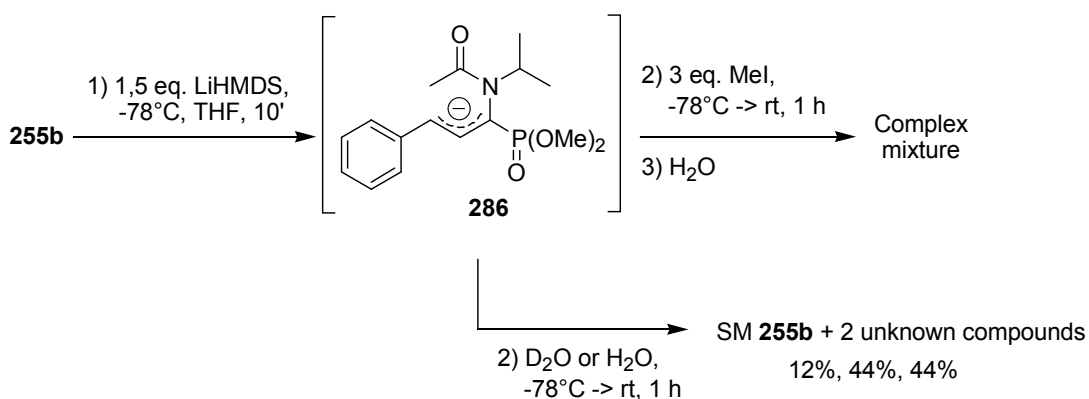
In order to avoid unwanted deprotonation of the acetyl group by the bulky LiHMDS base, sodium hydride was then evaluated to generate anion **286**. No colour change occurred at -78°C and therefore, the reaction mixture was allowed to warm up to room temperature over a one hour period prior to addition of the electrophile. In this way, complete deprotonation occurred which was again indicated by the red-brown colour. Addition of water or deuterium oxide now resulted in the original yellow colour. Two products were obtained after further aqueous work-up (with 90% of total mass recovered), which could now be separated using column chromatography. Next to the starting allyl phosphonate **255b** ($\delta(^{31}P) = 26.6$), also the vinyl phosphonate **287** ($\delta(^{31}P) = 15.7$) was found (ratio 13:87), which is formed through γ-protonation of the ambident anion **286**. The structure was confirmed using 2D NMR techniques (especially HMBC, Figure 12). Only the (*E*)-isomer of **287** is formed, which was concluded after comparing C-P and H-P coupling constants with literature data.[333]

In a second experiment, MeI was used as the electrophile. According to the ^{31}P NMR spectrum, two vinyl phosphonates were formed ($\delta(^{31}P) = 16.2$ and 16.3). From the carbon spectrum of the crude reaction mixture, it was concluded that only the (E/Z)-isomers of **288** were formed. The introduction of a methyl group was confirmed via a LC/MS analysis. Purification via column chromatography, however, failed.
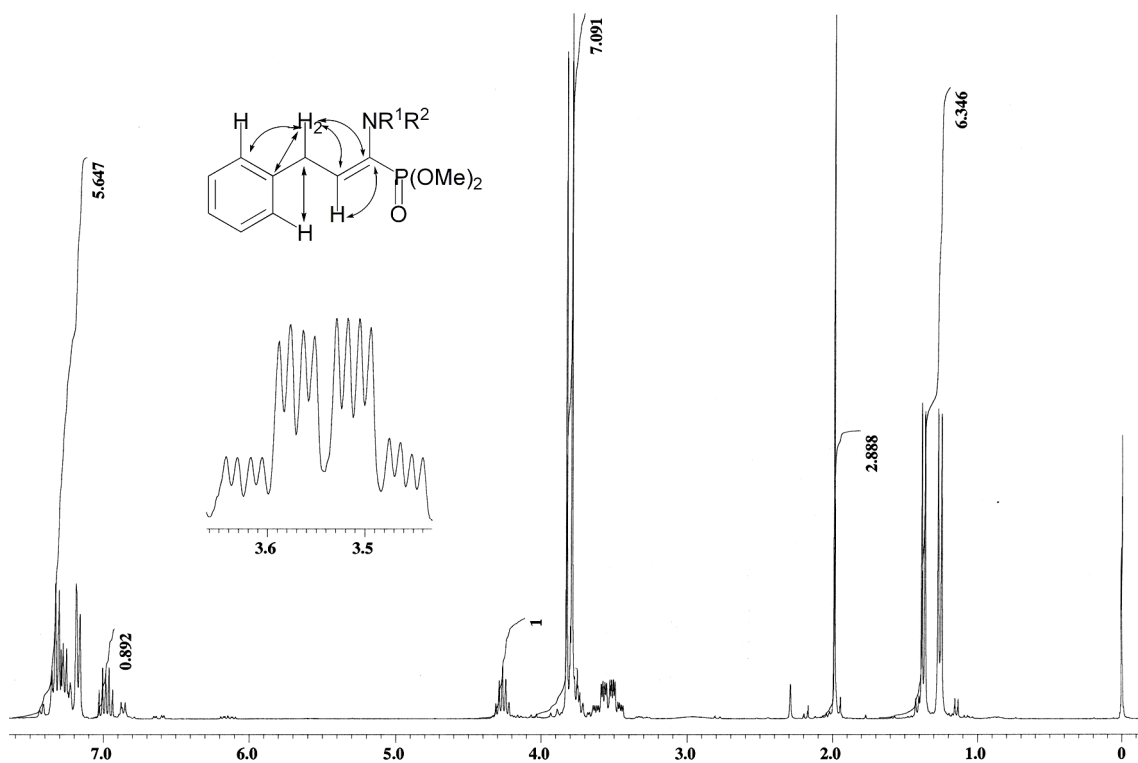
Figure 12: ^{1}H NMR spectrum of vinyl phosphonate **287** (R^1 = *i*Pr, R^2 = CH${}_3$CO). Selected HMBC couplings are indicated.
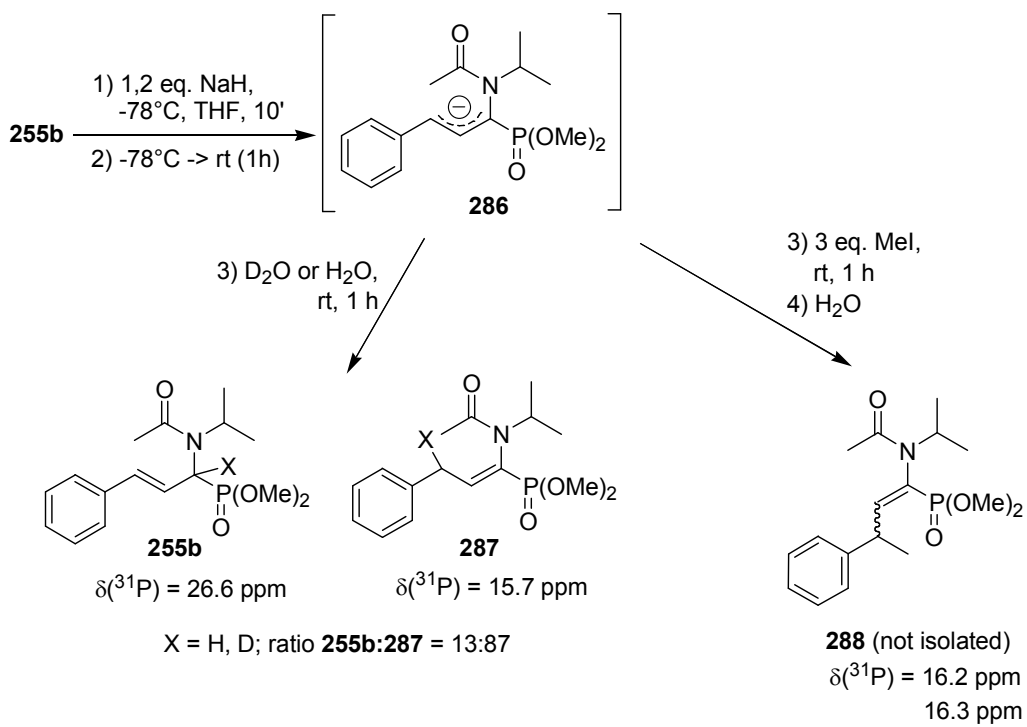
In conclusion, these experiments confirm the ambident nature of the allyl anion, as already calculated by Denmark and coworkers for less complex compounds.[331] The complete γ-alkylation with methyl iodide is remarkable, however, and has also been reported for similar allyl phosphonates carrying a trimethylsilyloxy instead of an amide group in α-position.[334] On the contrary, complete α-alkylation is observed α-aminoalkenyl phosphonates having the amine incorporated in a morpholine ring.[335] Therefore, it must be concluded that HSAB principles do not play an important role in the regioselectivity in this specific case.

2.4.3 Geometry of the allyl anion

So far, the allyl anion was always presented as a single isomer. However, given the complex substitution pattern of allyl phosphonates **21a-f**, the actual geometry of the anion should be investigated. This geometry can have a profound influence on the ring closure to the six membered ring. No ring closure is possible starting from the (*Z*)-allyl anion **284**, since a six-membered ring containing a double bond with "*trans*" geometry would be obtained. Both isomeric anions (*E*)-**284** and (*Z*)-**284** can, however, ring close to the four-membered ring without any complication of this kind.
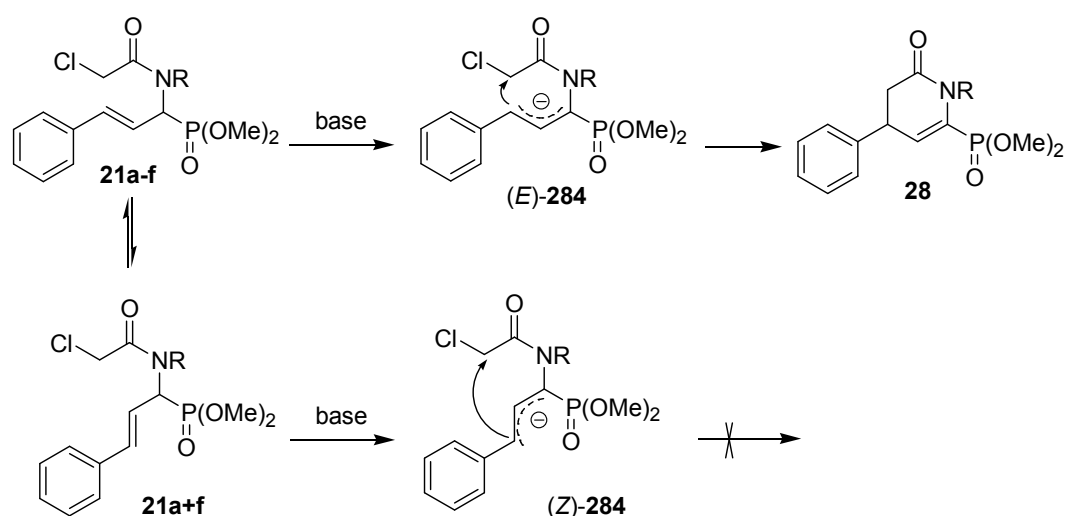
To investigate this issue, the energetically most favoured structure of the free carbanion is calculated with the GAUSSIAN 03 software package[336] in cooperation with the Center for Molecular Modelling of Ghent University (Head: Prof. Waroquier). This structure was found by applying various internal rotations around single bonds and selecting stepwise the most stable conformation along the rotational potential (B3LYP/6-31+g(d) level). Since THF was used as a solvent, solvation may be expected to be important. The solvation originates from two contributions: coordination of ether oxygens to

the sodium cation (coordination solvation) and the electrostatic effect of the solvent dielectric (dielectric solvation). The latter effect is the simplest to treat from computational point of view, as it is usually approximated by enclosing the molecule in a cavity within a continuous dielectric. The coordination solvation energy (CSE) is estimated by coordinating the sodium ion to one or more ether oxygens. Dimethyl ether (DMEt) was chosen as the coordinating solvent instead of THF. DMEt has about the same basicity and steric effect, but is significantly smaller for computations. An important question then concerns the degree of coordination. For solvent separated ion pairs, four-coordinated lithium cations have been recognized in NMR studies.[337,338] But for contact ion pairs as encountered here, the coordination may be expected to be less due to the electrostatic effect of the counterion. The degree of coordination for our system is estimated by coordinating the sodium cation with one or two DMEt molecules and calculating the CSE energies. Coordination of the first two ethers is highly exothermic as the CSE amounts to -53.8 kJ/mol and -88.7 kJ/mol. These results indicate that coordination with two ether molecules will be preferred.

The optimized structures for anion **284b** (R = Bn) are represented in Figure 13. It can be concluded from these structures, that these anions adopt a conformation which allows six-membered ring formation. However, according to the indicated distances, the geometry seems to be better suitable for four-membered ring formation at first sight. Of course, these structures do not reveal the actual transition state of the ring closure reaction, which will be discussed in chapter 3, section 2.4.4.

284b

284b + Na + 1DMEt
(CSE = -53.82 kJ/mol)

284b + Na
(DSE = -12.22 kJ/mol)

284b + Na + 2DMEt
(CSE = -88.67 kJ/mol)
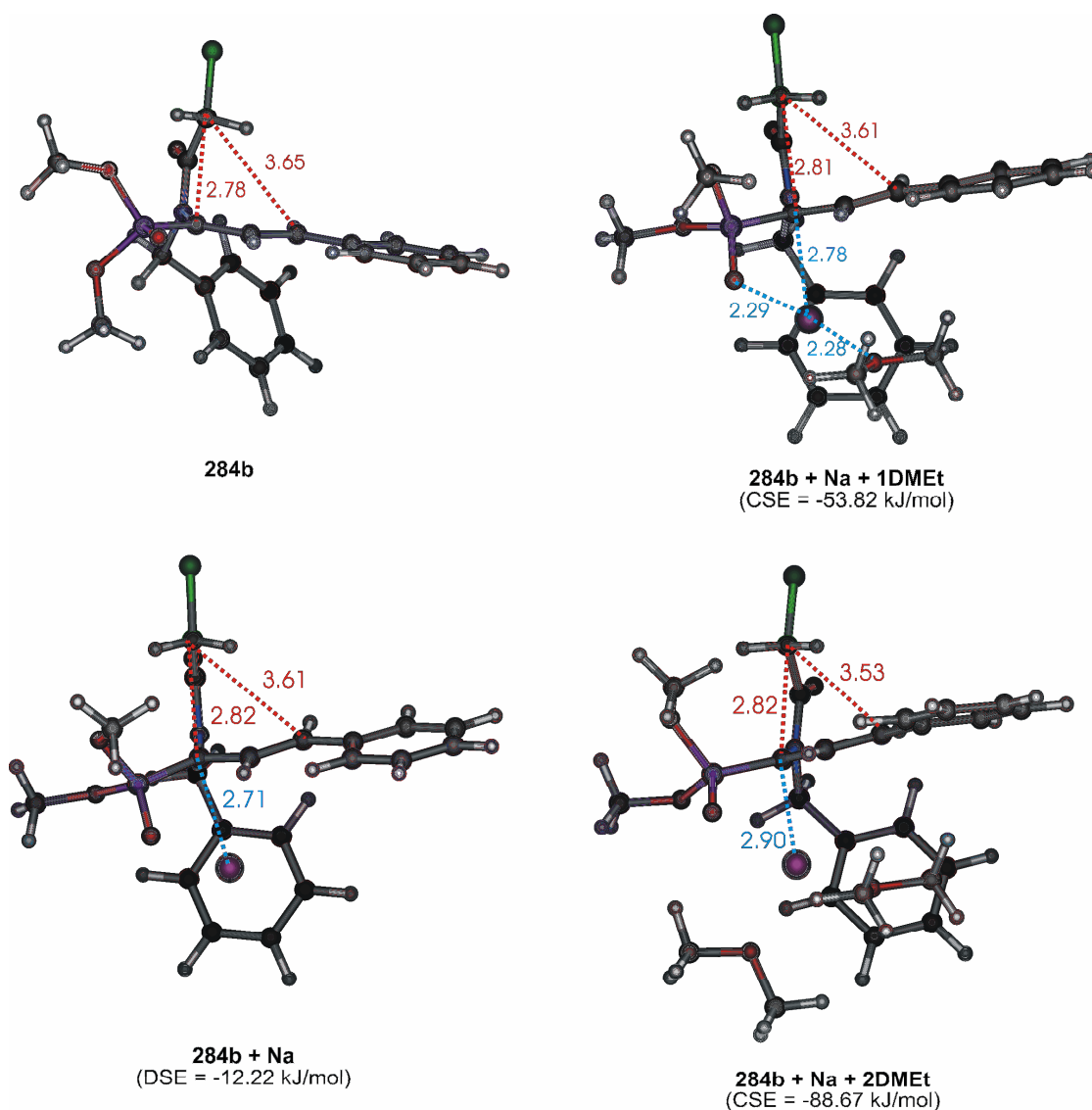
Figure 13: Optimized conformation of the anion **284b** (R = Bn) in the gas phase, including a Na⁺ counterion, or including the counterion together with one or two DME molecules.

From these optimized structures, the atomic charges could be calculated according to the CHELPG scheme at the B3LYP/6-31+g(d) level of theory (Table 18). It is clear from these results that the major part of the negative charge is almost equally divided over both the α- and the γ-carbon. The remaining negative charge can be found mainly at the phosphoryl oxygen atom. The phosphorus atom remains highly positively charged, which illustrates the conclusion of Denmark & Dorow[329] that the stabilizing effect of the anion by the phosphonate group is primarily coulombic.

Table 18: Atomic charges

	284b + Na	284b + Li	284b + Na + 1DMEt	284b + Na + 2DMEt
C^1	-0.34	-0.42	-0.34	-0.30
C^2	0.04	0.01	0.09	0.10
C^3	-0.51	-0.40	-0.47	-0.49
N	-0.04	0.02	-0.01	-0.02
P	0.81	0.96	0.80	0.83
O^1	-0.64	-0.69	-0.70	-0.61

2.4.4 Transition state conformation

To unravel the experimentally determined reaction preference towards the four-membered lactams, calculations were required to determine the reaction barriers. The transition states towards four- and six-membered ring formation are visualized in Figure 14. Both transition states resemble an intramolecular S_{N2}-like reaction characterized by an umbrella-like inversion. In the reacting anion, the C^5 carbon atom is oriented towards the α-carbon atom, which is the reactive center for four-membered ring formation.

In case of six-memberd ring formation, large distortions are needed from the original geometry of the anion in order to adapt the S_{N2}-like transition state (the $C^2C^1NC^4$ dihedral angle has to evolve from -82.2° to -36.0°). In order to get an idea about the energetic variations in terms of the $C^2C^1NC^4$ dihedral angle, the rotational potential was calculated in relation to of this geometrical variable. This was done by stepwise varying the $C^2C^1NC^4$ torsional angle and optimizing all other degrees of freedom. The results are shown in Figure 15. In the transition state for four- and six-membered ring formation, this tortion angle reaches a value of -116° and -36° respectively. Due to the strongly asymmetric shape of the rotational potential around the minimum, the associated energy to induce this distortion amounts to approximately 10 and 38 kJ/mol.

TS4

TS6

TS4 + Na

TS6 + Na

TS4 + Na + 1DMEt

TS6 + Na + 1DMEt
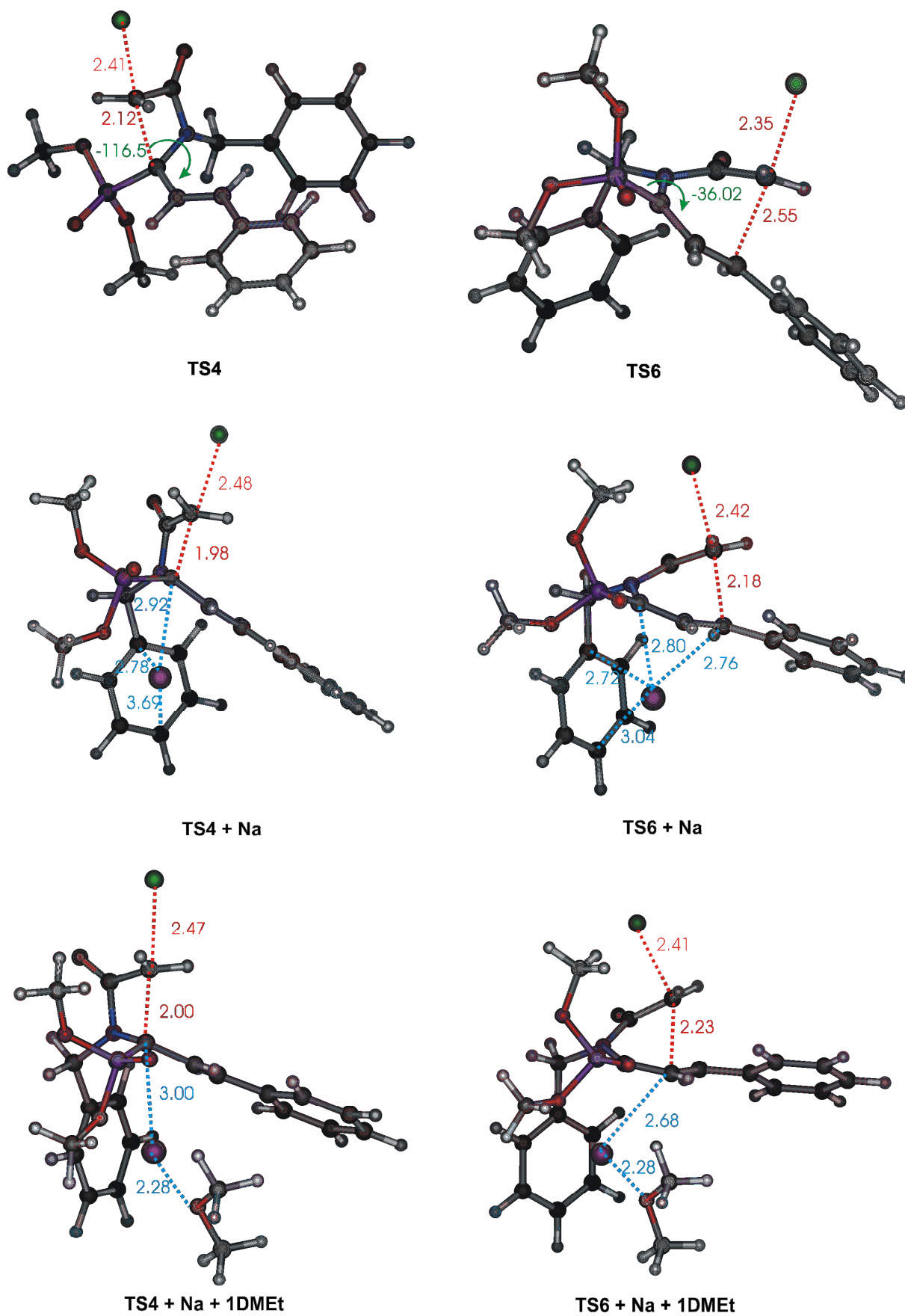
Figure 14: Conformers of the transition state
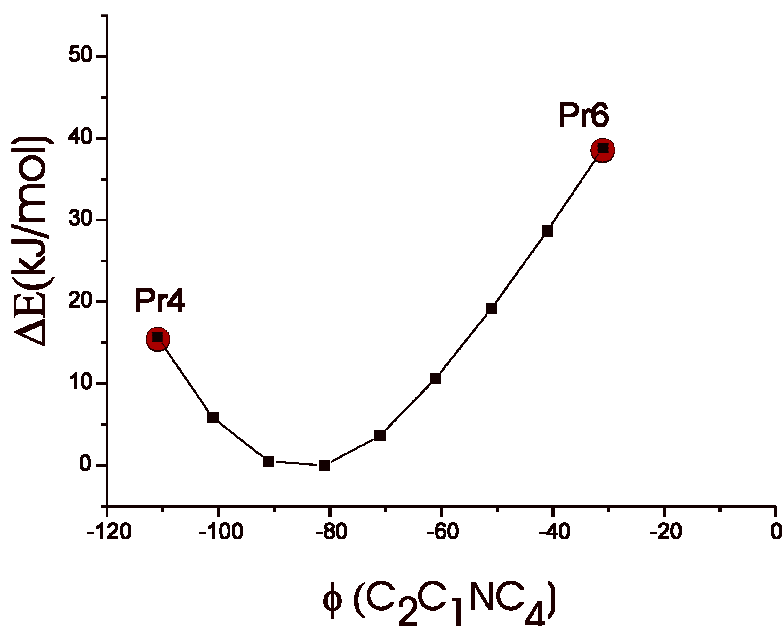
Figure 15: Part of the rotational potential in terms of the $C^2C^1NC^4$ dihedral angle. The required transition states for four- and six-membered ring formation are indicated by a grey circle.

When focussing on reaction barriers instead of rotational potentials, the energy difference $\Delta(\Delta E^{\ddagger})$ between the transition state and the reactant can be calculated. For the current application we are interested in the difference between the reaction barrier for four- and six-memberd ring formation ($\Delta(\Delta E^{\ddagger})$ = $\Delta E^{\ddagger}(6)$ - $\Delta E^{\ddagger}(4)$). Calculations for the gas phase predict a preference for the four-membered ring ($\Delta(\Delta E^{\ddagger})$ = 16 to 22 kJ/mol depending on the level of theory used). Inclusion of the sodium cation increases the reaction barriers with approximately 60-80 kJ/mol at all levels of theory. Similar findings were found by Ando.[339] Moreover, there is no clear preference anymore between four- and six-membered ring formation. (($\Delta(\Delta E^{\ddagger})$ = 3.4 kJ/mol). However, since all reactions were performed in THF, solvation of the counterion is expected to be important. Including bulk solvent effects lowers the barriers to about 95 and 121 kJ/mol (at the B3LYP/6-31+g(d) level) for four- and six-membered ring formation and the preference for cyclization at the α-position is correctly predicted ($\Delta(\Delta E^{\ddagger})$ = 26 kJ/mol). Finally, also two explicit solvent molecules were taken into account as explained previously. Also in this case, a clear preference for four-membered ring formation is found ($\Delta(\Delta E^{\ddagger})$ = 26.8 kJ/mol).

In conclusion, the experimental four-membered ring preference is in accordance with theoretical predictions, provided solvent effects are taken into account properly. The underlying reason for this preference must be tracked back to the high amount of energy needed to reach a conformation suitable for six-membered ring formation in the transition state. *Anchoration*

of the phosphoryl group with a carbonyl group has already been suggested as the basis for stereoselectivity in certain intermolecular reactions.[340-342] The same type of coordination may cause the hindered rotation around the C-N bond in this case (Figure 16). The results of the theoretical calculations have shown that the lithium or sodium counterion is coordinated to a large extent with the phosphoryl oxygen atom. However, nor in the optimised anion structures, nor in the transition state structure, the amide carbonyl group was found in close vicinity to the phosphoryl group and the counterion. Therefore, the observed hindered rotation should be attributed to the steric bulk of the substrates, rather than to anchoration by the lithium cation after deprotonation.
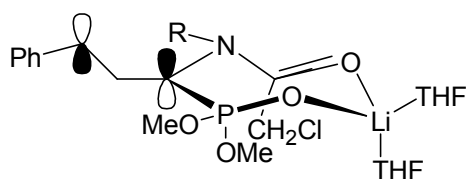
Figure 16: Intramolecular anchoration

The effect of the steric bulk is expected to be similar in the anion and in the parent protonated form **21a-f** (compared to anchoration which would only be possible in the anion state). Therefore, an important feature of the optimized anion structure (Figure 13) is also applicable to its parent *N*-chloroacetyl aminoalkenyl phosphonate: namely, the amide part of the molecule is directed towards the phosphonate side, or is more easily rotated in that direction, while the nitrogen alkyl substituent points towards the alkenyl system. These specific conformational properties can be demonstrated and exploited in more complex intramolecular reactions using this type of substrates (see chapter 3, section 3 and 4).

2.5 Biological evaluation of 4-phosphono β-lactam dialkyl esters

The influence of several 4-phosphono β-lactams **23** on the growth of fungi (Table 19) and bacteria (Table 20) was tested in cooperation with Kemin Pharma Europe. However, no promising activity could be observed. The growth of microorganisms was measured in the presence of the test compound at a concentration of 100 ppm. For comparison, the used control substances (antibiotics) result in 0% growth at a concentration of 1 ppm and lower. The test organisms were carefully chosen to represent each a specific class of microorganisms: yeasts (*Candida albicans, Cryptococcus neoformans*), moulds (*Aspergillus fumigatus, Trichophyton mentagrophytes*), Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and Gram positive bacteria (*Staphylococcus aureus, Enterococcus faecalis, Chlostridium perfringens*).
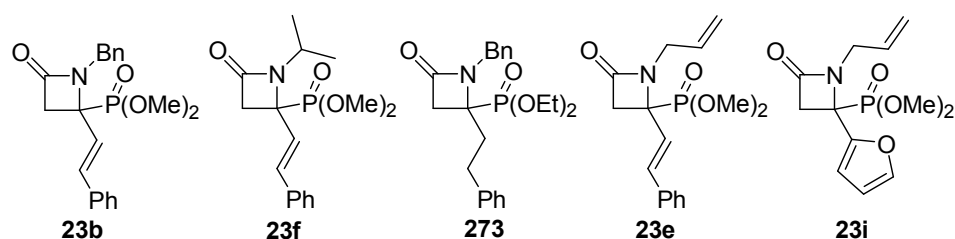
Table 19: Percentage growth of fungi in the presence of 100 ppm 4-phosphono β-lactams **23**

	C. albicans	*C. neoformans*	*A. fumigatus*	*T. mentagrophytes*
23b	93.7	56.2	94.7	54.6
23f	89.8	43.0	83.5	58.3
273	96.8	53.2	79.3	40.3
23e	89.8	49.2	88.9	51.0
23i	91.6	52.2	84.8	58.6

Table 20: Percentage growth of bacteria in the presence of 100 ppm 4-phosphono β-lactams **23**

	E. Coli	*P. Aeruginosa*	*S. Aureus*	*E. faecalis*	*C. perfringens*
23b	95.6	95.3	89.0	93.8	99.3
23f	95.4	95.7	94.0	94.7	98.7
273	97.3	95.0	89.7	89.4	96.6
23e	95.2	94.7	91.8	94.7	98.5
23i	97.0	92.5	94.4	94.7	99.3

2.6   Conclusion

In conclusion, preparation of 4-phosphono β-lactams starting from *N*-chloroacetyl aminoalkyl phosphonates can be conveniently performed through the formation of a phosphorus stabilized anion and subsequent intramolecular alkylation. The required *N*-chloroacetyl aminoalkyl phosphonates can be prepared in two ways. The first one involves a two-step sequence starting with the phosphonylation of a suitable imine followed by *N*-acylation of the resulting aminoalkyl phosphonates. This method proved to be the most versatile in regard to substrate variability and product yields. The second method involves a one-pot acylation – phosphonylation of an aromatic imine through an intermediate acyliminium ion. More side reactions are observed using this pathway. However, within a narrow spectrum of imines, it can be a valuable, fast alternative to the two step method.

The ring closure of *N*-chloroacetyl aminoalkenyl phosphonates was studied in more details. When these substrates are deprotonated, an allyl anion is formed which can be alkylated at two positions. Even though γ-alkylation would provide a six-membered ring, only α-alkylation is observed yielding a more strained four-membered ring. The main reason four this unexpected behaviour was found in the specific conformation of the *N*-chloroacetyl aminoalkenyl phosphonates and the corresponding anions. Due to a restricted rotation about the N–C(P) σ-bound, the transition state required for six-membered ring formation is considerably higher in energy than that for four-membered ring formation. From these results it is clear that the *N*-alkyl and *P*-alkenyl group are rotated easily towards each other. This property will be exploited in the next chapters to perform other intramolecular conversions of this type of substrates.

Finally, transformations of the obtained 4-phosphono β-lactams appeared to be very difficult. The corresponding free phosphonic acids could not be obtained in pure form. Nevertheless, the parent esters were tested for their activity against bacteria and fungi, however without any success.

3   Synthesis of 2-phosphono pyrroles

3.1   Introduction

Pyrroles represent an important class of heterocycles that display remarkable physiological (antibacterial, antiviral, anti-inflammatory, antitumor, antioxidant, hypocholesterolemic and immunosuppressant) activities.[343-348] Furthermore, they are useful intermediates in the synthesis of natural products as well as in heterocyclic chemistry[349] and they are widely used in material science.[350] As a consequence, many synthetic methods are known for the construction of the pyrrole nucleus. The most frequently used methods include the classical Hantzsch procedure, the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal-Knorr synthesis), and various cycloaddition strategies.[351,352] Nevertheless, only very little is known about the properties of phosphonylated pyrroles. This might be caused by the limited number of synthetically useful pathways towards these class of compounds.

289 (PNU-156804)
immunosuppressant

290 (prodigiosin)
anti-malaria, cytotoxic

291 (Atorvastatin)
hypocholesterolemic

292 (AWD140-190)
anticonvulsant

293 (Zomepirac)
anti-inflammatory

294 (Pyrrolnitrin)
antifungal,
antibacterial
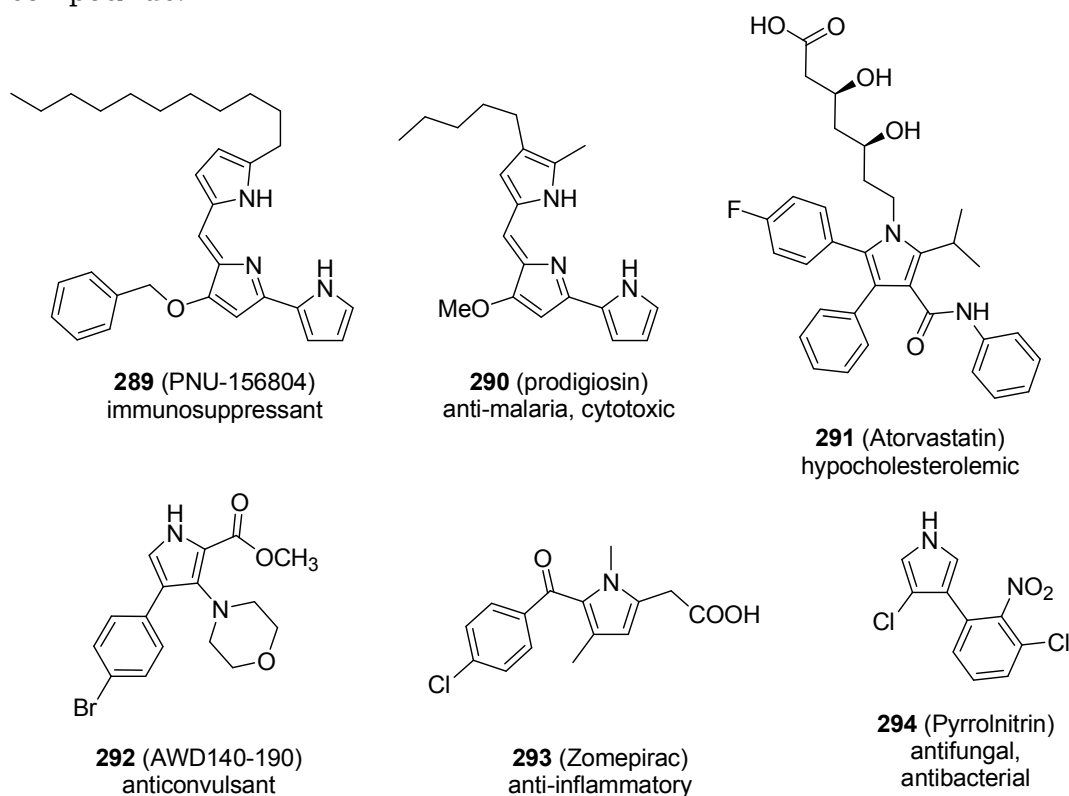
2-Phosphono pyrroles can be obtained through direct phosphorylation of a pyrrole nucleus, however only in low to moderate yields (23-54%).[353-355] Nitrile ylids containing an electron withdrawing phosphonate group have been reacted with alkynes[131,356,357] or alkenes containing a suitable leaving group[130,133,358] to yield 2-phosphono pyrroles via a 1,3-dipolar cycloaddition (for an example, see chapter 2, section 2.5). Addition of enolates and enamines to phosphono azoalkenes **296** or addition of cyano methyl

phosphonate anion to azoalkenes was shown to lead to 1-amino 3-phosphono pyrroles.[359-361] One example was presented in which a Boc protected 3-oxo 2-phosphono pyrrolidine was converted to the corresponding 3-hydroxy 2-phosphono pyrrole by treatment with trifluoroacetic acid.[166] Finally, only one example of a metal mediated ring closure between an alkyne and a C-N double bond using Pd has been reported.[362]

$R = COOEt, C(O)CH_3$
$R'_2 = (CH_2)_2O(CH_2)_2, (CH_2)_4$
$EWG = COOMe, P(O)Ph_2$
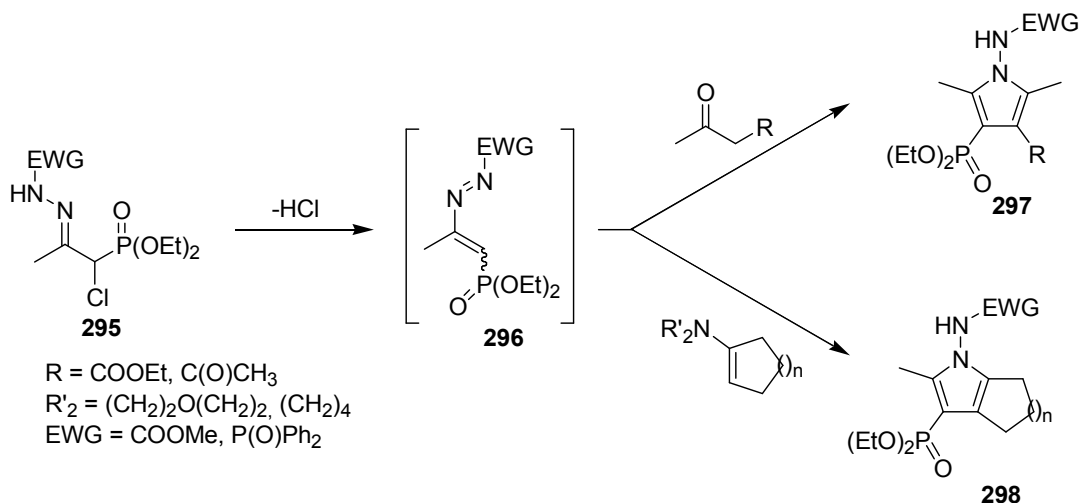
For the synthesis of 2-phosphono pyrroles, we focussed our attention to another organometallic reaction which found its great breakthrough in the late 1990's: ring-closing metathesis. Retrosynthetically, ring closure of a suitable functionalized diallylamine **32** would lead to the 2-phosphono 3-pyrroline **31** which would be converted to the corresponding pyrrole **30** by oxidation. Diallylamine **32** would be obtained for instance from a suitable aldehyde **299** and an allylamine through phosphonylation (see chapter 3, section 1.4) and benzylation.[363]
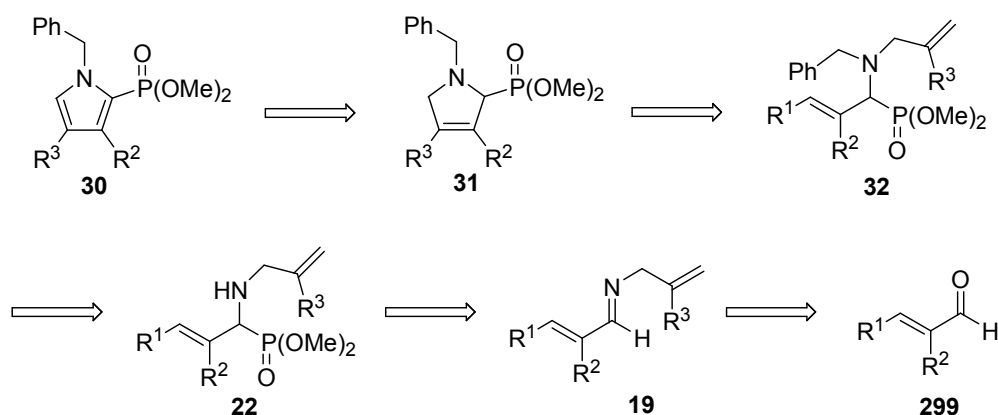
Olefin metathesis was discovered in the 1960's and was observed as a rearrangement around the double bounds in a mixture of olefins.[364] Various (mixtures of) metals could be used for these reactions and a generally

accepted mechanism for this metal mediated rearrangement was proposed by Chauvin.[365] When two alkenes are present in the same molecule, intramolecular rearrangement may result in a cyclic structure. This type of metathesis is known as <u>R</u>ing-<u>C</u>losing <u>M</u>etathesis (RCM). Since the discovery and development of practical useful, well-defined ruthenium based metathesis catalysts (e.g. **300 – 301**) in the past decennium,[364,366-368] ring-closing metathesis has found wide application in the synthesis of complex (hetero)cyclic compounds.[369-373] The use of RCM to form heteroaromatic compounds, however, has only recently appeared in the literature.[374-376]

300   **301**   **302**
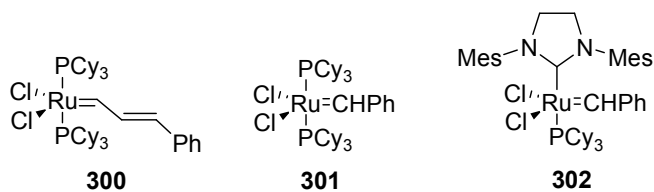
3.2 Benzylation of α-aminoalkenyl phosphonates

Cinnamaldehyde could be easily condensed with allylamine and phosphonylated using dimethyl phosphite in high yield and purity (see chapter 3, section 1.4). The resulting α-aminoalkenyl phosphonate **22e** was then treated with 1 equivalent of benzyl bromide in the presence of a large excess (7 equivalents) of K_2CO_3 in acetone (dilution: 0.35 M). Complete conversion was only obtained after more than 22 h of reflux. When repeating the experiment for preparative reasons, a rate enhancement could be observed when the reaction medium was more concentrated. Therefore, a solid state experiment was evaluated in wich the starting material **22e** was coated onto solid K_2CO_3 together with 1 equivalent of benzyl bromide by evaporating the solvent from the previously made dispersion. To obtain an optimal result, very fine K_2CO_3 should be used, for instance by grinding it in a mortar. The reaction medium obtained by this procedure was very much suited for microwave (MW) heating[377] in an open vessel.

The results of microwave irradiation are compared to those of conventional heating in Table 21. An enormous rate enhancement can be observed using MW conditions and solid state reaction media: up to 93% conversion to **32a** as a single reaction product in 5.5 minutes (entry 4). However, one should not neglect the effect of the higher concentration in the solid state medium: 1.5 minutes of MW heating followed by storage for 14 h at room temperature (entry 5) nearly gives the same result as 2.5 minutes of MW heating (entry 3). Also a sample left at room temperature for 12 minutes without any irradiation, already showed 22% conversion. Furthermore, the results obtained using this MW protocol are poorly reproducible, probably because of the problematical diffusion in the solid state reaction medium.

Table 21: Evaluation of different heating conditions for the synthesis of *N*-benzyl aminoalkenyl phosphonates **32a**
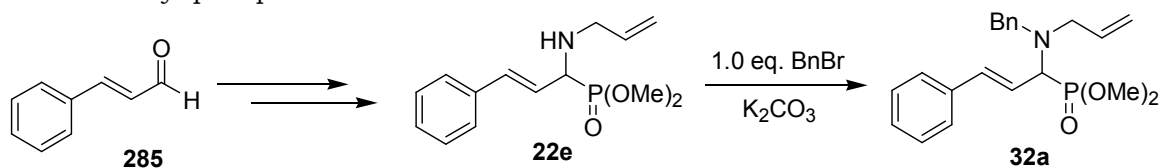
	Dilution	Heating	Reaction time	Conversion
1	0.35 M	Conventional heating (Δ)	22 h	99%
2	-	MW, open vessel, 450 W	30"	16%
3	-	MW, open vessel, 850 W	2'30"	63%
4	-	MW, open vessel, 850 W	5'30"	93%
5	-	MW, open vessel, 850 W	1'30" + 14 h rt	66%

Several other substrate/reagent combinations were tested under conventional and MW heating conditions. In all cases, either no reaction or complex mixtures were observed. Changing to KOH as a stronger base instead of K₂CO₃ also resulted in complex mixtures. In conclusion, no good general alkylation method for α-aminoalkenyl phosphonates using MW heating could be developed.
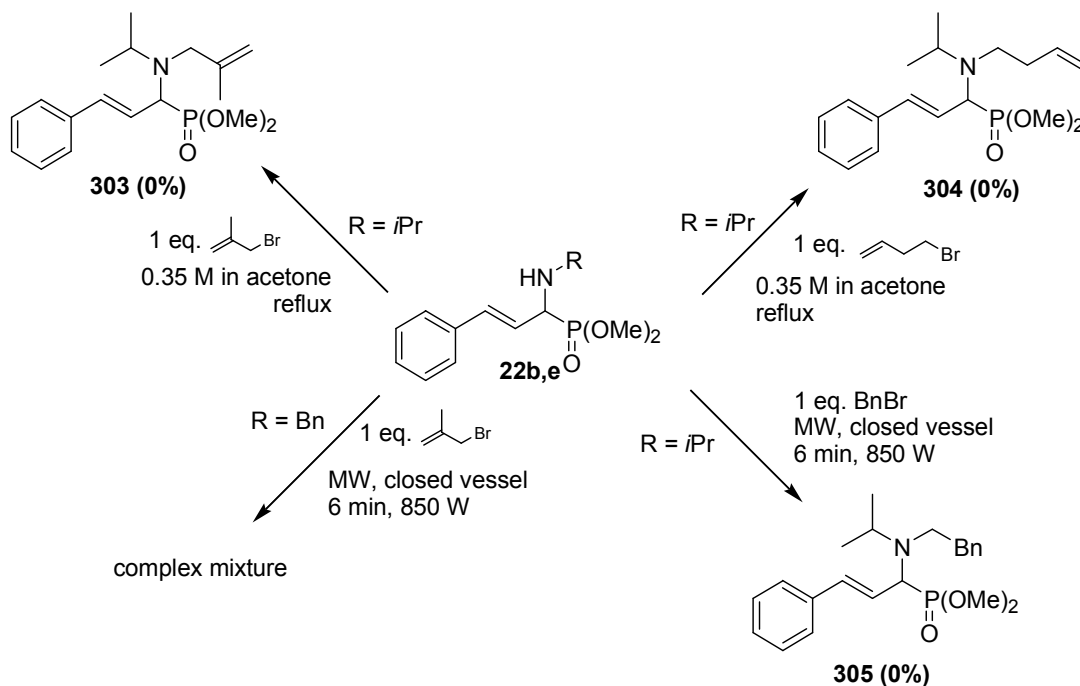
Benzylation of *N*-allyl α-aminoalkenyl phosphonates is possible in reasonable reaction times (16 to 20 h) using a slight excess (1.5 equivalents) of benzyl bromide and high substrate concentrations (e.g. 1 to 1.5 M). Even shorter reaction times are possible by adding 0.5 equivalent of NaI to the reaction mixture (5-10 h). The reaction can be conveniently monitored using ³¹P NMR. After complete conversion of the starting material, the obtained reaction mixture mainly consists of the end product and the excess of benzyl bromide. Acid base extraction was not useful to isolate the benzylated aminoalkenyl phosphonates. Pure samples were obtained using column chromatography, however, resulting in considerable product losses. The results of the benzylation, phosphonylation and condensation reaction are presented in Table 22. Commercial aldehydes **299d** and **299e** were purchased as E/Z-mixtures. Although both isomers displayed different reaction rates, they were equally converted to the corresponding end products.

Table 22: Synthesis of *N*-benzyl aminoalkenyl phosphonates **32**
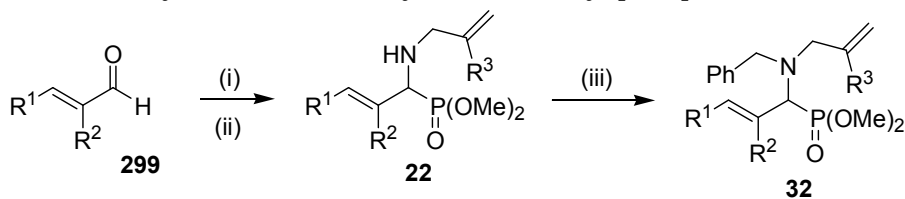
(i) 1.1 eq. of amine, 2 eq. MgSO$_4$, CH$_2$Cl$_2$, rt., 12 h;

(ii) 2 eq. DMP, MeOH, Δ, 2-3 h;

(iii) 1.5 eq. BnBr, acetone (1.0 M solution), K$_2$CO$_3$, 0.5 eq. NaI, Δ, 5 - 10 h.

SM	R^1	R^2	R^3	22$^¤$		32$^\#$	
299a	Ph	H	H	**22e**	95%	**32a**	61%
299b	Ph	Me	H	**22l**	90%	**32b**	50%
299c	Me	Bn	H	**22p**	27%	**32c**	50%
299d	Ph	isoamyl	H	**22m**	88%*	**32d**	54%*
299e	Me	Ph	H	**22o**	80%*	**32e**	35%*
299f	Me	CH$_2$CH$_2$Ph	H	**22q**	44%	**32f**	92%
299a	Ph	H	Me	**22f**	74%	**32g**	86%
299g			H	**22v**	80%	**32h**	66%
299h	Ph	Cl	H	**22n**	63%		-

$^¤$ Yield from **299** after acid/base extraction (see chapter 3, section 1.4)

$^\#$ Yield after column chromatography

* Mixture of *E* and *Z* isomers

Next to the commercial aldehydes, a literature procedure[378] was evaluated in order to prepare more diverse substrates **299c,f**. For this reason, cyclohexyl imine **19p** was prepared using 10 g of crotonaldehyde **276**, 30 g of cyclohexylamine (2.2 eq.), 14 ml of benzene and 5.9 g of K$_2$CO$_3$. The imine can only be obtained in pure form as a colourless oil (40% yield) after two consecutive vacuum distillations (at 10 and 42 mbar respectively) and should be stored at –20°C, shielded from sunlight.
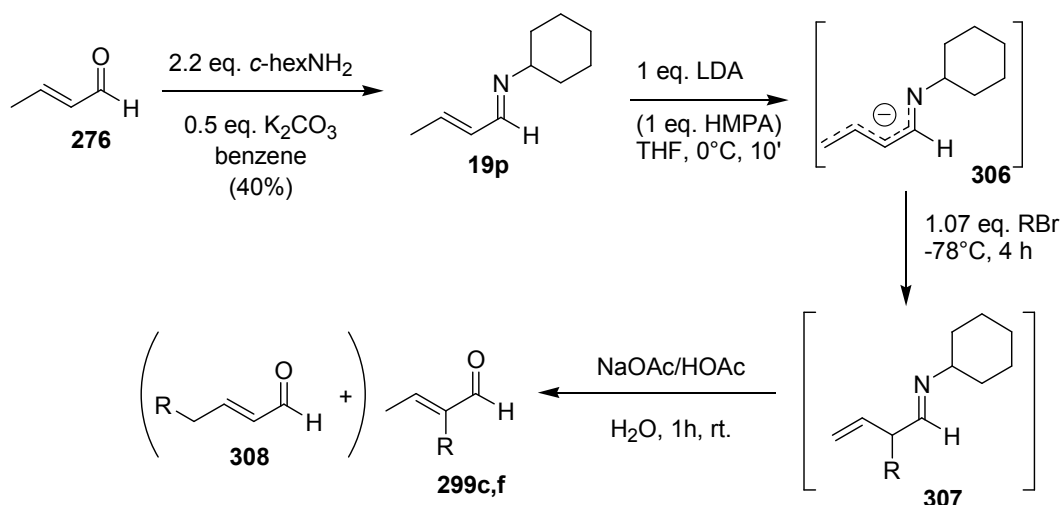
Treatment of imine **19p** with LDA at 0°C yields an ambient anion **306** which is subsequently trapped with an alkyl bromide at –78°C.[379,380] The intermediate imine **307** is then treated with an aqueous acetate buffer mixture to perform the hydrolysis and the double bond isomerization[#] yielding the desired 2-butenal derivatives **299**. Complete regioselectivity was claimed in the original paper for the *c*hex-imine.[378] Although the corresponding *t*Bu imine is far more easy to prepare and to isolate, it is not selected for this alkylation reaction since regioselectivity is known to be rather poor.[381]

Table 23: Preparation of α-substituted crotonaldehydes **299c,f**

	R	HMPA	Yield	299:308[§]
1	Allyl	+	77%	86:14
2	Bn	+	95%	93:7
3	Bn	-	82%	97:3
4	CH_2COOMe	+	To low conversion	
5	CH_2COOMe	-	To low conversion	
6	CH_2CH_2Ph	+	80%	92:8

[§] Determined from the crude reaction mixture using GC-MS

Unfortunately, the yields as well as the regioselectivity were less advantageous in our hands (Table 23). HMPA[382] seemed to have a beneficial influence on the reaction yield, but lowered the regioselectivity somewhat. No separation of the isomeric products was possible using column chromatography and therefore, only the benzyl and phenylethyl derivatives were useful in the following reaction steps. In both cases, the crude reaction mixture was used to form the imines and α-aminoalkenyl phosphonates. Phosphonate **22p** could be obtained in pure form by crystallization.

[#] In one case (R = CH_2COOMe) spontaneous isomerization of the double bond in imine **307** occurs from the 3-position to the 2-position.

3.3 Ring closure to 2-phosphono 3-pyrrolines

Grubbs' 2nd generation catalyst **302** was selected to perform the ring closure of substrates **32**, because of its stability to ambient conditions, its high activity and its excellent thermal stability.[367,383] The catalyst **302** was added to a 0.1 M solution of substrates **32** in dry dichloromethane and the reaction was conveniently monitored using ^{31}P NMR. Notwithstanding the presence of a nucleophilic nitrogen atom, pyrrolines **31** were formed very smoothly in 3 to 5 h at room temperature as a single reaction product ($\delta(^{31}P) = 24.58$-24.91 ppm).[¤] Most examples of azaheterocyclic ring formation presented in literature are dealing with non-nucleophilic nitrogen groups (e.g. amides, carbamates, sulfonamides,...).[371-373] Failure of RCM reactions with substrates containing a nucleophilic nitrogen atom adjacent to the metathesized alkene is often attributed to poisoning of the catalyst or disfavoured conformation of the substrate.[384-390] After complete conversion of the starting aminoalkyl phosphonates **32** (3-5 h at room temperature), the phosphono pyrrolines **31** could be obtained in pure form as a colourless oil via an acid base extraction of the reaction mixture, which illustrated the basic properties of the pyrroline (Table 24). Pyrroline **31f** could not be isolated. Instead, 1-benzyl-3-(2-phenylethyl)-*1H*-pyrrole was formed, probably due to aromatization through elimination of the phosphonate group during work-up. This reaction was not observed in any of the other cases.

Table 24: Synthesis of 2-phosphono 3-pyrrolines **31** via RCM
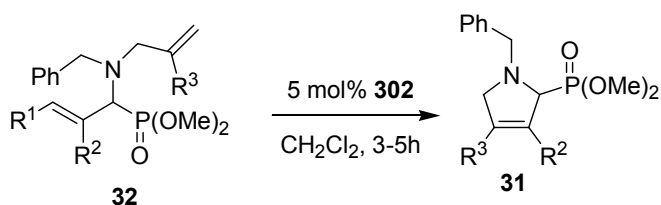
SM	R^1	R^2	R^3	Product*	
32a	Ph	H	H	**31a**	44%
32b	Ph	Me	H	**31b**	58%
32c	Me	Bn	H	**31c**	62%
32d	Ph	isoamyl	H	**31d**	70%
32e	Me	Ph	H	**31e**	54%[§]
32f	Me	CH$_2$CH$_2$Ph	H	-	-
32g	Ph	H	Me	-	-

*Yield after acid/base extraction
[§] Spontaneous oxidation to pyrrole **30e** using air
was observed during work-up.

In the case R^1 is phenyl, styrene is formed during the ring-closing reaction, which unlike ethene does not boil off from the reaction mixture. Liberation of

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[¤] In case of phosphonate **32e**, complete conversion to pyrroline **31e** needed 3 h at reflux temperature. The E/Z isomers of phosphonates **32d** and **32e** were converted at different eaction rates to the same product.

ethene from the reaction mixture is often indicated as the driving force in RCM reactions. A closer look to the crude ^{1}H NMR spectrum revealed the presence of stilbene, which could also be obtained as colourless crystals from the reaction mixture. Stilbene is probably formed together with ethene via cross metathesis of styrene in a second catalytic cycle. It should be noticed that two active species of the catalyst are present in the reaction mixture: carbene **310**, which is presented as the propagating species in the general Chauvin mechanism,[365] and Grubbs' carbene **302**, which is regenerated during the catalytic cycle in this case.
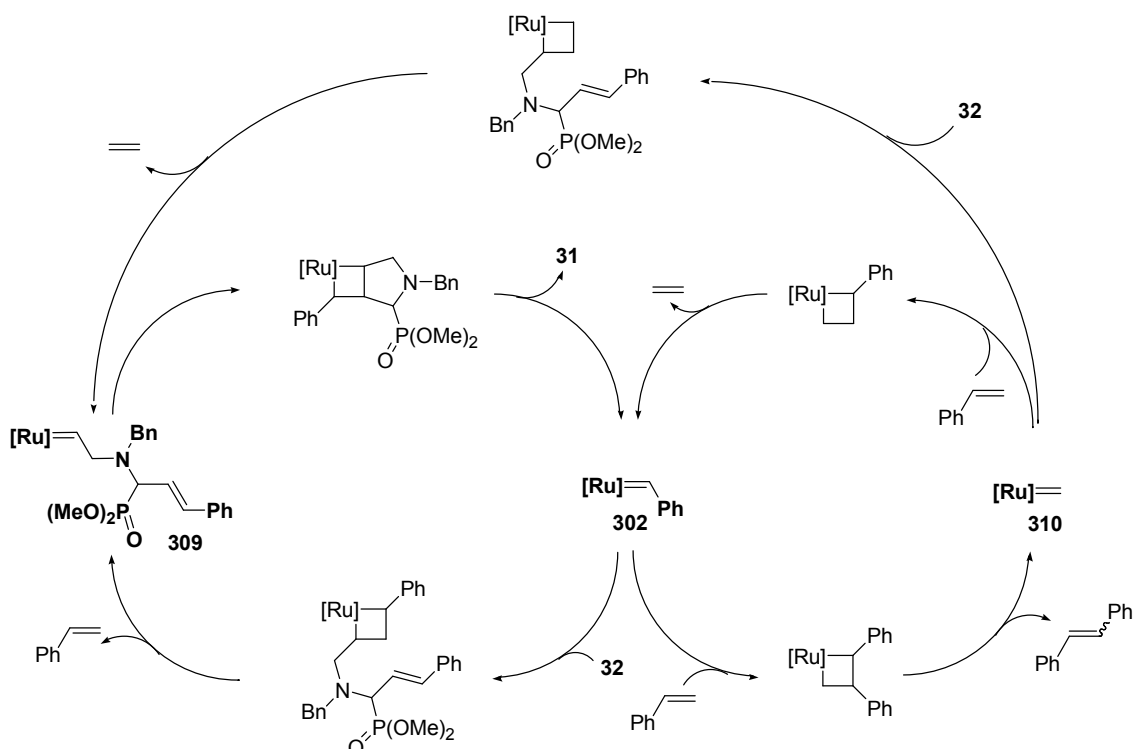
While substituted double bounds are often not well tolerated by ruthenium based catalysts,[391] R^1 (Ph or Me) and R^2 groups very much are in this case, even under very mild conditions. However, when phosphonate **32g** (R^3 = Me) was selected as a substrate in the RCM reaction, no reaction occurred at all and the starting material was recovered, even under reflux conditions in CH$_2$Cl$_2$ or benzene. When switching to refluxing chlorobenzene as a solvent, ^{31}P NMR showed the disappearance of the starting material and the simultaneous appearance of a signal at 10.4 ppm. Upon work-up, this signal proved to be the corresponding enaminophosphonate resulting from the migration of the double bound towards the phosphonate. These observations indicated that the RCM reaction is most likely initiated via the least hindered double bond and that the following intramolecular conversions are less dependent on the steric bulk of the olefin. When two substituted double bonds are present in the molecule, the initiation seems to be delayed to such a large extent that no reaction is possible anymore.[391]

3.4 Ring closure – oxidation to 2-phosphono pyrroles

In order to obtain phosphono pyrroles **30**, the use of tetrachloroquinone (TCQ) has already proven effective in combination with catalyst **302**.[392] An increasing interest exists in combining ring-closing metathesis with a second reaction step (such as RCM and a Pd mediated coupling reaction,[393,394] a double bond isomerisation,[395-397] a Diels-Alder,[398] an oxidation[399] or a dihydroxylation reaction[400]) in order to obtain complex, highly functionalized molecules in a one-pot reaction. When phosphonates **32** are treated with catalyst **302** and 1 equivalent of TCQ, the expected pyrroles **30** are formed as a single reaction product ($\delta^{31}P$ = 13-15 ppm) after stirring for up to 16 h at room temperature. Monitoring the reaction using ^{31}P NMR, a minor decrease of the RCM reaction rate was observed by the action of TCQ. When catalyst **302** was allowed to react for 2 h with the substrate (giving approximately 60% conversion to the pyrroline) before the addition of TCQ, the pyrroles were obtained after 5-7 h at room temperature.[#]

Table 25: Synthesis of 2-phosphono pyrroles **30** via RCM
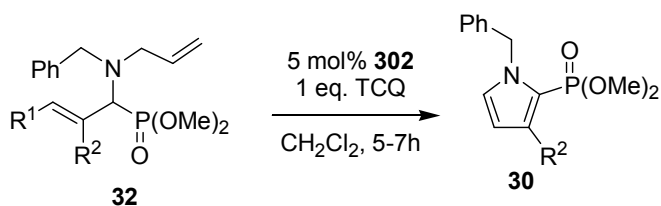
SM	R^1	R^2	30*	
32a	Ph	H	**30a**	75%
32b	Ph	Me	**30b**	84%
32c	Me	Bn	**30c**	72%
32d	Ph	isoamyl	**30d**	70%
32e	Me	Ph	**30e**	75%[#]
32f	Me	CH$_2$CH$_2$Ph	**30f**	71%

* Yield after column chromatography

A mechanism for this ring-closing metathesis with *in situ* oxidative aromatization has already been proposed before, in which TCQ is considered as a hydrogen acceptor.[392] No ruthenium is really required for the oxidation,[401,402] as pure **31b** and **31d** are also converted to the corresponding pyrroles **30b,d** by stirring with TCQ at room temperature for 22 h. However, this is considerably slower than in the presence of catalyst **302**. Two reaction pathways may be considered to explain these results: (a) hydrogen atoms are transferred in the process of oxidative addition and reductive elimination which involves hydride complexes with the metal or (b) hydrogen donor and

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[#] Complete conversion to pyrrole **30e** was achieved after 5 h at reflux followed by 12 h at room temperature.

acceptor are brought together by simultaneous coordination to the central metal of the catalyst, followed by direct transfer of the hydrogen atoms from the pyrroline to the TCQ.[403] In light of the mild reaction conditions in combination with the fact that no pyrrole formation is observed in the absence of TCQ, the assumption that hydrogens are transferred via pathway (b) seems to be reasonable.

With these excellent RCM results in hand, we tried to ring close phosphonates **22e** and **22m** possessing a free NH group. When the reaction was monitored using ^{31}P NMR, decreasing reaction rates were observed, and a maximum conversion of only 30% was reached (Figure 17). This kind of behaviour suggests catalyst inhibition by the pyrroline **311a,b** rather than by the starting material **22e,m**.
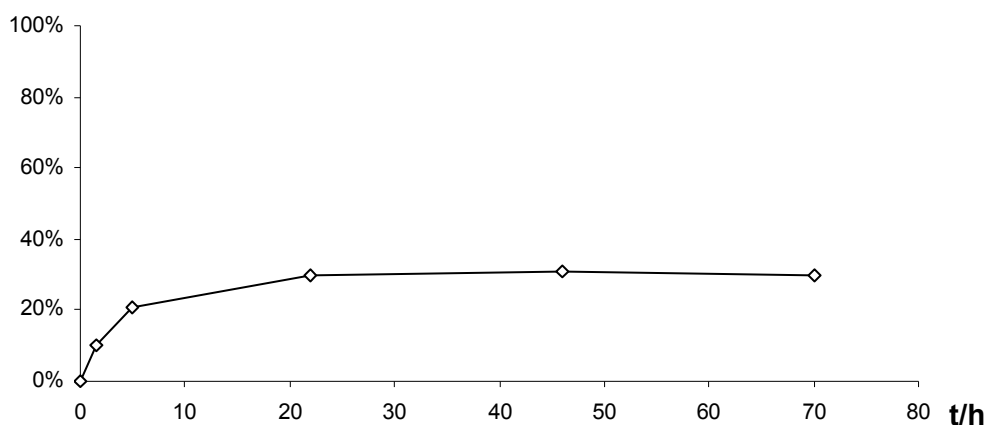
Figure 17: Conversion of **22e** to **311a** at room temperature in the presence of 5 mol% of catalyst **302**, measured by ^{31}P NMR. (%**311a** in the reaction mixture versus time in hours).

When TCQ was added together with catalyst **302**, the formed pyrroline **311** was oxidized immediately in the reaction mixture and 100% conversion to the pyrrole **312a,b** was observed at room temperature in dichloromethane in 75 h. However, during the course of the reaction, side products started to appear. Therefore, the reaction was repeated at higher temperatures in order to decrease the reaction time and the concomitant side product formation. Cleaner reaction mixtures were obtained at reflux temperatures in 23 h in dichloromethane or in 7 h in benzene. Even though the reaction mixture was much less clean than in the case of the *N*-benzyl substrates **32**, and pyrroles **312** could only be obtained in low yields after a laborious chromatographic purification, the reaction sequence clearly illustrates the synergism between ruthenium mediated ring-closing metathesis and oxidation by TCQ: inhibition of the catalyst is avoided by instantaneous conversion of the

nucleophilic nitrogen atom to a non-nucleophilic form and aromatization is probably the major driving force of the reaction sequence. To the best of our knowledge, this is the first example of RCM using the 2nd generation Grubbs' catalyst **302** on secondary free amines without the need to convert them to a hydrochloric salt. Furthermore, the failure of RCM reactions with substrates containing a NH functionality should be attributed to its nucleophilic properties rather than to the need of a proper conformation for ring closure.
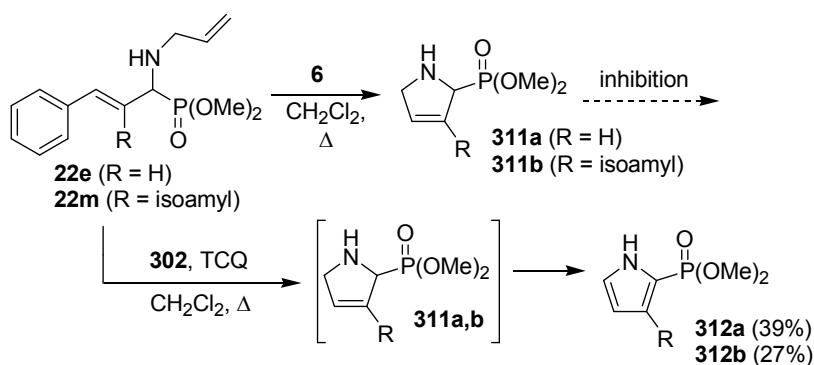
We tried then to exploit the observed synergism between RCM catalyst **302** and TCQ to perform a *ring-rearrangement metathesis* (RRM)[404] using substrate **32h** derived from myrtenal. RRM is a combination of ring opening metathesis (ROM) and RCM. ROM has been used already to polymerize highly strained cycloalkenes like cyclobutenes[405] and norbornenes.[406] The high strain in these rings constitutes the driving force for the ROM reaction. However, with the development of highly active metathesis catalysts in the last decade, a wide area of substrates has been used in RRM reactions.[407-409] Nevertheless, even with the powerful new catalysts, an equilibrium is always established which can be shifted to one side by means of a sufficient change in free energy. This can be achieved by means of the properties of the substrate (e.g. release of ring strain, decrease of steric bulk,...) or by presenting a "sink" to one of the products of the equilibrium (e.g. an additional RCM with release of ethene).[410] The sink would be provided in this case by the aromatization of pyrroline **31h** to the corresponding pyrrole **30h**.
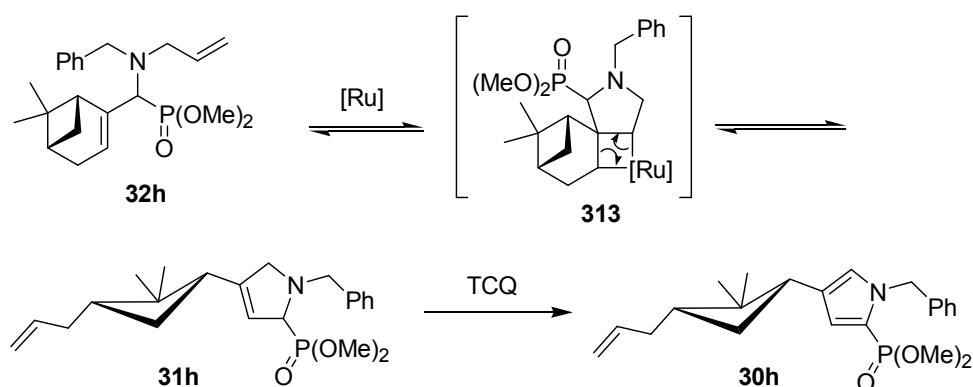
Several reaction conditions were evaluated with 5 mol% of catalyst **302** in 0.1 M solutions of the amine **32h** (Table 26). However, when no TCQ was added, the reaction mixture mainly consisted of starting material next to five or six unidentified side products (entry 1, 3). No reaction occurred at all in the presence of TCQ at room temperature or when refluxing in dichloromethane or benzene (entry 2, 4, 5). Finally, the hydrochloride salt of **32h** was formed prior to the metathesis reaction. However, regardless of the temperature profile of the reaction, only starting material was recovered after aqueous work-up (entry 6, 7).

Table 26: Evaluation of the RRM reaction of **32h** with 5 mol% of Ru catalyst **302**

	SM	Solvent	TCQ	Conditions	Result
1	**32h**	CH_2Cl_2	-	rt., 23 h	SM + unidentified side products
2	**32h**	CH_2Cl_2	1 eq.	rt., 24 h	SM
3	**32h**	CH_2Cl_2	-	Δ, 2.5 h	SM + unidentified side products
4	**32h**	CH_2Cl_2	1 eq.	Δ, 3.5 h	SM
5	**32h**	Benzene	1 eq.	Δ, 2 h	SM
6	**32h**.HCl	CH_2Cl_2	-	rt., 3.5 h	SM
7	**32h**.HCl	CH_2Cl_2	-	Δ, 1 h	SM

The failure of the reaction may be explained in terms of steric bulk, which inhibits the catalyst initiation. Substituent effects have been shown to have a large effect on the course of an RRM reaction.[410] Furthermore, the release of ring strain from **32h** is only minor, since the most strained four-membered ring continues to exist in the pyrroline **31h**.

3.5 Spectral characteristics of 2-phosphono pyrroles

When looking at the ^{13}C chemical shifts in the 2-phosphono pyrrole nucleus, a surprising influence of the phosphonate group can be noted. Due to the inductive effect of the nitrogen atom, C^4 is clearly shifted downfield, while C^3 is more shielded because of the mesomeric effect of the nitrogen atom. The electron withdrawing phosphonate group is able to invert the nitrogen mesomeric effect at C^2 causing it to appear at lower field. Notwithstanding the electron withdrawing capacities of the nitrogen atom, C^1 is very much shielded. This illustrates the electron donating capacities of the phosphonate group.[225] Phosphorus, carbon couplings are present throughout the pyrrole nucleus and are fairly constant in all derivatives. More detailed spectral data can be found in the experimental section (chapter 4, section 5.4) and in appendix E.
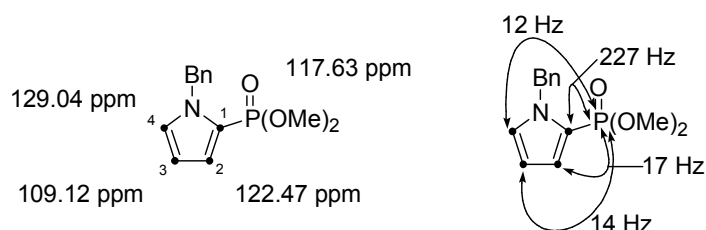
3.6 Evaluation of the preparation of bicyclic phosphono β-lactams via RCM

Although most antibiotics possess a bicyclic β-lactam core (see chapter 3, section 2.1), phosphonylated bicyclic β-lactam compounds have only been studied very scarcely, without any promising antibacterial activity so far.[64,411-416] From the results in the previous section, it was clear that the Grubbs' 2nd generation catalyst **302** is able to convert phenyl or methyl substituted double bonds and furthermore well tolerates the phosphonate and amino groups in the substrate. Furthermore, β-lactams are well tolerated under metathesis conditions.[417] Therefore, RCM constitutes a valuable technique for the preparation of bicyclic phosphono β-lactams starting from the already obtained monocyclic derivatives.

Phosphono β-lactam **23e** was selected as the substrate for the RCM reaction, which should lead to a carbapenem-like skeleton **33**. A 0.3 M solution of the β-lactam **23e** in dichloromethane was refluxed in the presence of 5 mol% of catalyst **302**. Complete conversion was obtained in only 1h. However, only the dimer **314** was formed as a mixture of (*E*)- and (*Z*)-isomers. A more dilute reaction medium (up to 0.03 M) and prolonged reaction times were believed

to lower the degree of dimerization in the final reaction mixture. Nevertheless, the desired bicyclic lactam was never formed, which may that the rigid β-lactam has lost the favourable conformation of its precursor **21**.
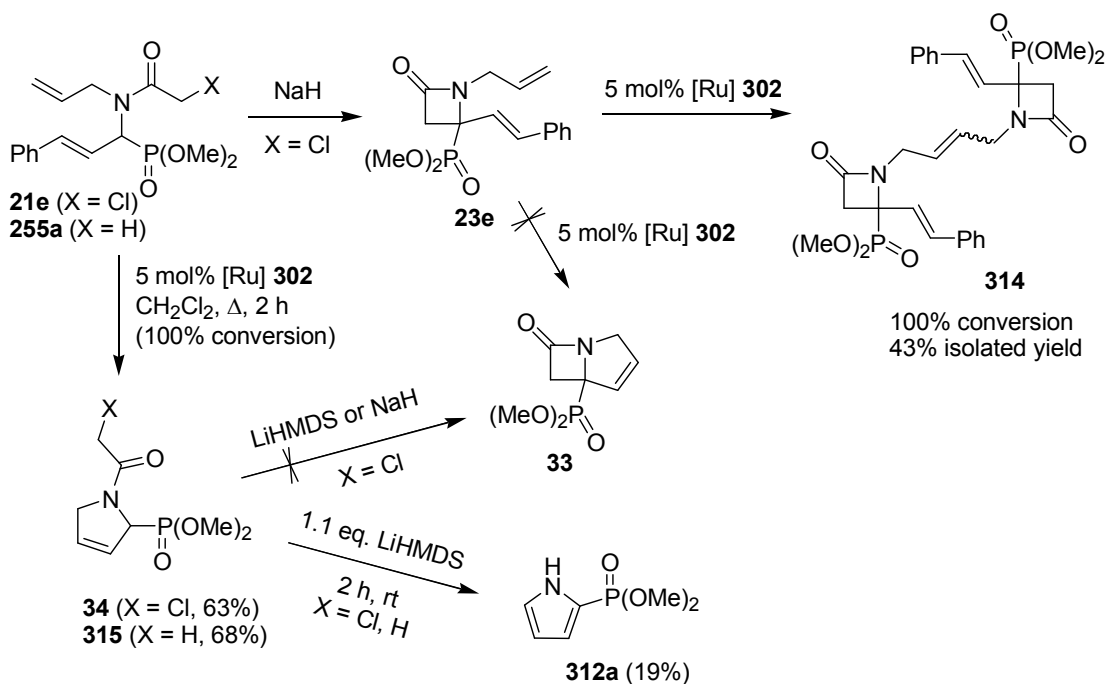
To avoid these conformation problems, the five-membered ring was formed first via RCM with *N*-chloroacetyl aminoalkenyl phosphonate **21e**. It was shown in chapter 3, section 2.4.4 that both alkenyl ends are directed towards each other. The reaction proceeded very smoothly indeed, affording pyrroline **34** in 63% yield after column chromatography. The pyrroline **34** was then treated with LiHMDS in order to invoke ring closure. However, no ring-closed product could be detected in the final reaction mixture. Aqueous work-up resulted in considerable losses and only pyrrole **312a** could be isolated in low yield using column chromatography. With NaH, a more complex reaction mixture was obtained, however also containing pyrrole **312a**. Chlorine was expected to play an essential role in the mechanism of this transformation. However, when *N*-acetyl pyrroline **315** was submitted to treatment with LiHMDS, the same pyrrole **312a** was obtained in low yield. No further investigations were performed to reveal the reaction mechanism.

3.7 Conclusion

From the results in chapter 3, section 2.4 it was clear that *N*-allyl aminoalkenyl phosphonates should be excellent substrates for a RCM reaction. This was confirmed by their conversion to 2-phosphono 3-pyrrolines and 2-phosphono pyrroles. Notwithstanding the presence of a

basic nitrogen atom in the substrates, the RCM reaction was performed smoothly by Grubbs' 2nd generation ruthenium catalyst. The resulting pyrrolines were smoothly oxidezed to the corresponding pyrroles in one-pot or in a second step using TCQ.

Inhibition of the RCM catalyst by the pyrrolines was observed, however, when secondary amines were used in the reaction. Nevertheless, the corresponding *1H*-pyrroles could be obtained when the oxidation of the intermediate pyrrolines was performed *in situ*. This behaviour indicates the great synergism between TCQ and the Grubbs' 2nd generation catalyst.

4 Synthesis of tricyclic phosphono pyrrolidines

4.1 Introduction

Few reactions can compete with the Diels-Alder cycloaddition with respect to the degree of structural complexicity that can be achieved in a single synthetic step. It is well-known that aromatic heterocycles, such as furans and thiophenes, can undergo Diels-Alder reactions as the 4π diene components despite their aromaticity and hence expected decreased reactivity.[418-421] Also the intramolecular Diels-Alder reaction (IMDA) is amenable to the use of furans as dienes and is frequently designated as the IMDAF reaction. The scope of the reaction is quite broad with respect to the diene (furan), the dienophile, and the tether linking the two.[422] Furthermore, the IMDAF reaction is particularly attractive as two or more rings can be constructed in a single step with high regio- and stereocontrol, providing a convenient entry into polycyclic targets including natural products.[423-430]

4.2 Synthesis and structural characterization

The allylaminofuran-2-ylmethyl phosphonate **22z** is a suitable substrate for the IMDAF reaction. Furthermore, it was clear from the results in chapter 3, section 2.4 that when aminoalkyl phosphonate **22z** was acylated at nitrogen, the *N*-alkyl substituent should be directed towards the furane heterocycle, or should be easily rotated in that direction. This predicted conformation would greatly enhance the IMDAF reaction. To investigate this hypothesis, aminoalkyl phosphonate **22z** (see chapter 3, section 1.4) was treated with various acid chlorides. As reported in chapter 3, section 2.2.1 these reactions proceeded smoothly at room temperature, yielding the corresponding amides **36** in high purity. With pyvaloyl chloride, however, complex mixtures were obtained under different reaction conditions. When allylaminofuran-2-ylmethyl phosphonate **22z** was refluxed in toluene, only break down of the starting material was observed upon prolonged heating times. However, when the corresponding amides **36** were refluxed in toluene, complete conversion to the ring closed products **35** was observed in all cases. The results in Table 27 indicate that the reaction time was strongly dependent on the steric bulk of the amide chain. With a chloroacetyl group, 24 h of reflux was required, while the ring-closed product **35e** (R = CCl$_3$) was already formed during the acylation reaction at room temperature and subsequent aqueous work-up. This reactivity order was in accordance with the results reported for similar substrates **317** only missing the phosphonate group and can be explained by a combined steric and electronic effect in the amide side chain.[431]
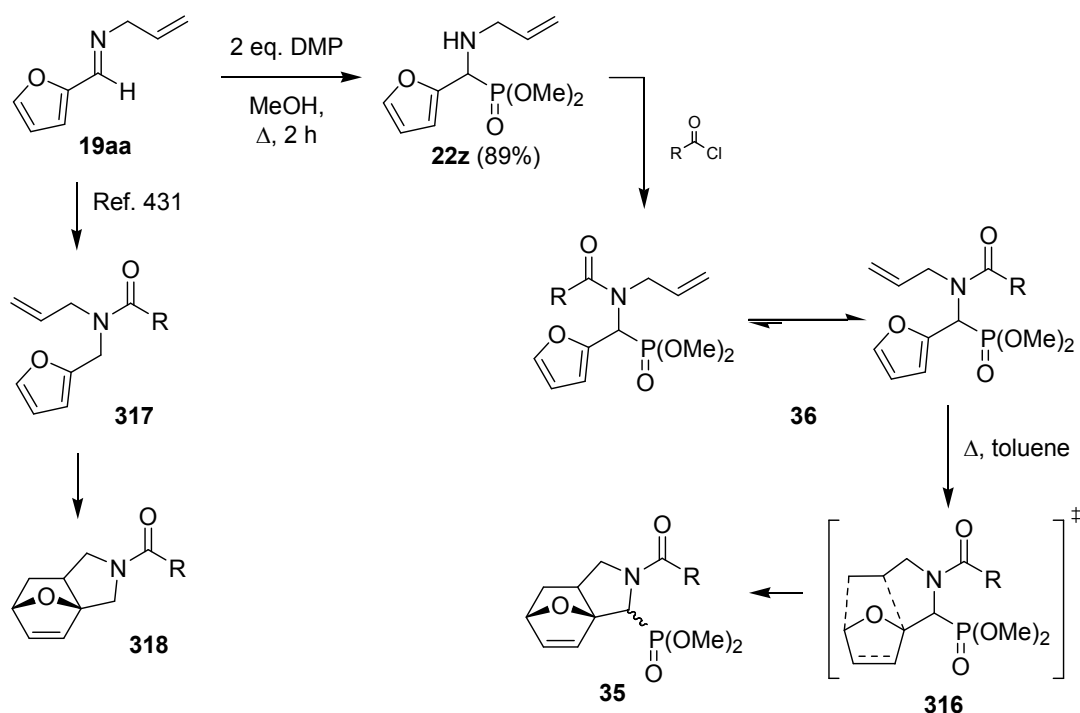
However, a remarkable influence of the phosphonate group was observed. While amides **318a** and **318c** could only be obtained in low yield because of the poor conversion, the corresponding phosphono amides **36a,c** gave complete conversion and could be obtained in reasonable yields after column chromatography. The positive influence of high tether substitution on IMDAF reactions is often attributed to the *Thorpe-Ingold effect* (*gem-dialkyl effect*) or to the *active rotamer effect*.[422,431,432] The latter is in complete accordance with the results discussed in chapter 3, section 2.4.

Table 27: IMDAF reaction of (acylallylamino)furan-2-ylmethyl phosphonates **36**

	R	Yield 36	Yield 35[§]	Isomer ratio 35	Time 35	Conversion 317→318[#]
a	CH$_2$Cl	98%	75%	27/73	20 h	43%
b	(CH$_2$)$_2$CH$_2$Cl	88%	47%	20/80	4.5 h	-
c	*i*Pr	88%	53%	17/83	7 h	62%
d	CHCl$_2$	96%	94%	35/65	3 h	100%
e	CCl$_3$	99%[¤]	99%	21/79	1 h[¤]	100%

[§] All adducts **35** are formed with 100% conversion. Yields reported are isolated yields, after column chromatography or crystallization
[#] 30-40 h reflux in acetonitrile (results from ref. 431)
[¤] The cycloadduct **35e** was already formed at room temperature during the acylation reaction and subsequent work-up. The obtained mixture of **36e** and **35e** is refluxed for 1 h in order to obtain complete conversion to **35e**.

The structure of the tricyclic pyrrolidines was confirmed by its 2D DQFCOSY, HSQC (Figure 18) and HMBC spectra and on comparison with data from compounds **318**. The ^{1}H NMR spectrum is characterized by a large difference

in chemical shift of both NCH$_2$ protons, clearly indicating that they are on opposite sides of a rigid ring system. Similar to pyrrolidines **318**, the phosphono pyrrolidines **35** were isolated as a mixture of two isomers. Ghelfi and coworkers showed, based on a NOESY experiment, that the configuration of the tricyclic skeleton in **318** was *exo* and that the two isomers were amide rotamers.[431] However, in case of phosphono pyrrolidines **35**, the isomers might originate from three diverse structural properties: (i) amide rotamers, (ii) *endo-* or *exo*-annulation, or (iii) configuration of the C(2) centre.
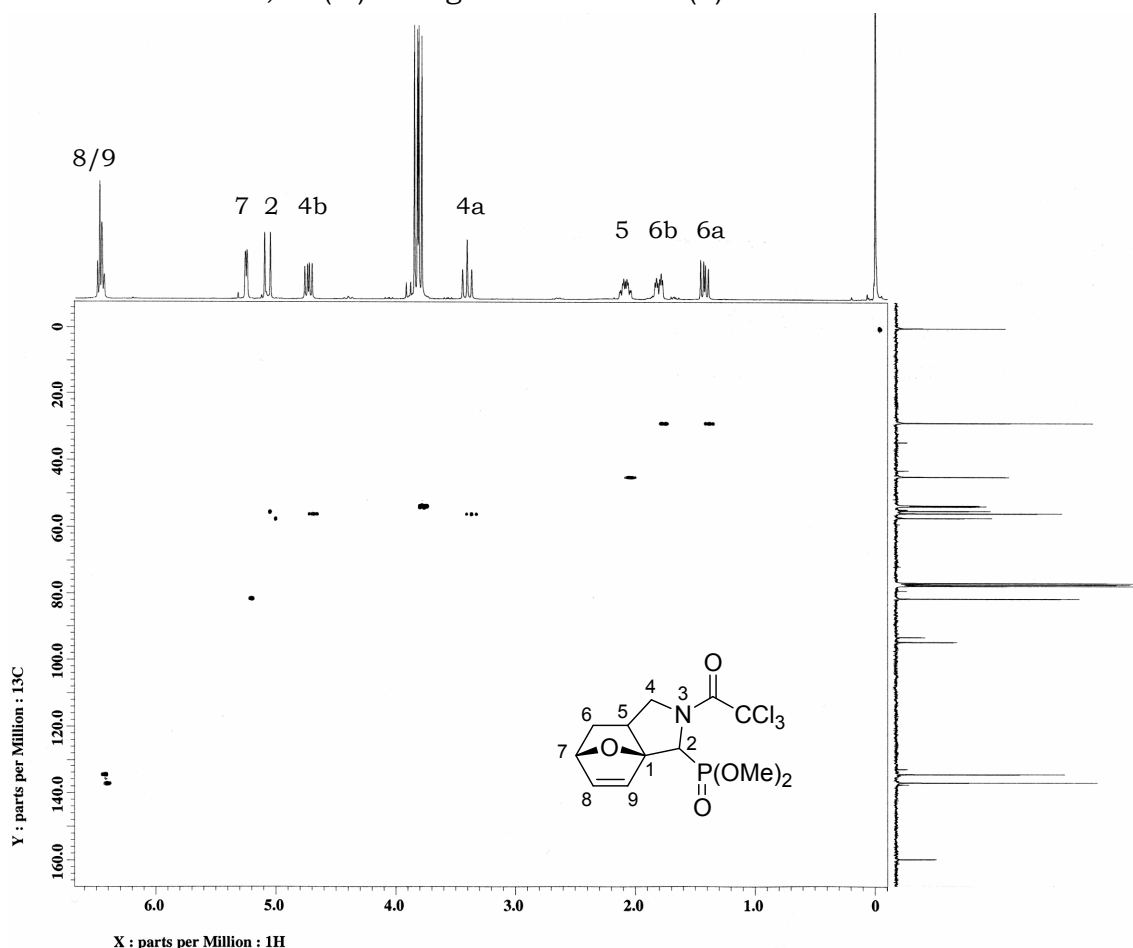
Figure 18: HSQC spectrum of the major isomer of **35e** (R = CCl$_3$).

The exclusive formation of *exo*-fused adducts in the research of Ghelfi and coworkers is by no means an exception. Most studies using similar substrates show exclusive *exo*-adduct formation when the reaction is performed under thermodynamic control.[422-438] *Endo*-fused (kinetic) products are normally formed under high-pressure-mediated conditions.[434] Nevertheless, it is reasonable to suggest the appearance of an *endo*-fused isomer next to the *exo*-fused isomer based on the results of Tromp and coworkers.[439] They found that more steric substituents on the tether can favour the formation of *endo*-fused adducts. Therefore, the bulky phosphonate group may be able to alter the

reaction selectivity, yielding a mixture of both adducts. However, having a close look to the ^{1}H NMR and DQFCOSY data of both isomers of **35e**, the differences in the multiplicities and coupling constants are too little to explain a complete transformation of the tricyclic skeleton. Comparison with typical coupling constants from similar compounds revealed the presence of an *exo*-fused skeleton in both isomers (Figure 19).
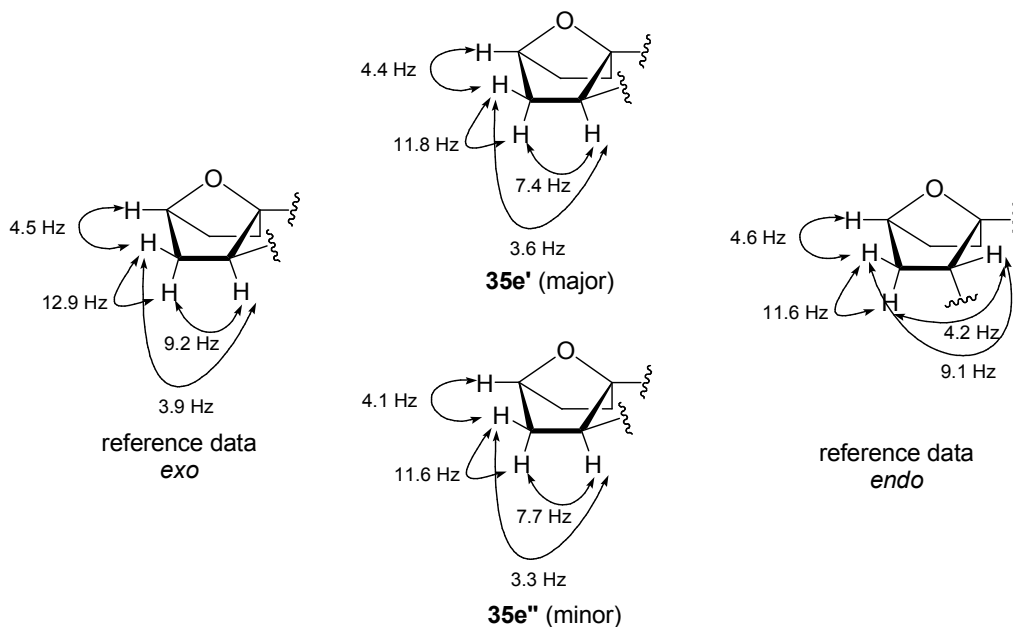
Figure 19: Comparison of typical coupling constants from literature sources[439-441] with those measured in both isomers of pyrrolidine **35e**.§

Both isomers were also submitted to a catalytic amount of CuCl in dichloromethane with TMEDA as a ligand under an argon atmosphere. Under these conditions a radical is typically generated at the CCl_3 moiety, causing ring closure to the double bond. However, both isomers were recovered unchanged after the reaction. This result might - suggest that both isomers have indeed an *exo*-configuration, since only in the *endo-fused* product, the CCl_3 moiety would be able to come in the close neighbourhood of the double bond, giving rise to the formation of an additional six-membered ring.
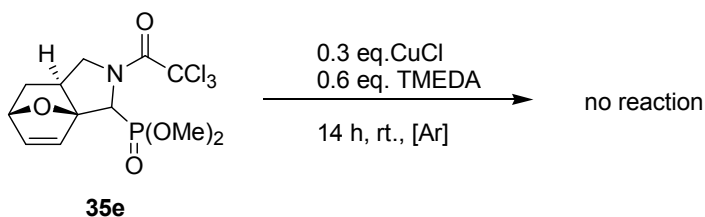
§ Similar coupling constants were measured for pyrrolidines **35a-d** (see chapter 4, section 6.3 or appendix F

In a further attempt to reveal their identity, we tried to separate both isomers of pyrrolidine **35e**. This was conveniently achieved by washing the crystals three times with acetone. The remaining solid was the pure major isomer **35e'**, while the acetone contained a mixture of both isomers. From this mixture, the minor isomer **35e"** could then be recovered in pure form using column chromatography. Both isomers were stable at room temperature for at least 1 month. Amide rotamers generally show rotational barriers between 63 and 96 kJ/mol[442] and are thus in thermal equilibrium at room temperature. Furthermore, no rotamers were observed in NMR for the open precursors **36**. Therefore it was concluded that the observed isomers were not rotamers, but originated from an incomplete stereocontrol of the IMDAF reaction at C(2).

In order to reveal the three-dimensional positioning of the phosphonate group, DIFNOE experiments were performed on both isomers. Optimal results in terms of minimal signal overlap, substraction artefacts and signal to noise ratio were obtained when using highly dilute samples in benzene-*d6* instead of in deuterated chloroform. Oxygen was removed from the solutions by flushing with nitrogen gas. Considerable nuclear Overhauser effects were observed between CH(5) and CH_a(6) and CH_a(4), confirming the *exo*-fused skeleton of both isomers (Figure 20). A clear difference between both isomers was observed, however, when the nuclear Overhauser effect at CH(2) was studied: the bulky phosphonate is β-oriented in the major isomer **35e'**.

While absolute stereocontrol of substituents on the diene or dienophile is often observed, this is not always the case for tether substituents, regularly giving mixtures of both isomers.[434-436] Furthermore, the observed stereoisomer ratio may be the result of thermodynamic control and may not be the isomer ratio formed in the initial reaction mixture. Equilibration can occur under thermal conditions via a consecutive retro-Diels-Alder, Diels-Alder reaction.[422,443,444] To investigate this kind of behaviour, pure samples of the major **35e'** and minor isomer **35e"** were heated in toluene (110°C). No change at all occurred to the minor isomer **35e"** over a 20 h period. The major isomer **35e'** on the other hand, was slowly converted to the minor isomer **35e"**. After 1 h at 110°C, only 2% conversion was observed. This did not reflect at all the 25/75 ratio observed after 1 h at 110°C starting from the open precursor **36e** (Table 27) and again contested the presence of rotamers. When heating was continued for 20 h, 95% conversion to **35e"** was observed. The slow conversion of the major to the minor isomer suggests retrocycloaddition of the less stable cycloadduct. This is in agreement with the stereochemistry generally observed during IMDAF reactions: when a single bulky substituent is present on the tether, the most stable cycloadduct will be formed in such a way as to minimize non-bonded interactions.
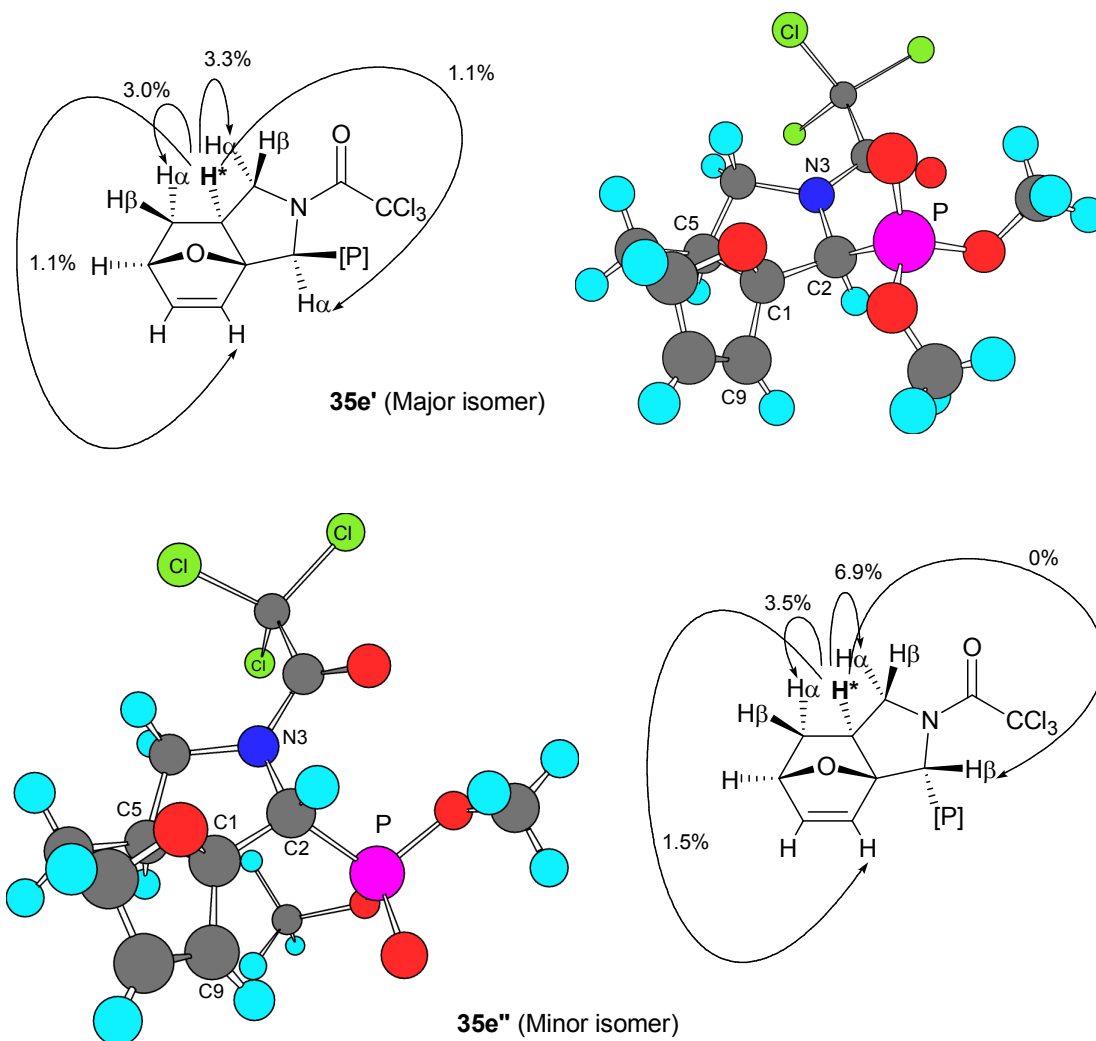
Figure 20: Stereochemical analysis of isomers **35e'** and **35e"**. Percent nuclear Overhauser effect (NOE) is indicated (measured via a DIFNOE experiment with irradiation of CH(5)). Energy optimized 3D structures (MM2) of both isomers are depicted for reference purpose.

An additional experiment was performed using a substrate without an amide substituent. In order to circumvent the need for an amide substituent to increase the amount of active rotamer (*vide supra*), *N*-allyl aminoalkyl phosphonate **22z** was allylated using an excess of allyl bromide in the presence of NaI. After refluxing for 4 h in acetone, complete conversion of the starting material **22z** was obtained, yielding a mixture of diallylamine **319** and the ring closed product **320**. This mixture was then refluxed in toluene during 4 h, yielding the ring-closed product **320**. Notwithstanding the presence of the chiral CHP centre, only one isomer could be detected by NMR. Therefore, the relative stereochemistry at the CHP centre apparently

was fixed during the ring closure reaction or equilibration via retrocycloaddition was fast in this case.
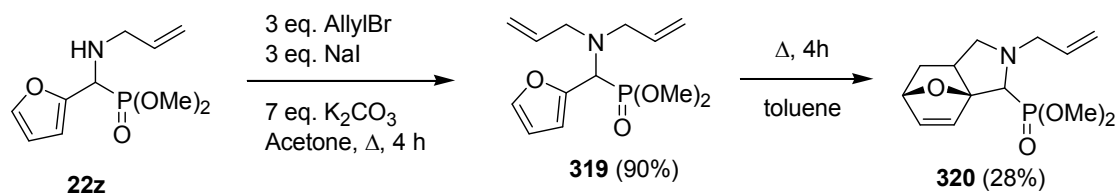
This was also observed when the amide group was included in the tricyclic skeleton. For this reason, aminoalkyl phosphonates **22y,ab** were treated with acryloyl and cinnamoyl chloride respectively. The corresponding pyrrolidinones **323** were obtained as single isomers upon refluxing the amides **321** and **322** in toluene or THF. However, the stereochemistry of the two stereocentres could not be determined via DIFNOE experiments.
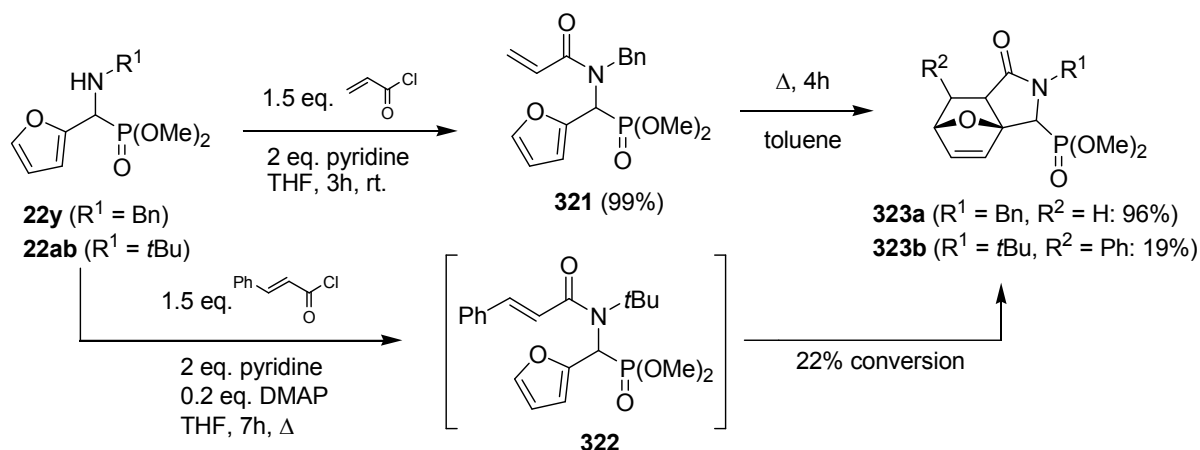
4.3   Conclusion

In conclusion, the excellent results of the IMDAF reaction with (acyl-allylamino)furan-2-ylmethyl phosphonates **36** additionally reflect the particular conformational properties of *N*-acyl aminoalkyl phosphonates as described in chapter 3, section 2.4. Using this cycloaddition methodology, complex azaheterocyclic phosphonates can be obtained in a small number of synthetic steps that might be used as novel conformationally-constrained amino acid analogues.[445] Furthermore, a high degree of stereocontrol is observed during the cycloaddition reaction. Only the *exo*-fused products were obtained. Two isomers can be formed originating form incomplete stereocontrol at the C2 stereocentre. However, the most stable stereoisomers, having an α-oriented phosphonated group, are formed under thermodynamic control.

*E*xperimental *P*rocedures

❧❧❧❧❧❧

1   Instrumental Material

1.1   Column Chromatography

The purification of the reaction mixtures was performed by column chromatography with silica gel (*Acros*, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis (*Merck* Kieselgel 60F$_{254}$, precoated 0.25 mm). As detection methods UV light, adsorption with iodine vapours or colouring with $KMnO_4$ was used.

1.2   NMR Spectroscopy

High resolution ^{1}H NMR (270 MHz), ^{13}C NMR (68 MHz) and ^{31}P NMR (109 MHz) spectra were recorded on a *Jeol* JNM-EX 270 NMR spectrometer. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were acquired at 300 MHz, 75 MHz and 121 MHz, respectively, with a *Jeol* JNM-EX 300 NMR spectrometer. Peak assignments were obtained using DEPT, HSQC, HMBC, COSY and DQFCOSY spectra. The compounds were diluted in deuterated solvents, with tetramethylsilane (TMS) as internal standard.

1.3   Mass Spectrometry

Low resolution mass spectra were recorded on a *Varian MAT 112 spectrometer* (EI, 70 eV) by using GC-MS coupling or via a direct inlet system on an *Agilent 1100 Series VS* (ESI, 4000V) mass spectrometer. Some volatile samples were recorded on a *HP 6890* GC coupled with a *HP 5973 MSD* (Mass Selective Detector, quadrupole).

1.4   Infrared Spectrometry

IR spectra were obtained using a *Perkin Elmer Spectrum One* infrared spectrometer. For liquid samples, the spectra were collected by preparing a

thin film of compound between two sodium chloride plates. Crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained.

1.5 Gas Chromatography

Gas chromatography was performed using an Agilent 6890 Series gas chromatograph. A fused silica capillary column was used (type AT-1, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm) with He as carrier gas. The GC was coupled with a FID detector (H_2 gas).

1.6 Dry Solvents

Diethyl ether, tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl prior to use, whereas dichloromethane was distilled from calcium hydride. Methanol was heated in the presence of magnesium metal, distilled and kept over molecular sieves. Acetonitrile was distilled from calcium hydride and kept over molecular sieves.

1.7 Melting Point

Melting points of crystalline compounds were determined with a *Büchi 540* apparatus.

2 Synthesis of aldimines

Unless otherwise stated, aldimines have been prepared by mixing the aldehyde with 1 equivalent of amine (1.1 equivalent in case of volatile amines) and 2 equivalents of $MgSO_4$ in dry dichloromethane. The mixture was then stirred overnight and shielded from moisture using a $CaCl_2$ tube. The imines were obtained in high purity and yield after filtration of the solids and evaporation of the solvent under reduced pressure.

Phenyl-(3-phenylpropenylidene)amine (19a)
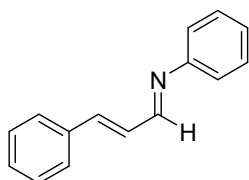
¹H NMR δ (300 MHz, ppm): 7.12-7.55 (12H, multiplet, =CH, CH_{arom}); 8.27 (1H, dd, J = 6.1 Hz, J = 2.2 Hz, N=CH). **Yield:** 96%. Orange solid.

Benzyl-(3-phenylpropenylidene)amine (19b)
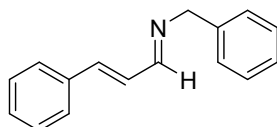
¹H NMR δ (300 MHz, ppm): 4.69 (2H, s (br.), NCH_2); 6.95-6.97 (2H, multiplet, HC=CH); 7.20-7.37 (8H, multiplet, CH_{arom}); 7.43-7.48 (2H, multiplet, CH_{arom}); 8.09-8.13 (1H, multiplet, N=CH). **Yield:** 96%. Orange oil.

(4-Methoxybenzyl)(3-phenylpropenylidene)amine (19c)
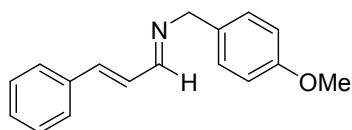
¹H NMR δ (300 MHz, ppm): 3.77 (3H, s, OCH₃); 4.64 (2H, s, NCH₂); 6.85-6.90 (2H, multiplet, HC=CH); 6.95 (2H, d, J = 4.1 Hz, CH$_{arom}$); 7.19-7.38 (5H, multiplet, CH$_{arom}$); 7.44-7.48 (2H, multiplet, CH$_{arom}$); 8.08-8.12 (1H, multiplet, N=CH). **¹³C NMR δ (75 MHz, ppm):** 55.39 (OCH₃); 64.79 (NCH₂); 114.12 (CH$_{PMB}$); 127.36 (CH$_{arom}$); 128.38 (=CH); 128.95, 129.28, 129.42 (CH$_{arom}$); 131.42 (C$_{q,arom}$); 135.86 (C$_{q,arom}$); 141.99 (=CHPh); 158.84 (OC$_{q,arom}$); 163.15 (N=CH). **Yield:** 94%. Orange oil.

Allyl-(3-phenylpropenylidene)amine (19d)
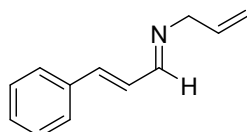
¹H NMR δ (300 MHz, ppm): 4.15 (2H, ~dq, J = 5.8 Hz, J = 1.4 Hz, NCH₂); 5.12-5.25 (2H, multiplet, =CH₂); 6.03 (1H, ddt, J = 17.3 Hz, J = 10.2 Hz, J = 5.8 Hz, HC=CH₂); 6.88-6.99 (2H, multiplet, HC=CH); 7.27-7.48 (5H, multiplet, CH$_{arom}$); 8.03-8.06 (1H, multiplet, N=CH). **Yield:** 97%. Yellow oil.

Isopropyl-(3-phenylpropenylidene)amine (19g)
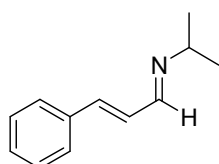
¹H NMR δ (300 MHz, ppm): 1.22 (6H, d, J = 6.3 Hz, CH₃); 3.41 (1H, septet, J = 6.3 Hz, CH); 6.90 (1H, d, J = 3.0 Hz, =CH); 6.92 (1H, s, =CH); 7.26-7.38 (3H, multiplet, CH$_{arom}$); 7.44-7.48 (2H, multiplet, CH$_{arom}$); 8.04 (1H, dd, J₁ = 5.5 Hz, J₂ = 3.0 Hz, N=CH). **Yield:** 98%. Yellow oil.

t-Butyl-(3-phenylpropenylidene)amine (19h)
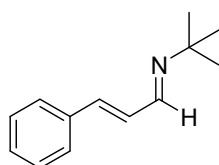
¹H NMR δ (300 MHz, ppm): 1,27 (9H, s, CH₃); 6.89-7.00 (2H, multiplet, HC=CH); 7.26-7.59 (5H, multiplet, CH$_{arom}$); 8.03-8.07 (1H, multiplet, N=CH). **Yield:** 98%. Yellow crystals.

Allyl-(2-methyl-3-phenylpropenylidene)amine (19i)
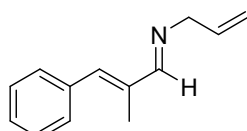
¹H NMR δ (300 MHz, ppm): 2.17 (3H, d, J = 1.4 Hz, CH₃); 4.20 (2H, ~dq, J = 5.0 Hz, J = 1.4 Hz, NCH₂); 5.14 (1H, dq, J = 10.3 Hz, J = 1.7 Hz, =CH$_A$H$_B$); 5.20 (1H, dq, J = 17.2 Hz, J= 1.7 Hz, =CH$_A$H$_B$); 6.03 (1H, ddt, J = 17.2 Hz, J = 10.3 Hz, J = 5.5 Hz, HC=CH₂); 6.80 (1H, s (br.), =CHPh); 7.25-7.43 (5H, multiplet, CH$_{arom}$); 8.00 (1H, s (br.), N=CH). **Yield:** 96%. Yellow oil.

Allyl-(2-benzylidene-5-methylhexylidene)amine (19j)
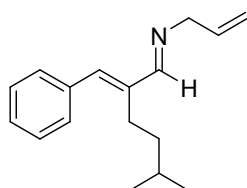
Predominantly *E*.

¹H NMR δ (300 MHz, ppm): 0.88 (3H, ~t, J = 6.3 Hz, CH=); 1.26-1.43 (4H, multiplet, CH, CH₃); 1.50-1.63 (2H, multiplet, CH₂); 2.59-2.65 (2H, multiplet, CH₂C$_q$=); 4.15-4.19 (2H, multiplet, NCH₂); 5.09-5.22 (2H, multiplet, =CH=); 5.95-6.10 (1H, multiplet,

=CH); 6.72 (1H, s, =CHPh); 7.18-7.42 (5H, multiplet, CH$_{arom}$); 7.89 (1H, s, N=CH).
Yield: 94%. Yellow oil.

But-2-enylidene-*t*-butylamine (19q)
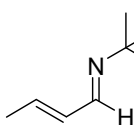
¹H NMR δ (270 MHz, ppm): 1.20 (9H, s, CH3); 1.86 (3H, d, J = 7.6 Hz, CH$_3$CH=); 6.20 (2H, multiplet, HC=CH); 7.85 (1H, d, J = 8.4 Hz, N=CH).
Yield: 94%.

Benzyl-[3-(2-nitro-phenyl)propenylidene]amine (19s)
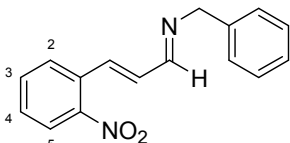
¹H NMR δ (300 MHz, ppm): 4.74 (2H, s, CH$_2$Ph); 6.92 (1H, dd, J = 8.8 Hz, J = 16.0 Hz, =CHNCH); 7.21-7.38 (5H, multiplet, CH$_{Bn}$); 7.41-7.48 (1H, multiplet, CH(4)); 7.49 (1H, d, J = 16.0 Hz, =CHPh); 7.57-7.63 (1H, multiplet, CH(3)); 7.66-7.69 (1H, multiplet, CH(2)); 7.98 (1H, d, J = 8.3 Hz, CH(5));
8.20 (1H, d, J = 8.8 Hz, N=CH). **Yield:** 95%.

[3-(2-Nitro-phenyl)propenylidene]prop-2-ynylamine (19t)
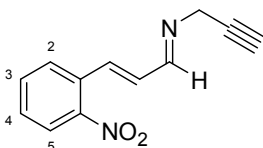
¹H NMR δ (300 MHz, ppm): 2.54 (1H, t, J = 2.2 Hz, ≡CH); 4.48 (2H, t, J = 2.2 Hz, NCH$_2$); 6.91 (1H, dd, J = 15.7 Hz, J = 8.8 Hz, =CH); 7.41-7.72 (CH$_{arom}$, =CHPh); 8.01 (1H, dd, J = 8.1 Hz, J = 1.2 Hz, CH(5)); 8.40 (1H, dt, J = 8.8 Hz, J = 2.0 Hz, N=CH).
Mp.: 105-106°C. **Yield:** 91%. Orange Crystals.

Benzyl-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethylidene)amine (19u)
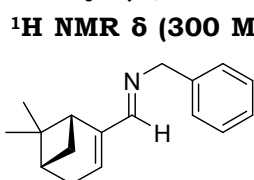
¹H NMR δ (300 MHz, ppm): 0.81 (3H, s, CH$_3$); 1.13 (1H, d, J = 9.1 Hz, CH$_A$H$_B$); 1.33 (3H, s, CH$_3$); 2.10-2.21 (1H, multiplet, CH); 2.35-2.55 (3H, multiplet, CH$_2$CH= & CH$_A$H$_B$); 3.05 (1H, ~t, J = 5.6 Hz, CHC$_q$=); 4.61 (1H, d, J$_{AB}$ = 14.0 Hz, NCH$_A$H$_B$); 4.70 (1H, d, J$_{AB}$ = 14.0 Hz, NCH$_A$H$_B$); 6.03 (1H, s br., =CH); 7.19-7.33 (5H, multiplet, CH$_{arom}$);
7.91 (1H, s, NCH). **¹³C NMR δ (75 MHz, ppm):** 21.06 (CH$_3$); 26.04 (CH$_3$); 31.46 (CH$_2$); 32.53 (CH$_2$CH=); 37.74 (C$_q$); 40.26 (CHC$_q$=); 41.10 (CH); 64.76 (NCH$_2$); 126.87 (CH$_{arom}$); 127.96 (2 x CH$_{arom}$); 128.46 (2 x CH$_{arom}$); 134.78 (=CH); 139.90 (C$_{q,arom}$); 148.51 (=C$_q$); 163.09 (N=CH). **IR ν (cm⁻¹):** 1634 (C=N). **MS m/z (%):** 240 (100, [M+H]⁺). **Yield:** 99%. Yellow oil.

Allyl-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethylidene)amine (19v)
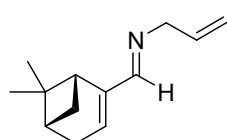
¹H NMR δ (300 MHz, ppm): 0.79 (3H, s, CH$_3$); 1.12 (1H, d, J = 9.1 Hz, CH$_A$H$_B$); 1.33 (3H, s, CH$_3$); 2.11-2.19 (1H, multiplet, CH); 2.35-2.58 (3H, multiplet, CH$_2$CH= & CH$_A$H$_B$); 3.05 (1H, td, J = 5.6 Hz, J = 1.4 Hz, CHC$_q$=); 4.06 (1H, dd, J$_{AB}$ = 15.0 Hz, NCH$_A$H$_B$);
J = 6.0 Hz, NCH$_A$H$_B$); 4.13 (1H, dd, J$_{AB}$ = 15.0 Hz, J = 6.0 Hz, NCH$_A$H$_B$); 5.07-5.17 (2H, multiplet, =CH$_2$); 5.93-6.06 (2H, multiplet, 2x =CH); 7.82 (1H, s (br.), N=CH). **Yield:** 97%. Yellow oil.

Isopropyl-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethylidene)amine (19w)
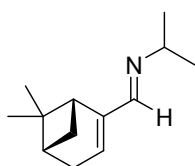
¹H NMR δ (270 MHz, ppm): 0.79 (3H, s, CH₃); 1.12 (1H, d, J = 9.1 Hz, CH_AH_B); 1.15 (3H, d, J = 6.3 Hz, CH(CH₃)₂); 1.17 (3H, d, J = 6.3 Hz, CH(CH₃)₂); 1.33 (3H, s, CH₃); 2.11-2.17 (1H, multiplet, CH); 2.34-2.52 (3H, multiplet, CH_AH_B, CH₂CH=); 2.97 (1H, td, J = 5.8 Hz, J = 1.4 Hz, CHC_q=); 3.34 (1H, septet, J = 6.3 Hz, CH(CH₃)₂); 5.94 (1H, multiplet, =CH); 7.82 (1H, s, N=CH). **¹³C NMR δ (75 MHz, ppm):** 20.85 (CH₃); 24.19 (CH(CH₃)₂); 24.27 (CH(CH₃)₂); 25.91 (CH₃); 31.36 (CH₂); 32.27 (CH₂CH=); 37.59 (C_q); 40.03 (CHC_q=); 40.94 (CH); 61.28 (CH(CH₃)₂); 133.29 (CH=); 148.39 (=C_q); 159.32 (N=CH). **IR ν (cm⁻¹):** 1634 (C=N). **MS m/z (%):** 192 (100, [M+H]⁺). **Yield:** 99%. Yellow oil.

t-Butyl-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethylidene)amine (19x)
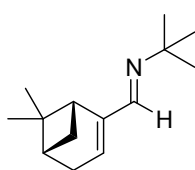
¹H NMR δ (300 MHz, ppm): 0.78 (3H, s, CH₃); 1.11 (1H, d, J = 8.8 Hz, CH_AH_B); 1.18 (9H, 3x CH₃); 1.33 (3H, s, CH₃); 2.10-2.16 (1H, multiplet, CH); 2.34-2.52 (3H, multiplet, CH_AH_B, CH₂CH=); 3.01 (1H, td, J = 5.8 Hz, J = 1.4 Hz, CHC_q=); 5.93 (1H, multiplet, =CH); 7.81 (1H, s, N=CH). **¹³C NMR δ (75 MHz, ppm):** 20.86 (CH₃); 25.99 (CH₃); 29.90 (3x CH₃); 31.42 (CH₂); 32.28 (CH₂CH=); 37.56 (C_q); 39.68 (CHC_q=); 40.99 (CH); 56.37 (C_q(CH₃)₃); 132.60 (CH=); 148.98 (=C_q); 156.06 (N=CH). **IR ν (cm⁻¹):** 1633, 1616, (C=N, C=C). **MS m/z (%):** 206 (100, [M+H]⁺). **Yield:** 95%. Yellow oil.

Phenyl-(furan-2-ylmethylidene)amine (19y)
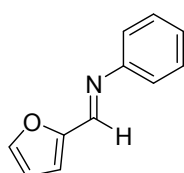
¹H NMR δ (270 MHz, ppm): 6.55 (1H, multiplet, =CH); 6.95 (1H, multiplet, =CH); 7.20-7.26 (3H, multiplet, CH_arom); 7.36-7.41 (2H, multiplet, CH_arom); 7.61 (1H, multiplet, =CHO); 8.28 (1H, s, N=CH). **Yield:** 95%.

Benzyl-(furan-2-ylmethylidene)amine (19z)
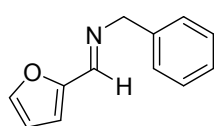
¹H NMR δ (270 MHz, ppm): 4.77 (2H, s, NCH₂); 6.45-6.48 (1H, multiplet, =CH); 6.75-6.77 (1H, multiplet, =CH); 7.30-7.33 (5H, multiplet, CH_arom); 7.49-7.51 (1H, multiplet, =CHO); 8.15 (1H, s, N=CH). **Yield:** 91%. Brown oil.

Allyl-(furan-2-ylmethylidene)amine (19aa)
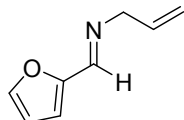
¹H NMR δ (300 MHz, ppm): 4.23 (2H, ~dq, J = 6.0 Hz, J = 1.4 Hz, NCH₂); 5.13-5.30 (2H, multiplet, =CH₂); 5.99-6.13 (1H, multiplet, HC=CH₂); 6.46-6.49 (1H, multiplet, =CH); 6.75-6.77 (1H, multiplet, =CH); 7.51 (1H, s (br.), =CHO); 8.10 (1H, d, J = 0.8 Hz, N=CH). **Yield:** 92%. Brown oil.

t-Butyl-(furan-2-ylmethylidene)amine (19ab)
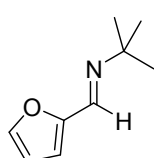
¹H NMR δ (300 MHz, ppm): 1.30 (9H, s, 3x CH₃); 6.47 (1H, dd, J = 3.3 Hz, J = 1.1 Hz, CH=C_q); 6.69-6.71 (1H, multiplet, CH=CHO); 7.51 (1H, s (br.), =CHO); 8.08 (1H, d, J = 1,4 Hz, CH=N); **Yield:** 93%. Brown oil.

Benzylidene-benzylamine (19ad)
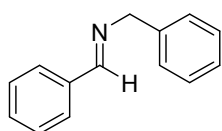
¹H NMR δ (270 MHz, ppm): 4.75 (2H, s, NCH$_2$); 7.19-7.36 (8H, multiplet, CH$_{arom}$); 7.74-7.76 (2H, multiplet, CH$_{arom}$); 8.29 (N=CH). **Yield:** 97%. Yellow oil.

Benzylidene-isopropylamine (19af)
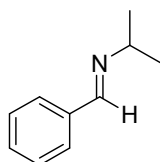
¹H NMR δ (300 MHz, ppm): 1,26 (6H, d, J = 6,3 Hz, CH$_3$); 3,52 (1H, septet, J = 6,3 Hz, CH); 7,38 (3H, multiplet, CH$_{arom}$); 7,72 (2H, multiplet, CH$_{arom}$); 8,29 (1H, s, N=CH). **Yield:** 98%. Yellow oil.

(Cyclohexylmethylidene)isopropylamine (19ag)
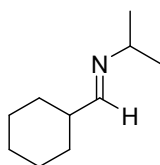
¹H NMR δ (300 MHz, ppm): 1.14 (6H, d, J = 6.3 Hz, CH$_3$); 1.08-1.37 (5H, multiplet, CH$_2$); 1.61-1.83 (5H, multiplet, CH$_2$); 2.05-2.19 (1H, multiplet, CH); 3,21 (1H, septet, J = 6,3 Hz, CH); 7.47 (1H, dd, J = 5.8 Hz, N=CH). **Yield:** 95%.

Benzyl-isobutylidene-amine (19ah)
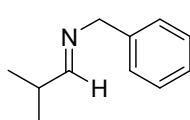
¹H NMR δ (300 MHz, ppm): 1.11 (6H, d, J = 6.9 Hz, CH$_3$); 2.42-2.58 (1H, multiplet, CH); 4.55 (2H, s, NCH$_2$); 7.20-7.35 (5H, multiplet, CH$_{arom}$); 7.65 (1H, ~d, J = 5.0 Hz, N=CH). **Yield:** 91%. Colourless oil.

Benzyl-(pyridin-3-ylmethylidene)amine (19aj)
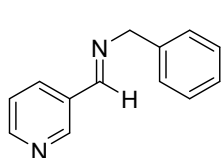
¹H NMR δ (270 MHz, ppm): 4.82 (2H, multiplet, NCH$_2$); 7.26-7.31 (5H, multiplet, CH$_{arom}$); 7.33-7.35 (1H, multiplet, CH$_{arom}$); 8.11-8.12 (1H, multiplet, CH$_{arom}$); 8.37 (1H, s, N=CH); 8.62-8.63 (1H, multiplet, CH$_{arom}$); 8.87-8.89 (1H, multiplet, CH$_{arom}$). **Yield:** 99%. Yellow oil.

3 Synthesis of α-aminoalkyl phosphonates

3.1 Phosphonylation using dialkyl trimethylsilyl phosphite

A solution of 5 mmol of DEP and 5.5 mmol of triethyl amine in 8 ml of dry dichloromethane was stirred at 0°C under a nitrogen atmosphere. Then 5.5 mmol of TMSCl in 2 ml of dry dichloromethane was added using a syringe. Precipitation of ammonium salts occurred immediately and stirring was continued for 30 minutes at 0°C. The reaction was monitored using ³¹P NMR. When the conversion was not complete, TMSCl was added in portions of 0.5 mmol until a complete conversion was obtained. The mixture was then

allowed to warm to room temperature before 5 mmol of the selected imine, dissolved in 2 ml of dry dichloromethane, was added using a syringe. Further reaction proceeded under the conditions mentioned in Table 2. Then the mixture was poured into 20 ml of a saturated $NaHCO_{3(aq)}$ solution. The organic phase was collected and the aqueous phase was extracted two more times with 5 ml of dichloromethane. The crude products were obtained after drying using $MgSO_4$ and evaporation of the solvent under reduced pressure. Further purification was performed using column chromatography.

Diethyl (*2E*)-1-anilino-3-phenylprop-2-enyl phosphonate (22a)
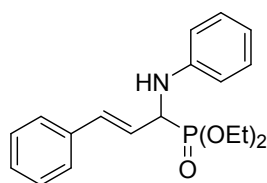
¹H NMR δ (300 MHz, ppm): 1.31 (3H, t, J = 7.2 Hz, CH_3); 1.36 (3H, t, J = 7.2 Hz, CH_3); 4.03-4.25 (4H, multiplet, CH_2O); 4.48 (1H, ddd, J_{HP} = 25.9 Hz, J = 6.1 Hz, J = 1.4 Hz, CHP); 6.27 (1H, ddd, J = 15.8 Hz, J = 6.1 Hz, J_{HP} = 5.1 Hz, =CH); 6.66-6.77 (4H, multiplet, =CHPh, 3 x CH_{arom}); 7.13-7.36 (7H, multiplet, CH_{arom}). **¹³C NMR δ (75 MHz, ppm):** 16.40 (d, J_{CP} = 5.8 Hz, CH_3); 16.58 (d, J_{CP} = 5.8 Hz, CH_3); 54.06 (d, J_{CP} = 154.6 Hz, CHP); 63.11 (d, J_{CP} = 6.9 Hz, CH_2O); 63.59 (d, J_{CP} = 6.9 Hz, CH_2O); 113.86, 118.60 (CH_{arom}); 123.57 (d, J_{CP} = 4.6 Hz, =CH); 126.67, 127.93, 128.63, 129.35 (CH_{arom}); 133.05 (d, J_{CP} = 12.7 Hz, =CHPh); 136.36 (d, J_{CP} = $C_{q,arom}$, $C_{q,arom}$); 146.62 ($NC_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 22.95. **IR ν (cm⁻¹):** 3293 (NH); 1224 (P=O); 1043, 1017 (P-O). **MS m/z (%):** 208 (100, $[M+H-PO(OEt)_2]^+$); 346 (74, $[M+H]^+$). **Mp.:** 84.5°C. **Yield:** 63%. Yellow crystals.

Diethyl {(*2E*)-1-[2-(*1H*-indol-3-yl)ethylamino]-3-phenylprop-2-enyl} phosphonate (22g)
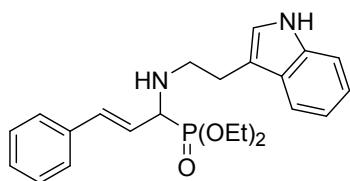
¹H NMR δ (300 MHz, ppm): 1.22 (3H, t, J = 7.2 Hz, CH_3); 1.24 (3H, t, J = 7.2 Hz, CH_3); 1.32 (1H, s (br.), NH); 2.86-3.00 (3H, multiplet, $NCH_AH_BCH_2$); 3.02-3.12 (1H, multiplet, NCH_AH_B); 3.70 (1H, ddd, J_{HP} = 19.1 Hz, J = 8.3 Hz, J = 0.7 Hz, CHP); 4.01-4.15 (4H, multiplet, OCH_2); 6.08 (1H, ddd, J = 15.9 Hz, J = 8.3 Hz, J = 5.8 Hz, =CHCHP); 6.49 (1H, dd, J = 15.9 Hz, J = 4.8 Hz, =CHPh); 6.92 (1H, d, J = 2.2 Hz, =CHN); 7.03 (1H, ~dt, J = 7.4 Hz, J = 1.1 Hz, CHCHC$_q$NH); 7.13 (1H, J = 7.7 Hz, J = 1.1 Hz, CHCHC$_q$C$_q$); 7.17-7.33 (6H, multiplet, 5 x CH_{arom}, CHC$_q$NH); 7.56 (1H, d, J = 7.7 Hz, CHC$_q$C$_q$); 8.91 (1H, s, NH_{indole}). **¹³C NMR δ (75 MHz, ppm):** 16.41 (CH3); 16.44 (CH3); 25.57 (CH_2CH_2N); 48.15 (d, J_{CP} = 16.2 Hz, CH_2N); 59.11 (d, J_{CP} = 155.8 Hz, CHP); 62.72, 52.81, 62.84, 62.95 (OCH_2); 111.38 (CHC_qNH); 112.92 (=C$_q$); 118.65 (CHC_qC_q); 118.94 ($CHCHC_qN$); 121.64 ($CHCHC_qC_q$); 122.42 (=CHN); 124.23 (d, J_{CP} = 6.9 HZ, =$CHCHP$); 126.49 (2 x CH_{arom}); 127.29 ($C_qC_qCH_2$); 127.79 (CH_{arom}); 128.52 (2 x CH_{arom}); 133.96 (d, J_{CP} = 13.9 Hz, =CHPh); 136.30 (d, JCP = 2.3 Hz, $C_{q,arom}$); 136.52 (C_qN). **³¹P NMR δ (121 MHz, ppm):** 24.44. **IR ν (cm⁻¹):** 3257 (NH); 1231 (P=O); 1052, 1026 (P-O). **MS m/z (%):** 275 (100, $[M+H-PO(OEt)_2]^+$); 413 (30, $[M+H]^+$). **Yield:** 44%. Yellow oil.

Diethyl (2*E*)-1-(isopropylamino)-3-phenylprop-2-enyl phosphonate (22i)
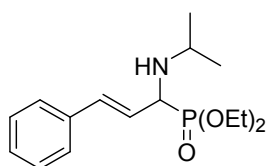
¹H NMR δ (300 MHz, ppm): 1.02 (3H, d, J = 6.1 Hz, CHC$\underline{H}_3$); 1.09 (3H, d, J = 6.3 Hz, CHC$\underline{H}_3$); 1.31 (3H, t, J = 7.3 Hz, CH$_3$); 1.33 (3H, t, J = 7.3 Hz, CH$_3$); 1.60 (1H, s (br.), NH); 2.95 (1H, septet, J = 6.2 Hz, NCH); 3.77 (1H, dd, J_{HP} = 21.2 Hz, J = 8.5 Hz, CHP); 4.09-4.26 (4H, multiplet, CH$_2$O); 6.12 (1H, ddd, J = 16.0 Hz, J = 8.5 Hz, J_{HP} = 5.6 Hz, =CH); 6.60 (1H, dd, J = 16.0 Hz, J_{HP} = 4.7 Hz, =CHPh); 7.23-7.41 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.58 (CH$_3$); 16.62 (CH$_3$); 21.72 (CH$\underline{C}$H$_3$); 24.01 (CH$\underline{C}$H$_3$); 46.23 (d, J_{CP} = 16.2 Hz, NCH); 56.71 (d, J_{CP} = 155.8 Hz, CHP); 62.76 (d, J_{CP} = 6.9 Hz, CH$_2$O); 63.14 (d, J_{CP} = 6.9 Hz, CH$_2$O); 125.27 (d, J_{CP} = 6.9 Hz, =CH); 126.57; 127.86; 128.67 (CH$_{arom}$); 133.62 (d, J_{CP} = 13.9 Hz, =CHPh); 136.60 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.85. **IR ν (cm⁻¹):** 3307 (NH); 1239 (P=O); 1056, 1028 (P-O). **MS m/z (%):** 174 (100, [M+H-P(O)(OEt)$_2$]⁺); 312 (17, [M+H]⁺). **Chromatography:** Rf = 0.20 (EtOAc). **Yield:** 40%. Yellow oil.

Diethyl (benzylamino)[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22u)
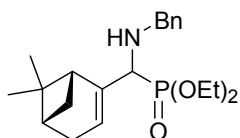
The product was obtained as a mixture of two diasteromers (ratio 45:55), indicated as m (minor) and M (Major) whenever possible.

¹H NMR δ (300 MHz, ppm): 0.91 (3H, s, CH$_3$, M); 0.94 (3H, s, CH$_3$, m); 1.20-1.32 (10H, multiplet, CH$_3$, CH$_2$CH$_3$, C$\underline{H}_A$H$_B$); 2.08-2.20 (2H, multiplet, NH, CH); 2.31-2.50 (4H, multiplet, CH$_A\underline{H}_B$, C$\underline{H}_2$CH=, C$\underline{H}$C$_q$=); 3.43 (1H, d, J_{HP} = 21.2 Hz, CHP, m); 3.45 (1H, d, J_{HP} = 20.9 Hz, CHP, M); 3.60 (1H, d, J_{AB} = 13.2 Hz, NC$\underline{H}_A$H$_B$, m); 3.63 (1H, d, J_{AB} = 13.2 Hz, NC$\underline{H}_A$H$_B$, M); 3.87 (1H, d, J_{AB} = 13.2 Hz, NCH$_A\underline{H}_B$, m$_+$, M); 4.01-4.18 (2 x 4H, multiplet, CH$_2$O); 5.58-5.52 (2 x 1H, multiplet, =CH); 7.23-7.31 (2 x 5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.34; 16.44; 16.52 ($\underline{C}$H$_3$CH$_2$); 21.18 (CH$_3$, M); 21.56 (CH$_3$, m); 26.28 (CH$_3$, m); 26.37 (CH$_3$, M); 31.64 (CH$_2$CH=, m); 31.67 (CH$_2$CH=, M); 32.11 (CH$_2$); 37.76 (C$_q$, m); 38.28 (C$_q$, M); 40.67 (CH, m); 40.87 (CH, M); 43.03 (CHC$_q$=, M); 43.25 (CHC$_q$=, m); 51.26; 51.44; 51.48; 51.67 (CH$_2$N); 59.90 (d, J_{CP} = 156.9 Hz, CHP, m); 60.29 (d, J_{CP} = 156.9 Hz, CHP, M); 61.94; 62.03; 62.40; 62.48; 62.57 (CH$_2$O); 122.82 (d, J_{CP} = 13.8 Hz, =CH, m); 123.20 (d, J_{CP} = 13.8 Hz=CH, M); 127.00 (CH$_{arom}$); 128.30 (3 x CH$_{arom}$); 128.36 (CH$_{arom}$); 139.73 (C$_{q,arom}$); 142.41 (d, J_{CP} = 5.8 Hz, =C$_q$); 142.51 (d, J_{CP} = 5.8 Hz, =C$_q$). **³¹P NMR δ (121 MHz, ppm):** 24.37 (M); 24.57 (m). **IR ν (cm⁻¹):** 3320 (NH); 1681 (C=C); 1237 (P=O); 1036 (P-O). **MS m/z (%):** 240 (100, [M+H-PO(OEt)$_2$]⁺); 378 (22, [M+H]⁺). **Chromatography:** Rf = 0.43 (EtOAc/PE 60/40). **Yield:** 32%. Yellow oil.

Diethyl (allylaminofuran-2-yl)methyl phosphonate (22aa)
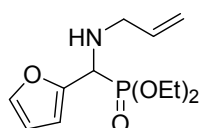
¹H NMR δ (300 MHz, ppm): 1.14 (3H, t, J = 7.0 Hz, CH$_3$); 1.24 (3H, t, J = 7.0 Hz, CH$_3$); 1.90 (1H, s (br.), NH); 2.99 (1H, dd, J_{AB} = 13.9 Hz, J = 6.6 Hz, NC$\underline{H}_A$H$_B$); 3.18-3.26 (1H, multiplet, NCH$_A\underline{H}_B$); 3.79-4.16 (5H, multiplet, CH$_2$O, CHP); 5.01-5.10 (2H, multiplet, =CH$_2$); 5.66-5.80 (1H, multiplet, $\underline{H}$C=CH$_2$); 6.25-6.30 (2H, multiplet, 2 x =CH); 7.32-7.34 (1H, multiplet, =CHO). **¹³C NMR δ (75 MHz, ppm):** 16.35 (d, J_{CP} = 5.8 Hz, CH$_3$); 16.48 (d, J_{CP} = 5.8 Hz, CH$_3$); 50.18 (d, J_{CP} = 16.2 Hz,

NCH$_2$); 53.29 (d, J$_{CP}$ = 161.5 Hz, CHP); 62.87 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 63.13 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 109.22 (d, J$_{CP}$ = 6.9 Hz, =CHC$_q$); 110.60 (=CH); 117.02 (=CH$_2$); 135.74 (H<u>C</u>=CH$_2$); 142.52 (=CHO); 149.84 (=C$_q$O). **^{31}P NMR δ (121 MHz, ppm):** 21.82. **IR ν (cm^{-1}):** 3471 (NH); 1248 (P=O); 1053, 1031 (P-O). **MS m/z (%):**136 (100, [M+H-PO(OEt)$_2$]$^+$) ; 274 (11, [M+H]$^+$). **Chromatorgraphy:** Rf = 0.25 (EtOAC/Et$_3$N : 99/1). **Yield:** 52%. Brownish oil.

3.2 Preparation of 3-phosphonyl-1-aminoalkyl phosphonates

3.2.1 General procedure for the preparation of DAPTMS

Dialkyl phosphite (30 mmol) was mixed with 33 mmol of triethylamine (1.1 eq.) in 40 mL of dry dichloromethane in an oven dry flask under a nitrogen atmosphere. The mixture was then cooled to 0°C and 33 mmol of TMSCl (1.1 eq.) was added using a syringe. After 1 h at 0°C, the DAP was completely converted to the DAPTMS (this could easily be monitored using ^{31}P NMR (DAP: δ = 5-15 ppm; DAPTMS: δ = 120-130 ppm). The triethylammonium chloride salts were removed by filtration (care had to be taken to avoid contact with moisture) and the dichloromethane was evaporated under reduced pressure. Then, 20 mL of dry diethyl ether was added to the residue in order to precipitate the remaining triethylammonium chloride from the mixture. After filtration and evaporation of the solvent, the DAPTMS was obtained as a clear, colourless liquid and could be stored for several weeks at -20°C when kept away from moisture.

3.2.2 Preparation of 3-phosphonyl aminoalkyl phosphonates (PAP's)

5 Mmol of a suitable α,β-unsaturated imine dissolved in 15 mL of dry dichloromethane was allowed to stirr at room temperature under a nitrogen atmosphere. Then, 10 mmol of DAPTMS and 2.5 mmol of sulfuric acid (1 eq. of H$^+$) were added consecutively. CAUTION: the reaction may proceed very vigorously upon addition of sulfuric acid and the solvent may start to boil. The mixture was allowed to react for 1 h at room temperature and was then poured into 20 mL of a saturated NaHCO$_{3(aq)}$ solution. The organic phase is recovered and the remaining aqueous phase is washed twice with 5 mL of dichloromethane. The PAP is obtained in satisfactory purity after drying (MgSO$_4$) and evaporation of the solvent under reduced pressure. In order to have the PAP's at higher purity, an acid/base extraction can be performed. Also column chromatography with silica gel as a stationary phase and a mixture of CH$_3$CN, EtOAc and MeOH (50/47/3) as a mobile phase is appropriate.
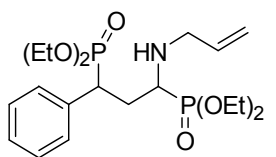
Tetramethyl 3-benzylamino-1-phenyl-3-phosphonopropyl phosphonate (196c)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 19/81). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
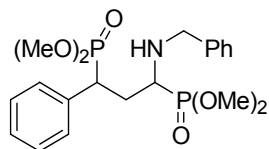
^{1}H NMR δ (300 MHz, ppm): 1.71 (1H, s (br.), NH); 2.08-2.50 (2x 2H, multiplet, CHPC$\underline{H}_2$CHP, m+M); 2.58 (1H, ~td, J = 12.1 Hz, J = 2.3 Hz, PCHN, M); 2.89 (1H, ~quintet, J = 6.9 Hz, PCHN, m); 3.43-4,04 (2x 15H, multiplet, 4x OC$\underline{H}_3$, PCHPh, CH$_2$Ph, m+M); 7.01-7.08 (2x 10H, multiplet, CH$_{arom}$, m+M).

^{13}C NMR δ (75 MHz, ppm): 30.18 (d, J_{CP} = 8.1 Hz, CH$_2$, M); 30.58 (CH$_2$, m); 39.18 (dd, J_{CP} = 139.6 Hz, J_{CP} = 13.8 Hz, PCHPh, M); 39.73 (d, J_{CP} = 137.3 Hz, PCHPh, m); 49.94 (dd, J_{CP} = 148.8 Hz, J_{CP} = 16.1 Hz, PCHNH, M); 50.57 (dd, J_{CP} = 145.4 Hz, J_{CP} = 12.7 Hz, PCHNH, m); 50.96 (OCH$_3$); 50.98 (d, J_{CP} = 6.9 Hz, CH$_2$Ph, m); 51.41 (OCH$_3$); 51.52 (CH$_2$Ph, M); 51.65 (OCH$_3$); 52.05 (OCH$_3$); 52.75 (OCH$_3$); 126.54, 126.62, 126.92, 127.76, 127.88, 128.19, 128.71, 128.86, 128.94 (CH$_{arom}$); 134.11 (d, J_{CP} = 5.8 Hz, C$_{q,arom}$, M); 135.32 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, m); 139.01 (C$_{q,arom}$, m); 139.53 (C$_{q,arom}$, M). **^{31}P NMR δ (121 MHz, ppm):** 30.41 (m); 31.23 (m); 31.27 (d, J_{PP} = 9.7 Hz, M); 32.08 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3467 (N-H); 1243 (br, P=O); 1030 (br., P-O). **MS: m/z (%) :** 333 (8, [M+H-PO(OCH$_3$)$_2$]$^+$); 442 (100, [M+H]$^+$);. **Yield:** 70%. Pale yellow oil.

## Tetraethyl 3-benzylamino-1-phenyl-3-phosphonopropyl phosphonate (196d)
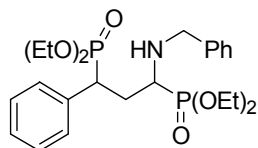
The product was obtained as a mixture of two diastereomeric pairs (ratio: 29/71). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

^{1}H NMR δ (300 MHz, ppm): 1.07 (3H, t, J = 6.6 Hz, CH$_3$, m); 1.09 (3H, t, J = 7.2 Hz, CH$_3$, M); 1.26-1.36 (2 x 9H, multiplet, CH$_3$, m+M); 2.04-2.48 (2 x 2H, multiplet, CH$_2$, m+M); 2.55 (1H, td, J = 11.8 Hz, J_{HP} = 2.2 Hz, NCHP, M); 2.81-2.94 (1H, multiplet, NCHP, m); 3.53-4.19 (2 x 7H, multiplet, CH$_2$N, CHP, OCH$_2$, m+M); 7.12-7.36 (2 x 10H, multiplet, CH$_{arom}$, m+M).

^{13}C NMR δ (75 MHz, ppm): 16.20, 16.28, 16.37, 16.46, 16.52, 16.60 (CH$_3$); 30.68 (d, J_{CP} = 8.1 Hz, CH$_2$, M); 31.15 (CH$_2$, m); 40.32 (dd, J_{CP} = 139.6 Hz, J_{CP} = 14.4 Hz, CHP, M); 40.89 (dd, J_{CP} = 137.3 Hz, J_{CP} = 5.8 Hz, CHP, m); 51.17 (dd, J_{CP} = 141.9 Hz, J_{CP} = 16.2 Hz, NCHP, M); 51.57 (d, J_{CP} = 8.1 Hz, NCH$_2$, m); 51.74 (dd, J_{CP} = 150.0 Hz, J_{CP} = 13.3 Hz, NCHP, m); 52.03 (NCH$_2$, M); 61.82, 61.91, 62.03, 62.31, 62.42, 62.49, 62.58, 62.68 (OCH$_2$); 126.99, 127.09, 127.28, 127.31, 128.24, 128.37, 128.42, 128.56, 128.59, 129.35, 129.44, 129.50, 129.60 (CH$_{arom}$, m + M); 135.07 (d, J_{CP} = 5.8 Hz, C$_{q,arom}$, M); 136.21 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, m); 139.72 (C$_{q,arom}$, m); 140.31 (C$_{q,arom}$, M). **^{31}P NMR δ (121 MHz, ppm):** 28.16 (m); 28.91 (d, J_{PP} = 9.7 Hz, M); 28.99 (m); 29.86 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3306 (NH); 1243 (P=O); 1051, 1026 (P-O). **MS m/z (%):** 360 (37, [M+H-PO(OCH$_2$CH$_3$)$_2$]$^+$); 498 (100, [M+H]$^+$). **Yield:** 80%. Pale yellow oil.

## Tetramethyl 3-allylamino-1-phenyl-3-phosphonopropyl phosphonate (196e)
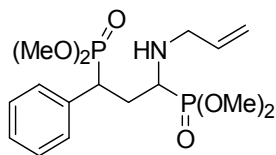
The product was obtained as a mixture of two diastereomeric pairs (ratio: 71/29). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

¹H NMR δ (300 MHz, ppm): 1.79 (2x 1H, s (br.), NH); 2.02-2.28 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 2.30-2.46 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 2.53 (1H, td, J = 12.4 Hz, J = 2.5 Hz, NCHP, M); 2.85 (2x 1H, ddd, J = 14.0 Hz, J = 8.0 Hz, J = 6.1 Hz, NCHP, m); 3.01 (1H, ddd, J$_{AB}$ = 13.8 Hz, J = 6.1 Hz, J = 1.4 Hz, CH$_A$H$_B$N, M); 3.13 (1H, dd, J = 14.0 Hz, J = 6.3 Hz, CH$_A$H$_B$NH, m); 3.25 (1H, ddd, J = 14.0 Hz, J = 6.3 Hz, J = 1.4 Hz, CH$_A$H$_B$NH, m); 3.41 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 5.9 Hz, J = 1.4 Hz, CH$_A$H$_B$NH, M); 3.46-3.87 (2x 1H, multiplet, CHP, m+M); 3.47 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.49 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 3.70 (6H, d, J$_{HP}$ = 10.2 Hz, 2x OCH$_3$, M); 3.71 (3H, d, J$_{HP}$ = 12.0 Hz, OCH$_3$, m); 3.72 (3H, d, J$_{HP}$ = 11.9 Hz, OCH$_3$, m); 3.73 (3H, d, J$_{HP}$ = 10.2 Hz, OCH$_3$, M); 3.79 (3H, d, J$_{HP}$ = 10.7 Hz, m); 4.93-5.14 (2x 2H, multiplet, =CH$_2$, m+M); 5.62-5.82 (2x 1H, multiplet, CH=, m+M); 7.24-7.40 (2x 5H, multiplet, CH$_{arom}$, m+M). **¹³C-NMR δ (75 MHz, ppm):** 30.28 (d, J$_{CP}$ = 8.1 Hz, CH$_2$, M); 30.90 (CH$_2$, m); 39.66 (dd, J$_{CP}$ = 139.6 Hz, J$_{CP}$ = 15.0 Hz, CHP, M); 40.37 (dd, J$_{CP}$ = 137.3 Hz, J$_{CP}$ = 5.8 Hz, CHP, m); 50.36 (dd, J$_{CP}$ = 141.9 Hz, J$_{CP}$ = 16.2 Hz, NCHP, M); 50.07 (d, J = 9.2 Hz, CH$_2$NH, m); 50.63 (CH$_2$N, M); 51.12 (dd, J$_{CP}$ = 152.3 Hz, J$_{CP}$ = 13.9 Hz, NCHP, m); 52.55, 52.66, 52.78, 53.24, 53.34, 53.41, 53.51 (OCH$_3$, m+M); 116.05 (=CH$_2$, M); 116.54 (=CH$_2$, m); 127.53, 127.58, 128.73, 129.27, 129.37, 129.49, 129.58 (CH$_{arom}$); 134.58 (d, J$_{CP}$ = 5.8 Hz, C$_{q,arom}$, M); 135.69 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, m); 136.04 (CH=, m); 136.51 (CH=, M). **³¹P-NMR δ (121 MHz, ppm):** 30.41 (m); 31.20 (m); 31.37 (d, J$_{PP}$ = 9.7 Hz, M); 32.14 (d, J$_{PP}$ = 8.9 Hz, M). **IR ν (cm⁻¹):** 3455 (NH); 1242 (br., P=O); 1183, 1031 (br., P-O). **MS: m/z (%) :** 392 (100, [M+H]⁺). **Yield:** 36%. Yellow oil.

Tetraethyl 3-allylamino-1-phenyl-3-phosphonopropyl phosphonate (196f)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 33/67). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
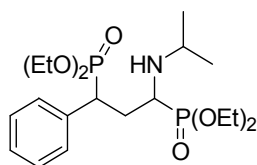
¹H NMR δ: (300 MHz, ppm): 1.06-1.36 (2x 6H, multiplet, CH$_3$, m+M); 1.60 (2x1H, s(br.), NH, m+M); 2.01-2.28 (2x1H, multiplet, CH$_A$H$_B$, m+M); 2.37-2.55 (2H + 1H, multiplet, CH$_A$H$_B$, m+M, NCHP, m); 2.80 (1H, ddd, J = 14.0 Hz, J = 8.0 Hz, J = 5.8 Hz, CHPNH, M); 3.00-3.06 (1H, multiplet, CH$_A$H$_B$N, m); 3.14 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 6.3 Hz, CH$_A$H$_B$N, M); 3.26 (1H, dd, J$_{HP}$ = 13.8 Hz, J = 5.7 Hz, CH$_A$H$_B$NH, M); 3.40-3.47 (1H, multiplet, CH$_A$H$_B$N, m); 3.53-4.18 (2x 9H, multiplet, CHP, OCH$_2$, m+M); 4.93-5.16 (2x 2H, multiplet, =CH$_2$, m+M); 5.62-5.84 (2x 1H, multiplet, =CH, m+M); 7.25-7.39 (2x 5H, CH$_{arom}$, m+M). **¹³C NMR δ (75 MHz, ppm):** 16.22, 16.29, 16.42, 16.52, 16.59, 16.65 (4x CH$_3$, m+M); 30.56 (d, J$_{CP}$ = 8.1 Hz, CH$_2$, m); 31.06 (CH$_2$, M); 40.29 (dd, J$_{CP}$ = 138.5 Hz, J$_{CP}$ = 13.8 Hz, CHP, m); 41.00 (dd, J$_{CP}$ = 137.3 Hz, J$_{CP}$ = 5.8 Hz, CHP, M); 50.22 (d, J$_{CP}$ = 8.0 Hz, CH$_2$N, M); 50.71 (CH$_2$N, m); 50.97 (dd, J$_{CP}$ = 152.3 Hz, J$_{CP}$ = 16.2 Hz, NCHP, m); 51.70 (dd, J$_{CP}$ = 151.1 Hz, J$_{CP}$ = 13.8 Hz, NCHP, M); 61.89, 61.98, 62.4, 62.43, 62.52, 62.67, 62.76, 62.93 (OCH$_2$, m+M); 115.94 (=CH$_2$, m); 116.46 (=CH$_2$, M); 127.39, 127.96, 128.61,

129.45, 129.53, 129.65, 129.74 (CH$_{arom}$, m+M); 135.10 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, m); 136.14 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, M); 136.25 (=CH, M); 136.78 (=CH, m). **31P NMR δ (121 MHz, ppm):** 28.25 (M); 28.98 (M); 29.02 (d, J$_{PP}$ = 9.7 Hz, m); 29.89 (d, J$_{PP}$ = 9.7 Hz, m). **IR ν (cm⁻¹):** 3469 (NH); 1239 (br., P=O); 1028 (br., P-O). **MS m/z (%):** 448 (100, [M+H]⁺). **Yield:** 40%. Yellow oil.

Tetraethyl 3-[2-(1H-indol-3-yl)ethylamino]-1-phenyl-3-phosphonopropyl phosphonate (196g)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 29/71). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
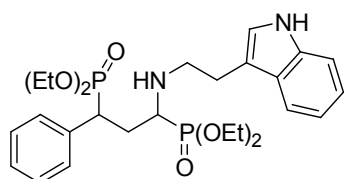
1H NMR δ (300 MHz, ppm): 1.04-1.27 (2 x 12H, multiplet, CH$_3$, m+M); 2.11-2.41 (2H, multiplet, CH$_2$CH, m+M); 2.43-2.54 (1H, ~t, NCH, M); 2.63-2.71 (1H, multiplet, CH$_A$H$_B$N, M); 2.78 (2H, t, J = 6.6 Hz, CH$_2$C$_q$=, m); 2.84 (2H, t, J = 6.6 Hz, CH$_2$C$_q$=, M); 2.89-2.98 (3H, multiplet, CH$_2$N, NCH, m); 3.16-3.24 (1H, multiplet, CH$_A$H$_B$N, M); 3.45-3.56 (2 x 1H, multiplet, CHPh, m+M); 3.59-4.13 (2 x 8H, multiplet, OCH$_2$, m+M); 6.85 (1H, d, J = 2.2 Hz, =CH, m); 6.91 (1H, d, J = 2.2 Hz, =CH; M); 7.00-7.41 (2 x 8H, multiplet, CH$_{arom}$, m+M, 3 x CH$_{indole}$, m+M); 7.49 (1H, d, J = 7.7 Hz, CHC$_{q,indole}$, m); 7.56 (1H, d, J = 7.7 Hz, CHC$_{q,indole}$, M); 9.58 (2 x 1H, s(br.), NH$_{indole}$, m+M). **13C NMR δ (75 MHz, ppm):** 16.13 (CH$_3$, m); 16.22 (CH$_3$, m); 16.34 (CH$_3$, M); 16.42 (CH$_3$, M); 25.92 (CH$_2$C$_q$=, m); 26.44 (CH$_2$C$_q$=, M); 30.15 (d, J$_{CP}$ = 6.9 Hz, CH$_2$CH, M); 30.94 (CH$_2$CH, m); 39.89 (dd, J$_{CP}$ = 138.5 Hz, J$_{CP}$ = 13.9 Hz, CHPh, M); 40.67 (dd, J$_{CP}$ = 136.2 Hz, J$_{CP}$ = 6.9 Hz, CHPh, m); 48.04 (d, J$_{CP}$ = 6.9 Hz, CH$_2$N, m); 48.35 (CH$_2$N, M); 51.70 (dd, J$_{CP}$ = 144.2 Hz, J$_{CP}$ = 16.2 Hz, NCH, M); 52.75 (dd, J$_{CP}$ = 150.0 Hz, J$_{CP}$ = 12.7 Hz, NCH, m); 61.74, 61.83, 61.87, 61.93, 62.29, 62.38, 62.47, 62.61 (OCH$_2$, m+M); 111.39 (CHC$_q$N$_{indole}$); 112.62 (=C$_q$, m); 112.93 (=C$_q$, M); 118.63, 118.66 (CH$_{indole}$); 121.37 (CHCHC$_q$C=); 122.41 (=CH); 127.30 (CH$_{arom}$); 127.42 (C$_{q,indole}$); 128.55 (2 x CH$_{arom}$); 129.28 (d, J$_{CP}$ = 6.9 Hz, 2 x CH$_{arom}$, m); 129.48 (d, J$_{CP}$ = 6.9 Hz, 2 x CH$_{arom}$, M); 134.84 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, M); 136.17 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, m); 136.64 (C$_q$N). **31P NMR δ (121 MHz, ppm):** 28.22 (m); 29.04 (m); 29.04 (d, J$_{PP}$ = 9.7 Hz, M); 29.99 (d, J$_{PP}$ = 9.7 Hz, M). **IR ν (cm⁻¹):** 1232 (P=O); 1030 (br., P-O). **MS m/z (%):** 551 (100, [M+H]⁺). **Yield:** 82%. Yellow oil.

## Tetramethyl 3-isopropylamino-1-phenyl-3-phosphonopropyl phosphonate (196h)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 32/68). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
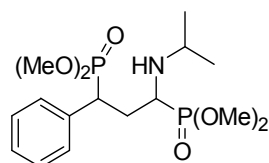
1H NMR δ (300 MHz, ppm): 0.67 (3H, d, J = 6.1 Hz, CH$_3$, M); 0.73 (3H, d, J = 6.1 Hz, CH$_3$, m); 0.94 (3H, d, J = 6.3 Hz, CH$_3$, m); 0.98 (3H, d, J = 6.3 Hz, CH$_3$, M); 1.55 (1H, s(br), NH); 2.02-2.20 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 2.41-2.52 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 2.64 (1H, td, J = 11.6 Hz, J$_{HP}$ = 2.8 Hz, PCHNH, M); 2.76-2.84 (1H, multiplet, PCHNH, m); 2.81 (1H, septet, J = 6.3 Hz, CH(CH$_3$)$_2$, m); 3.01 (1H, septet x d, J = 6.1 Hz, J$_{HP}$ = 2.8 Hz, CH(CH$_3$)$_2$, M); 3.47 (3H,

d, J_{HP} = 10.5 Hz, OCH$_3$, m); 3.49 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, M); 3.69 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, M); 3.71 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, M); 3.72 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, m); 3.74 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, M); 3.75 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, m); 3.77- 3.81 (2x1H, multiplet, CHP(Ph), m+M); 3.80 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, m); 7.26-7.36 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 22.11 (CH$_3$, M); 22.37 (CH$_3$, m); 23.15 (CH$_3$, m); 24.01 (CH$_3$, M); 30.53 (d, J_{CP} = 8.1 Hz, CH$_2$, M); 31.33 (s(br.), CH$_2$, m); 39.63 (dd, J_{CP} = 141.9 Hz, J_{CP} = 10.4 Hz, PCHPh, M); 40.47 (d (br.), J_{CP} = 137.3 Hz, PCHPh, m); 46.04 (d, J_{CP} = 9.2 Hz, $\underline{C}$H(CH$_3$)$_2$, m); 46.28 ($\underline{C}$H(CH$_3$)$_2$, M); 48.55 (dd, J_{CP} = 145.4 Hz, J_{CP} = 12.7 Hz, PCHNH, m); 49.27 (dd, J_{CP} = 153.5 Hz, J_{CP} = 13.9 Hz, PCHNH, m); 52.59 (OCH$_3$); 52.68 (OCH$_3$); 52.83 (OCH$_3$); 53.26 (OCH$_3$); 53.37 (OCH$_3$); 53.67 (OCH$_3$); 127.50 128.66, 129.30, 129.38, 129.61, 129.69 (CH$_{arom}$); 134.50 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, M); 135.58 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, m). **^{31}P NMR δ (121 MHz, ppm):** 30.66 (m); 31.28 (m); 31.62 (d, J_{PP} = 9.7 Hz, M); 32.10 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3477 (N-H); 1245 (br., P=O); 1051 (br., P-O). **MS m/z (%):** 176 (2, [M+H-2PO(OCH$_3$)$_2$]$^+$); 285 (12, [M+H-PO(OCH$_3$)$_2$]$^+$); 394 (100, [M+H]$^+$). **Yield:** 77%. Pale yellow oil.

## Tetraethyl 3-isopropylamino-1-phenyl-3-phosphonopropyl phosphonate (196i)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 33/67). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

^{1}H NMR δ (300 MHz, ppm): 0.70 (3H, d, J = 6.1 Hz, C$\underline{H}_3$CH, M); 0.72 (3H, d, J = 6.1 Hz, C$\underline{H}_3$CH, m); 0.94 (3H, d, J = 6.3 Hz, C$\underline{H}_3$CH, m); 0.99 (3H, d, J = 6.3 Hz, C$\underline{H}_3$CH, M); 1.08 (3H, t, J = 6.9 Hz, CH$_3$, m); 1.12 (3H, t, J = 7.3 Hz, CH$_3$, M); 1.26-1.36 (2 x 9H, multiplet, CH$_3$, m+M); 1.97-2.53 (2 x 2H, multiplet, CH$_2$, m+M); 2.60 (1H, td, J = 11.6 Hz, J = 2.5 Hz, NCHP, M); 2.71-2.81 (1H, multiplet, NCHP, m); 2.86 (1H, septet, J = 6.3 Hz, NCH, m); 3.06 (1H, septet x d, J = 6.3 Hz, J_{HP} = 2.6 Hz, NCH, M); 3.54-3.79 (2 x 1H, multiplet, CHP, m+M); 2.81-4.21 (2 x 8H, multiplet, OCH$_2$, m+M); 7.22-7.41 (2 x 5H, multiplet, CH$_{arom}$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 16.21, 16.29, 16.37, 16.46, 16.50, 16.58 (CH$_3$, m+M); 22.16 (C$\underline{H}_3$CH, M); 22.43 (C$\underline{H}_3$CH, m); 23.16 (C$\underline{H}_3$CH, m); 24.05 (C$\underline{H}_3$CH, M); 30.58 (d, J_{CP} = 6.9 Hz, CH$_2$, M); 31.51 (CH$_2$, m); 40.98 (dd, J_{CP} = 136.7 Hz, J_{CP} = 4.0 Hz, CHP, m); 41.19 (dd, J_{CP} = 136.2 Hz, J_{CP} = 15.0 Hz, CHP, M); 46.02 (d, J_{CP} = 4.0 Hz, NCH, m); 46.19 (NCH, M); 49.03 (dd, J_{CP} = 140.8 Hz, J_{CP} = 17.3 Hz, NCHP, M); 49.64 (dd, J_{CP} = 152.9 Hz, J_{CP} = 14.4 Hz, NCHP, m); 61.71, 61.75, 61.81, 61.85, 61.94, 62.37, 62.46, 62.54, 62.58, 62.63 (OCH$_2$, m+M); 127.29, 128.47, 128.49 (CH$_{arom}$, M); 129.49 (d, J_{CP} = 6.9 Hz, CH$_{arom}$, m); 129.78 (d, J_{CP} = 6.9 Hz, CH$_{arom}$, M); 135.05 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, M); 136.10 (d, J_{CP} = 6.9 Hz, C$_{q,arom}$, m). **^{31}P NMR δ (121 MHz, ppm):** 28.41 (m); 28.94 (m); 29.09 (d, J_{PP} = 9.7 Hz, M); 29.70 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3300 (NH); 1243 (P=O); 1047 (br., P-O). **MS m/z:** 312 (65, [M+H-PO(OCH$_2$CH$_3$)$_2$]$^+$); 450 (100, [M+H]$^+$). **Yield:** 78%. Pale yellow oil.

Tetramethyl 3-tert-butylamino-1-phenyl-3-phosphonopropyl phosphonate (196j)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 49/51). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
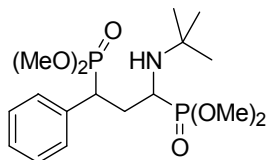
¹H NMR δ (300 MHz, ppm): 0.89 (3H, s, CH_3, m); 0.96 (3H, s, CH_3, M); 2.11-2.38 (2x 1H, multiplet, CH_AH_B, m+M); 2.39-2.56 (2x 1H, multiplet, CH_AH_B, m+M); 2.72 (1H, ddd, J = 15.1 Hz, J = 11.3 Hz, J = 3.3 Hz, NHP, m); 3.02 (1H, ddd, J = 16.0 Hz, J = 8.3 Hz, J = 4.7 Hz, NHP, M); 3.45 (3H, d, J_{HP} = 10.5 Hz, OCH_3, m); 3.48 (3H, d, J_{HP} = 10.5 Hz, OCH_3, m); 3.51-3.84 (2x 1H, multiplet, CHP, m+M); 3.68 (3H, d, J_{HP} = 10.7 Hz, OCH_3, m); 3.73 (3H, d, J_{HP} = 10.5 Hz, OCH_3, M); 3.74 (3H, d, J_{HP} = 10.7 Hz, OCH_3, M); 3.75 (3H, d, J_{HP} = 10.2 Hz, OCH_3, M); 3.76 (3H, d, J_{HP} = 10.2 Hz, OCH_3, M); 3.81 (3H, d, J_{HP} = 10.2 Hz, OCH_3, m); 7.25-7.44 (2x 5H, multiplet, CH_{arom}, m+M). **¹³C NMR δ (75 MHz, ppm):** 29.78 (CH_3, M); 30.32 (CH_3, m); 32.98 (CH_2, m); 35.19 (CH_2, M); 40.00 (d, J_{CP} = 140.8 Hz, CHP, m); 40.42 (d, J_{CP} = 138.5 Hz, CHP, M); 46.78 (dd, J_{CP} = 160.4 Hz, J_{CP} = 17.3 Hz, CHPN, m); 47.48 (dd, J_{CP} = 151.1 Hz, J_{CP} = 13.8 Hz, CHPN, M); 50.99 (C_q, M); 51.84 (C_q, m); 52.68, 53.34, 54.25 (OCH_3, m+M); 127.42, 127.56, 128.61, 129.65, 129.71 (CH_{arom}, m+M); 135.13 (d, J_{CP} = 6.9 Hz, $C_{q,arom}$, M); 135.45 (d, J_{CP} = 6.9 Hz, $C_{q,arom}$, m). **³¹P NMR δ (121 MHz, ppm):** 30.60 (M); 31.00 (d, J_{PP} = 5.9 Hz, m); 31.14 (M); 31.88 (d, J_{PP} = 5.6 Hz, m). **IR ν (cm⁻¹):** 3469 (NH); 1235 (br., P=O); 1051 (br., P-O). **MS: m/z (%):** 408 (100, [M+H]⁺). **Yield:** 82%. Colourless oil.

Tetraethyl 3-tert-butylamino-1-phenyl-3-phosphonopropyl phosphonate (196k)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 36/64). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
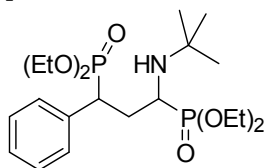
¹H NMR δ (300 MHz, ppm): 0.89 (3H, s, CH_3C_q, m); 0.97 (3H, s, CH_3C_q, M); 1.05 (3H, t, ³J(H,H) = 7.1 Hz, CH_3, m); 1.12 (3H, t, ³J(H,H) = 7.1 Hz, CH_3, M); 1.26-1.36 (2 x 9H, multiplet, CH_3, m+M); 2.10-2.33 (2 x 1H, multiplet, CH_AH_B, m+M); 2.39-2.60 (2 x 1H, multiplet, CH_AH_B, m+M); 2.70 (1H, ddd, J = 16.1 Hz, J = 11.3 Hz, J = 3.3 Hz, NCHP, m); 3.00 (1H, ddd, J = 16.0 Hz, J = 8.3 Hz, J = 4.7 Hz, NCHP, M); 3.63-4.28 (2 x 9 H, multiplet, OCH_2, CHP, m+M); 7.22-7.46 (2 x 5H, multiplet, CH_{arom}, m+M). **¹³C NMR δ (75 MHz, ppm):** 16.21, 16.27, 16.38, 16.46, 16.55 (CH_2CH_3); 29.56 (CH_3, m); 30.12 (CH_3, M); 32.87 (d, J_{CP} = 6.9 Hz, $CH_{2,M}$); 35.10 (CH_2, m); 40.28 (dd, J_{CP} = 136.1 Hz, J_{CP} = 9.2 Hz, CHP, M); 41.04 (d, J_{CP} = 136.1 Hz, CHP, m); 46.88 (dd, J_{CP} = 159.2 Hz, J_{CP} = 17.9 Hz, NCHP, m); 47.84 (dd, J_{CP} = 152.29 Hz, J_{CP} = 13.9 Hz, NCHP, M); 51.01 (NC_q, m); 51.81 (d, J_{CP} = 9.2 Hz, NC_q, M); 61.76, 61.85, 62.31, 62.41, 62.51, 63.02, 63.12 (OCH_2); 127.23, 127.38, 128.45, 129.75, 129.84, 129.95 (CH_{arom}); 135.58 (d, J_{CP} = 6.9 Hz, $C_{q,arom}$, m); 135.93 (d, J_{CP} = 8.1 Hz, $C_{q,arom}$, M). **³¹P NMR δ (121 MHz, ppm):** 28.74 (s(br.), m); 28.84 (d, J_{PP} = 6.0 Hz, M); 28.91 (s(br.), m); 29.64 (dd, J_{PP} = 6.0 Hz, M). **IR ν (cm⁻¹):** 3308 (NH); 1243 (P=O); 1049, 1028 (P-O). **MS m/z:** 326 (56, [M+H-PO(OCH_2CH_3)$_2$]⁺); 464 (100, [M+H]⁺). **Yield:** 85%. Pale yellow oil.

Tetramethyl 3-tert-butylamino-1-methyl-3-phosphonopropyl phosphonate (196l)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 36/64). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
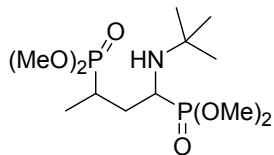
¹H NMR δ (300 MHz, ppm): 0.95 (9H, s, 3x C$\underline{H}_3$, m); 0.96 (9H, s, 3x C$\underline{H}_3$, M); 0.99-1.23 (2x 3H, multiplet, CH_3, m+M); 1.32-2.00 (2x 3H, multiplet, CH_2, NH, m+M); 2.02-2.32 (1H, multiplet, CHP, m+M); 2.98 (1H, ddd, J = 15.4 Hz, J = 9.9 Hz, J = 5.5 Hz, NCHP, m); 3.13 (1H, dt, J = 16.2 Hz, J = 7.4 Hz, NC$\underline{H}$P, M); 3.75 (3H, d, J_{HP} = 10.5 Hz, OC$\underline{H}_3$, m); 3.61 (3H, d, J_{HP} = 10.5 Hz, OC$\underline{H}_3$, m); 3.75 (3H, d, J_{HP} = 10.5 Hz, OC$\underline{H}_3$, M); 3.76 (3H, d, J_{HP} = 10.5 Hz, OC$\underline{H}_3$, M). **¹³C NMR δ (75 MHz, ppm):** 13.39 (d, J_{CP} = 4.6 Hz, CH_3, m); 14.72 (d, J_{CP} = 4.6 Hz, CH_3, M); 26.34 (dd, J_{CP} = 141.9 Hz, J_{CP} = 6.9 Hz, CHP, M); 27.03 (d, J_{CP} = 139.6 Hz, CHP, m); 29.71 (3x CH_3, m); 29.97 (3x CH_3, M); 34.72 (CH_2, s (br.), m); 35.02 (CH_2, s (br.), M); 46.94 (d, J_{CP} = 145.4 Hz, NCHP, M); 47.00 (d, J_{CP} = 163.8 Hz, NCHP, m); 51.37 (d, J_{CP} = 5.8 Hz, NC_q, m); 51.79 (d, J_{CP} = 8.1 Hz, NC_q, M); 52.41 (d, J_{CP} = 8.1 Hz, OCH_3, M); 52.66 (d, J_{CP} = 12.7 Hz, OCH_3, M); 53.74 (d, J_{CP} = 6.9 Hz, OCH_3, m); 54.29 (s(br.), OCH_3, m). **³¹P NMR δ (121 MHz, ppm):** 30.61 (d, J_{PP} = 2.2 Hz, m); 31.75 (d, J_{PP} = 5.2 Hz, M); 37.11 (d, J_{PP} = 2.2 Hz, m); 37.99 (d, J_{PP} = 5.2 Hz, M). **IR ν (cm⁻¹):** 3470 (NH); 1231 (br., P=O); 1034 (br., P-O). **MS m/z (%):** 346 (100, [M+H]⁺). **Yield:** 74%. Yellow oil.

Tetramethyl 3-tert-butylamino-1,1-dimethyl-3-phosphonopropyl phosphonate (196m)
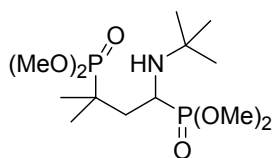
¹H NMR δ (300 MHz, ppm): 1.15 (9H, s, 3x C$\underline{H}_3$); 1.26 (3H, d, J_{HP} = 5.2 Hz, C$\underline{H}_3$); 1.32 (3H, d, J_{HP} = 5.2 Hz, C$\underline{H}_3$); 1.65-1.82 (1H, multiplet, C$\underline{H}_A H_B$); 1.91 (1H, s(br.), N$\underline{H}$); 2.15-2.30 (1H, multiplet, $CH_A\underline{H}_B$); 3.36 (1H, dt, J = 13.5 Hz, J = 6.3 Hz, C$\underline{H}$P); 3.75 (3H, d, J_{HP} = 10.2 Hz, OC$\underline{H}_3$); 3.76 (3H, d, J_{HP} = 10.2 Hz, OC$\underline{H}_3$); 3.77 (3H, d, J_{HP} = 10.2 Hz, OC$\underline{H}_3$); 3.80 (3H, d, J_{HP} = 10.2 Hz, OC$\underline{H}_3$). **¹³C NMR δ (75 MHz, ppm):** 20.67 (CH_3); 20.73 (CH_3); 28.81 (3x CH_3); 34.98 (dd, J_{CP} = 139.6 Hz, J_{CP} = 8.1 Hz, C_qP); 38.43 (d, J_{CP} = 6.9 Hz, CH_2); 45.11 (dd, J_{CP} = 150.0 Hz, J_{CP} = 12.1 Hz, CHP); 50.28 (d, J_{CP} = 4.6 Hz, NC_q); 51.25 (d, J_{CP} = 8.1 Hz, OCH_3); 51.72 (d, J_{CP} = 8.1 Hz, OCH_3); 51.82 (d, J_{CP} = 8.1 Hz, OCH_3); 52.18 (d, J_{CP} = 8.1 Hz, OCH_3). **³¹P NMR δ (121 MHz, ppm):** 31.36 (d, J_{PP} = 3.0 Hz); 38.85 (d, J_{PP} = 3.0 Hz). **IR ν (cm⁻¹):** 3429 (NH); 1242 (P=O); 1049 (br., P-O). **MS m/z (%):** 250 (7, [M+H-PO(OCH₃)₂]⁺); 360 (100, [M+H]⁺). **Yield:** 60%. Yellow oil.

Tetramethyl {2-[isopropylaminophosphonomethyl]-6,6-dimethyl-bicyclo[3.1.1]hept-3-yl} phosphonate (196n)
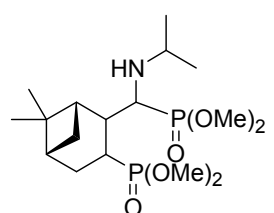
The product was obtained as a mixture of two diastereomeric pairs (ratio: 22/78). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

¹H NMR δ (300 MHz, ppm): 0.98-1.22 (2 x 13H, multiplet, C$\underline{H}_3 C_q$, C$\underline{H}_3$CH, C$\underline{H}_A H_B$, m+M); 1.73 (2 x 1H, s(br.), NH, m+M); 1.88-1.95 (2 x 1H, multiplet, C_qC$\underline{H}CH_2$, m+M); 2.10-2.20 (2 x

2H, multiplet, C$\underline{H}_2$CHP, m+M); 2.23-2.32 (1H, multiplet, CH$_A$$\underline{H}_B$, M); 2.34-2.40 (2 x 1H, multiplet, C$_q$C$\underline{H}$CH, m+M); 2.41-2.49 (1H, multiplet, CH$_A$$\underline{H}_B$, m); 2.56-2.79 (2 x 1H, multiplet, NCHP, m+M); 2.90-2.95 (1H, multiplet, C$\underline{H}$PCH$_2$, m); 2.98-3.04 (2H, multiplet, C$\underline{H}$PCH$_2$, NCHP, M); 3.13 (2 x 1H, septet x d, J = 6.3 Hz, J$_{HP}$ = 2.5 Hz, C$\underline{H}$CH$_3$, m+M); 3.52 (1H, dd, J = 17.6 Hz, J = 3.3 Hz, NCHP$_m$); 3.72-3.84 (2 x 12H, multiplet, OCH$_3$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 21.69 ($\underline{C}$H$_3$C$_q$); 22.64 ($\underline{C}$H$_3$CH, M); 23.71 ($\underline{C}$H$_3$CH, M); 24.06 (CH$_3$, m); 25.06 (dd, J$_{CP}$ = 139.6 Hz, J$_{CP}$ = 11.5 Hz, $\underline{C}$HPCH$_2$, M); 25.60 (CH$_3$, m); 26.44 (dd, J$_{CP}$ = 139.6 Hz, J$_{CP}$ = 16.2 Hz, $\underline{C}$HPCH$_2$, m); 26.51 (d, J$_{CP}$ = 4.6 Hz, $\underline{C}$H$_2$CHP); 27.06 ($\underline{C}$H$_3$C$_q$); 28.35 (CH$_3$, m); 29.51 (CH$_2$, M); 34.59 (CH$_2$, m); 37.68 (C$_q$, M); 37.84 (C$_q$, m); 38.73 (d, J$_{CP}$ = 4.6 Hz, C$_q$$\underline{C}HCH_2$, M); 40.41 (C$_q$$\underline{C}HCH_2$, m); 40.59 ($\underline{C}$HCHP); 40.67 ($\underline{C}$HCHP); 43.42 (d, J$_{CP}$ = 5.8 Hz, C$_q$$\underline{C}HCH_M$); 43.80 (d, J$_{CP}$ = 11.5 Hz, C$_q$$\underline{C}HCH_m$); 46.74 ($\underline{C}HCH_3$, m+M); 51.74 (OCH$_3$, m); 51.91 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$, M); 52.61 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 52.87 d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 53.18 (d, J$_{CP}$ = 132.7 Hz, NCHP$_m$); 53.48 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 55.30 (d, J$_{CP}$ = 148.8 Hz, NCHP$_M$). **^{31}P NMR δ (121 MHz, ppm):** 31.59 (d, J$_{PP}$ = 3.0 Hz, M); 32.87 (d, J$_{PP}$ = 2.2 Hz, m); 37.83 (d, J$_{PP}$ = 2.2 Hz, m); 39.02 (d, J$_{PP}$ = 3.0 Hz, M). **IR ν (cm^{-1}):** 3311 (NH); 1235 (P=O); 1054 (br., P-O). **MS m/z:** 302 (7, [M+H-PO(OCH$_3$)$_2$]$^+$); 412 (100, [M+H]$^+$). **Yield:** 46%. Yellow oil.

Tetramethyl {2-[tert-butylaminophosphonomethyl]-6,6-dimethyl-bicyclo[3.1.1]hept-3-yl} phosphonate (196o)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 12/88). Due to the low abundance of the minor isomer, peak identification in ^{1}H and ^{13}C NMR was limited to the major (M) isomer.
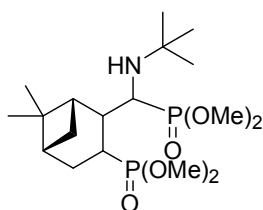
^{1}H NMR δ (300 MHz, ppm): 0.99 (3H, s, CH$_3$); 1.13 (9H, s, CH$_3$); 1.13-1.15 (1H, multiplet, C$\underline{H}_A$H$_B$); 1.19 (3H, s, CH$_3$, M); 1.90 (1H, s(br.), C$_q$C$\underline{H}$CH$_2$); 2.08-2.32 (3H, multiplet, C$\underline{H}_2$CHP, CH$_A$$\underline{H}_B$, m+M); 2.42 (1H, s (br.), C$_q$C$\underline{H}$CH); 2.55-2.88 (2x 1H, multiplet, $\underline{C}$HCHP, CHP); 3.20 (1H, ~t, J = 10.3 Hz, NCHP). **^{13}C NMR δ (75 MHz, ppm):** 22.99 ($\underline{C}$H$_3$C$_q$, M); 25.93 (dd, J$_{CP}$ = 139.6 Hz, J$_{CP}$ = 13.9 Hz, CHP); 27.21 ($\underline{C}$H$_3$C$_q$); 29.96 (br, $\underline{C}$H$_2$); 30.49 (3x CH$_3$); 37.74 (C$_q$); 39.80 (d, J$_{CP}$ = 4.6 Hz, C$_q$$\underline{C}HCH_2$); 41.68 (s (br.), CH$\underline{C}$HCHP); 43.12 (d, J$_{CP}$ = 5.8 Hz, C$_q$$\underline{C}$HCH); 50.78 (NC$_q$); 51.90 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$); 52.72 (d, J$_{CP}$ = 6.9 Hz, O$\underline{C}$H$_3$); 53.18 (d, J$_{CP}$ = 6.9 Hz, O$\underline{C}$H$_3$); 54.23 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 54.22 (dd, J$_{CP}$ = 148.8 Hz, N$\underline{C}$HP). **^{31}P NMR δ (121 MHz, ppm):** 31.59 (d, J$_{PP}$ = 3.7 Hz, M); 34.07 (m); 37.79 (m); 38.95 (d, J$_{PP}$ = 3.7 Hz, M). **IR ν (cm^{-1}):** 3320 (NH); 1227 (br., P=O); 1051 (br., P-O). **MS m/z (%) :** 426 (100, [M+H$^+$]). **Yield:** 20%. Yellow oil.

3.2.3 Preparation of 2-isopropylamino-4-phenylbut-3-ene nitrile (198)

The imine **19g** (5 mmol) was dissolved in 10 ml of dry dichloromethane and stirred under a nitrogen atmosphere at room temperature. Then 10 mmol of TMSCN and 2.5 mmol of sulphuric acid were added consecutively using a syringe. CAUTION: HCN may escape from the reaction vessel during this procedure. Therefore, the exhaust of the nitrogen flow was passed through two consecutive washbottles containing a 3 M NaOH$_{(aq)}$ solution prior to

discharge directly to the hood ventilation system. Stirring was continued for 24 h at room temperature. Then 10 ml of a saturated NaHCO$_{3(aq)}$ solution was added. After 30 minutes, the mixture was poured into a separatory funnel and extracted twice with 10 ml of dichlormethane. After drying (MgSO$_4$) and evaporation of the solvent under reduced pressure, the resulting oil was kept at -32°C until crystallization occurred. Nitrile **198** was obtained in pure form by recrystallization from ethanol/hexane.

¹H NMR δ (300 MHz, ppm): 1.12 (3H, d, J = 6.3 Hz, CH$_3$); 1.17 (3H, d, J = 6.3 Hz, CH$_3$); 1.33 (1H, s(br.), NH); 3.20 (1H, septet, J = 6.3 Hz, C<u>H</u>(CH$_3$)$_2$); 4.43 (1H, dd, J = 5.2 Hz, J = 1.1 Hz, <u>C</u>HCN); 6.20 (1H, dd, J = 16.0 Hz, J = 5.2 Hz, =C<u>H</u>CHCN); 6.92 (1H, dd, J = 16.0 Hz, J = 1.4 Hz, PhC<u>H</u>=); 7.29-7.43 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 21.39 (CH$_3$); 23.72 (CH$_3$); 46.98 (<u>C</u>H(CH$_3$)$_2$); 49.85 (<u>C</u>HCN); 118.51 (CN); 122.81 (<u>C</u>HCHCN); 126.83 (2x CH$_{arom}$); 128.60 (CH$_{arom}$); 128.77 (2x CH$_{arom}$); 133.79 (Ph<u>C</u>H=); 135.38 (C$_{q,arom}$). **MS m/z (%):** 174 (100, [M-CN]$^+$). **IR ν (cm^{-1}):** 3358 (N-H); 2224 (CN); 1627 (CH=CH). **Mp.:** 40-41°C. **Yield:** 81%. Yellow crystals.

3.2.4 Preparation of dimethyl 3-phenyl-2-propenyl phosphonate (210)

Cinnamyl bromide (5 mmol) was mixed with 5 mmol of trimethyl phosphite in a roundbottom flask under a nitrogen atmosphere. The mixture was heated at 80°C for 6 h. CAUTION: the reaction should be performed in a properly working hood since gaseous methyl bromide is deliberated from the reaction mixture. Phosphonate **210** was obtained after evaporation of the volatiles.

¹H NMR δ (300 MHz, ppm): 2,77 (2H, dd, J$_{HP}$ = 22,3 Hz, J = 7,4 Hz, CH$_2$); 3,75 (3H, d, J$_{HP}$ = 11,0 Hz, OCH$_3$); 3,76 (3H, d, J$_{HP}$ = 10,7 Hz, OCH$_3$); 6,09-6,22 (1H, multiplet, C<u>H</u>CH$_2$); 6,53 (1H, dd, J = 15,9 Hz, J$_{HP}$ = 4,7 Hz, CH); 7,19-7,37 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 30,11 (d, J$_{CP}$ = 39,6 Hz, CH$_2$P); 52,78 (OCH$_3$); 52,84 (OCH$_3$); 118,36 (d, J$_{CP}$ = 12,7 Hz, =<u>C</u>HCH$_2$); 126,28 (2x CH$_{arom}$); 127,70 (CH$_{arom}$); 128,59 (2x CH$_{arom}$); 134,90 (d, J$_{CP}$ = 15,0 Hz, =CH); 136,68 (d, J$_{CP}$ = 3,5 Hz, C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 29,99. **IR ν (cm^{-1}):** 1651, 1598, 1251 (br, P=O); 1048 (br, P-O). **MS m/z (%):** 227 (100, [M+H]$^+$). **Yield:** 98%. Orange oil.

3.2.5 Preparation of diethyl (3-oxo-1-phenylpropyl) phosphonate (217)

Imine **19h** (10 mmol) was mixed with 9.6 mmol of triethyl phosphite in 10 ml of dry ethanol (20 ml) under a nitrogen atmosphere. Then 10.4 mmol of formic acid was added dropwise to the reaction mixture. Stirring was continued for 10 minutes and then the solvent was evaporated under reduced pressure. The resulting oil was dissolved in 4 ml of dichloromethane and 6 ml of diethyl ether. Then 8 ml of a 1 M aqueous oxalic acid solution

was added and the resulting biphasic system was mixed very vigorously during 30 minutes. Both phases were separated and the aqueous phase was extracted twice with 5 ml of dichloromethane. The combined organic phases were then washed twice with 10 ml of water and twice with 10 ml of a saturated NaHCO$_{3(aq)}$ solution. After drying (MgSO$_4$) and evaporation of the solvent, the β-phosphono aldehyde **217** was obtained in 82% yield. Further purification could be performed using vacuum distillation (120-123°C/1 mbar).

^{1}H NMR δ (300 MHz, ppm): 1.11 (3H, t, J = 7.2 Hz, CH$_3$); 1.28 (3H, t, J = 7.2 Hz, CH$_3$); 3.05-3.26 (2H, multiplet, CH$_2$); 3.67-4.14 (5H, multiplet, OCH$_2$, CHP); 7.23-7.39 (5H, multiplet, CH$_{arom}$); 9.66-9.69 (1H, multiplet, CHO). **^{13}C NMR δ (75 MHz, ppm):** 16.18, 16.26, 16.34, 16.41 (CH$_3$); 37.96 (d, J$_{CP}$ = 140.8 Hz, CHP); 44.02 (d, J$_{CP}$ = 2.3 Hz, CH$_2$); 62.16, 62.25, 62.94, 63.03 (OCH$_2$); 127.57 (d, J$_{CP}$ = 2.3 Hz, CH$_{arom}$); 128.70 (d, J$_{CP}$ = 2.3 Hz, CH$_{arom}$); 129.13 (d, J$_{CP}$ = 5.7 Hz, CH$_{arom}$); 135.20 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$); 198.97 (d, J$_{CP}$ = 15.0 Hz, CHO). **^{31}P NMR δ (121 MHz, ppm):** 27.64. **IR ν (cm^{-1}):** 1725 (C=O); 1243 (P=O); 1050, 1027 (P-O). **MS m/z (%):** 271 (100, [M+H]$^+$). **Yield:** 42% (after distillation). Pale yellow oil.

3.2.6 Preparation of PAP's using trialkyl phosphites

To a solution of 5 mmol of a suitable imine in 10 ml of methanol (or ethanol, depending on the phosphite used) 10 mmol of trialkyl phosphite was added. Then 10 mmol of formic acid was added dropwise to the reaction mixture. CAUTION: the reaction may proceed highly exothermic upon addition of formic acid. After stirring for 30 minutes at room temperature, the solvent was evaporated under reduced pressure. The residual oil was dissolved in 10 ml of diethyl ether and mixed with 10 ml of 1 M HCl$_{(aq)}$ in a separatory funnel. The aqueous phase was washed two times more with 5 ml of diethyl ether. Then 10 ml of dichloromethane was added to the aqueous phase together with 3 M NaOH$_{(aq)}$ until the pH reached 9-10. The aqueous layer was then extracted two times more with 5 ml of dichloromethane and the combined organic phases were dried using MgSO$_4$. The PAP's were found in high purity after evaporation of the solvent under reduced pressure.

Tetramethyl 1-phenyl-3-anilino-3-phosphonopropyl phosphonate (196a)
The product was obtained as a mixture of two diastereomeric pairs (ratio: 34/66). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever


possible.
^{1}H NMR δ (300 MHz, ppm): 2.29 (2x 1H, multiplet, C$\underline{H}_A$H$_B$, m+M); 2.52-2.71 (2x 1H, multiplet, CH$_A$$\underline{H}_B$, m+M); 3.38-3.83 (2x 2H, NCHP, CHP, m+M); 3.48 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 3.49 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.54 (3H, d, J$_{HP}$ = 10.2 Hz, OCH$_3$, M); 3.65 (3H, d, J$_{HP}$ = 11.0 Hz, OCH$_3$, M); 3.68
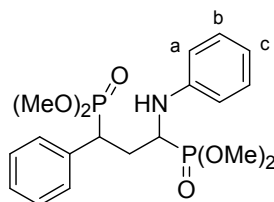
(3H, d, J_{HP} = 10.5 Hz, OCH$_3$, m); 3.69 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$, M); 3.71 (3H, d, J_{HP} = 9.1 Hz, OCH$_3$, m); 3.78 (3H, d, J_{HP} = 10.2 Hz, OCH$_3$, m); 6.34 (2H, d, J = 8.3 Hz, CH$_{arom}$(a), M); 6.43 (2H, d, J = 8.3 Hz, CH$_{arom}$(a), m); 6.46-6.61 (2x 1H, multiplet, CH$_{arom}$(c), m+M); 6.78-7.15 (2x 2H, CH$_{arom,}$(b), m+M); 7.16-7.37 (2x 5H, multiplet, CH$_{arom}$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 31.05 (d, J = 8.1 Hz, CH$_2$, M); 32.01 (CH$_2$, m); 39.88 (dd, J_{CP} = 139.6 Hz, J_{CP} = 13.8 Hz, CHP, M); 40.12 (dd, J_{CP} = 137.3 Hz, J_{CP} = 8.1 Hz, CHP, m); 48.09 (dd, J_{CP} = 154.6 Hz, J_{CP} = 16.2 Hz, NCHP, M); 48.63 (dd, J_{CP} = 155.9 Hz, J_{CP} = 11.5 Hz, NCHP, m); 52.56 (d, J_{CP} = 6.9 Hz, OCH$_3$, M); 52.77 (d, J_{CP} = 6.9 Hz, OCH$_3$, M); 53.36 (d, J_{CP} = 5,8 Hz, OCH$_3$, M); 53,51 (d, J_{CP} = 5,8 Hz, OCH$_3$, M); 113,63 (2x CH$_{arom}$(a), M); 113.87 (d, J_{CP} = 10.4 Hz, 2x CH$_{arom}$(a), m); 118.12 (CH$_{arom}$(c), m); 118.49 (CH$_{arom}$(c), M); 127.62, 127.69, 127.74, 128.56, 128.59, 128.72, 128.82, 128.98, 129.17, 129.25, 129.28, 129.33, 129.37, 129.51, 129.57, 129.63, 129.72 (CH$_{arom}$, m+M); 134.17 (d, J = 6.9 Hz, C$_{q,arom}$, M); 135.88 (C$_{q,arom}$, m); 146.12 (C$_{q,arom}$N, m); 146.63 (C$_{q,arom}$N, M). **^{31}P NMR δ (121 MHz, ppm):** 28.47 (m); 28.74 (d, J_{PP} = 9.7 Hz, M); 30.76 (m); 31.30 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3301 (NH); 1243 (br., P=O); 1043 (br., P-O). **MS m/z (%):** 428 (100, [M+H]$^+$); 318 (10, [M+H-PO(OMe)$_2$]$^+$). **Yield:** 86%. Yellow oil.

Tetraethyl 1-phenyl-3-anilino-3-phosphonopropyl phosphonate (196b)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 44/76). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
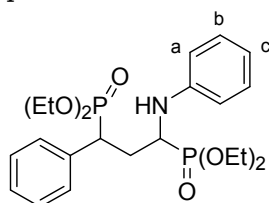
^{1}H NMR δ (300 MHz, ppm): 1.03-1.39 (2x 12H, multiplet, 4x CH$_3$, m+M); 2.11-2.44 (2x 1H, multiplet, C$\underline{H}_A$H$_B$, m+M); 2.55-2.80 (2x 1H, multiplet, CH$_A$$\underline{H}_B$); 3.40-3.51 (2x 2H, multiplet, 2x CHP, m+M); 3.67-4.20 (2x 8H, multiplet, OCH$_2$, m+M); 6.34 (2H, d, J = 8.0 Hz, CH$_{arom}$(a), M); 6.44 (2x 1H, d, J = 8.0 Hz, CH$_{arom}$, m); 6.65-6.72 (2x 1H, multiplet, CH$_{arom}$(c), m+M); 7.03-7.13 (2x 2H, multiplet, CH$_{arom}$(b), m+M); 7.14-7.33 (2x 5H, multiplet, CH$_{arom}$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 16.27 (CH$_3$, M); 16.36 (CH$_3$, m); 31.01 (d, J_{CP} = 8.1 Hz, CH$_2$, M); 32.0 (CH$_2$, m); 40.45 (dd, J_{CP} = 139.6 Hz, J_{CP} = 13.8 Hz, PhCHP, M); 40.74 (dd, J_{CP} = 145.4 Hz, J_{CP} = 8.1 Hz, PhCHP, m); 48.41 (dd, J_{CP} = 154.6 Hz, J_{CP} = 16.2 Hz, NCHPN, M); 48.99 (dd, J_{CP} = 166.1 Hz, J_{CP} = 11.5 Hz, NCHP, m); 61.74, 61.80, 61.89, 62.00, 62.09, 62.24, 62.56, 62.69, 62.78, 62.93, 63.02 (OCH$_2$, m+M); 113.63 (2x CH$_{arom}$(a), m); 113.73 (2x CH$_{arom}$(a), M); 118.29 (CH$_{arom}$(c), M); 118.50 (CH$_{arom}$(c), m); 127.42, 127.56, 128.57, 128.66 (CH$_{arom}$, m+M); 129.06 (2x CH$_{arom}$(b)); 129.15, 129.41, 129.50, 129.76, 129.85 (CH$_{arom}$); 134.66 (d, J_{CP} = 6.9 Hz, $\underline{C}_{q,arom}$CH, M); 136.32 (d, J_{CP} = 6.9 Hz, $\underline{C}_{q,arom}$CH, m); 146.41 (d, J_{CP} = 6.9 Hz, $\underline{C}_{q,arom}$N, m); 146.94 ($\underline{C}_{q,arom}$N, M). **^{31}P NMR δ (121 MHz, ppm):** 26.20 (m); 26.29 (d, J_{PP} = 9.7 Hz, M); 28.60 (m); 29.05 (d, J_{PP} = 9.7 Hz, M). **IR ν (cm^{-1}):** 3296 (N-H); 1243 (br, P=O); 1027 (br, P-O). **MS: m/z (%):** 484 (100, [M+H]$^+$). **Yield:** 86%. Yellow oil.

Tetraethyl 3-benzylamino-1-phenyl-3-phosphonopropyl phosphonate (196d)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 33/67). Spectral data can be found in chapter 4, section 3.2.2.

Tetraethyl 3-allylamino -1-phenyl-3-phosphonopropyl phosphonate (196f)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 72/28). Spectral data can be found in chapter 4, section 3.2.2.

Tetraethyl 3-isopropylamino-1-phenyl-3-phosphonopropyl phosphonate (196i)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 38/62). Spectral data can be found in chapter 4, section 3.2.2.

3.2.7 Preparation of diphosphonic acids

Method A: Dealkylation of the corresponding PAP esters

To a solution of 5 mmol of PAP ester in 10 ml of dry dichloromethane, 25 mmol of TMSBr was added under a nitrogen atmosphere. After stirring for 1 h at room temperature, 2 ml of water was added to the reaction mixture. Stirring was continued for 1 h. When a precipitate had formed in the mean time, it could be easily isolated using filtration. Otherwise, the solvent was evaporated under reduced pressure. Residual water wass conveniently removed under high vacuum.

Method B: Tandem addition of P(OTMS)$_3$

Preparation of P(OTMS)$_3$

Phosphoric acid (10 mmol) was added to 10 ml of dry dichloromethane under a nitrogen atmosphere. The mixture was stirred for 30 minutes while the phosphoric acid only partially dissolved in the organic solvent. Then the mixture is cooled to 0°C and 22 mmol of TMSCl was added using a syringe. After stirring for 15 minutes, 33 mmol of triethyl amine was added, causing immediate precipitation of ammonium salts. Care should be taken to avoid solidifying of the reaction medium (extra solvent may be added to assure proper stirring of the mixture). Then 11 mmol of TMSCl was added and the reaction was monitored using ^{31}P NMR. Additional TMSCl may be added if necessary in order to obtain complete conversion.

The imine of choice was added to the crude mixture of P(OTMS)$_3$ and triethyl ammonium chloride in dichloromethane at room temperature. Then the reaction mixture was heated under reflux. The reaction could be easily monitored using ^{31}P NMR. After complete conversion, the ammonium salts were removed by filtration and the solvent was evaporated under reduced pressure. The residual oil was dissolved in diethyl ether and filtered again in order to remove all ammonium salts. Then, 10 ml of methanol was added to the filtrate and the mixture was stirred during an overnight period. When a

precipitate had formed in the mean time, it could be easily isolated using filtration. Otherwise, the solvent was evaporated under reduced pressure.

3-Isopropylamino-1-phenyl-3-phosphonopropyl phosphonic acid (226a)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 31/69). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

^{1}H NMR δ (D$_2$O, 300 MHz, ppm): 0.84 (3H, d, J = 6.3 Hz, C$\underline{H}_3$, M); 1.04 (3H, d, J = 6.3 Hz, C$\underline{H}_3$, m); 1.05 (3H, d, J = 6.3 Hz, C$\underline{H}_3$, M); 1.16 (3H, d, J = 6.3 Hz, C$\underline{H}_3$, m); 2.19-2.39 (2x 1H, multiplet, C$\underline{H}_A$H$_B$, m+M); 2.47-2.56 (2x 1H, multiplet, CH$_A\underline{H}_B$, m+M); 2.76 (1H, ~t, J = 11.3 Hz, PC$\underline{H}$N, m); 2.07 (1H, ddd, J = 12.9 Hz, J= 9.1 Hz, J$_{HP}$ = 3.3 Hz, PC$\underline{H}$N, M); 3.30-3.58 (4H, multiplet, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}$PPh, m+M); 7.23-7.31 (5H, multiplet, C$\underline{H}_{arom}$, m+M). **^{13}C NMR δ (D$_2$O, 75 MHz, ppm):** 17.56 ($\underline{C}$H$_3$, M); 18.04 ($\underline{C}$H$_3$, m); 18.49 ($\underline{C}$H$_3$, M); 18.86 ($\underline{C}$H$_3$, m); 28.06 ($\underline{C}$H$_2$); 41.42 (dd, J$_{CP}$ = 133.8 Hz, J$_{CP}$ = 12.7 Hz, P$\underline{C}$HPh, M); 42.03 (d, J$_{CP}$ = 135.0 Hz, P$\underline{C}$HPh, m); 49.97 (dd, J$_{CP}$ = 143.1 Hz, J$_{CP}$ = 18.5 Hz, P$\underline{C}$HN, m); 50.26 ($\underline{C}$HCH$_3$, M); 51.00 (d, J$_{CP}$ = 111.9 Hz, P$\underline{C}$HN, M); 51.74 ($\underline{C}$HCH$_3$, m); 128.02, 128.18, 129.15, 129.23 ($\underline{C}$H$_{arom}$); 134.28 ($\underline{C}$$_{q,arom}$). **^{31}P NMR δ (D$_2$O, 121 MHz, ppm):** 12.71 (M); 12.89 (d, J$_{PP}$ = 3.7 Hz, m); 25.21 (d, J$_{PP}$ = 3.7 Hz, m); 25.72 (M). **IR ν (cm^{-1}):** 3414 (NH); 1245 (br., P=O); 1026 (br., P-O). **MS m/z (%):** 336 (100, [M-H]$^-$). **Yield:** 75%. Yellow, highly viscous oil.
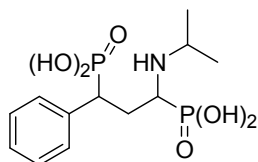
3-tert-Butylamino-1-phenyl-3-phosphonopropyl phosphonic acid (226b)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 47/53). Spectral data were collected from the corresponding triethyl amine salt, unless otherwise stated.
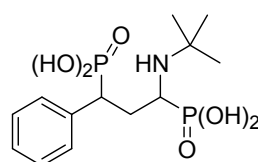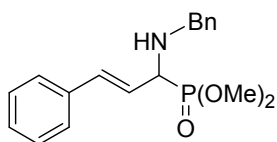

^{1}H NMR δ (D$_2$O, 300 MHz, ppm): 1.11 (9H, s, CH$_3$); 1.18 (18H, t, J = 7.2 Hz, N(CH$_2$C$\underline{H}_3$)$_3$); 1.30 (9H, s, CH$_3$); 2.22-2.67 (2x 2H, multiplet, CH$_2$); 2.76 (1H, ~t, J = 11.6 Hz, NCHP); 2.84-3.40 (1H + 2x 1H, multiplet, NC$\underline{H}$P, 2x CHP); 3.10 (12H, q, J = 7.2 Hz, N($\underline{C}$H$_2$CH$_3$)$_3$); 7.21-7.38 (2x 5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (D$_2$O, 75 MHz, ppm):** 8.35 (N(CH$_2$$\underline{C}H_3$)$_3$); 25.42 (CH$_3$); 25.90 (CH$_3$); 31.57 (CH$_2$); 32.36 (CH$_2$); 43.25 (dd, J$_{CP}$ = 125.8 Hz, J$_{CP}$ = 8.1 Hz, CHP); 43.44 (d, J$_{CP}$ = 128.1 Hz, CHP); 46.71 (N($\underline{C}$H$_2$CH$_3$)$_3$); 50.66 (dd, J$_{CP}$ = 132.1 Hz, J$_{CP}$ = 17.9 Hz, NCHP); 51.77 (dd, J$_{CP}$ = 131.5 Hz, J$_{CP}$ = 9.2 Hz, NCHP); 59.42 (NC$_q$); 59.89 (d, J$_{CP}$ = 4.6 Hz, NC$_q$); 126.87, 127.10, 128.69, 129.33, 129.39, 129.64, 129.72 (CH$_{arom}$); 138.16 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$); 138.78 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$). **^{31}P NMR δ (D$_2$O, 121 MHz, ppm):** 12.38, 12.54, 21.37, 22.05. **IR ν (cm^{-1}):** (acid): 1198 (br., P=O); 1005 (br., P-O). **MS m/z (%):** (salt, neg. mode): 350 (100, [M-H]$^-$). (salt, pos. mode): 102 (100, [Et$_3$N+H]$^+$); 352 (51, [M+H]$^+$); 453 (8, [M+H+Et$_3$N]$^+$); 703 (48, [2M+H]$^+$). (acid, neg. mode): 350 (100, [M-H]$^-$). **Mp.:** (acid): decomposition above 230°C. **Yield:** 99%.

3-Benzylamino-1-phenyl-3-phosphonopropyl phosphonic acid (226c)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 20/80). Spectral data were collected from the corresponding triethyl amine salt, unless otherwise stated.

^{1}H NMR δ (D$_2$O, 300 MHz, ppm): 1.10 (27H, t, J = 7.2 Hz, N(CH$_2$CH$_3$)$_3$); 2.22-2.81 (2H, multiplet, CH$_2$, M); 2.44-2.53 (1H, multiplet, CH$_2$, m); 2.67 (1H, dt, J$_{HP}$ = 20.4 Hz, J = 6.9 Hz, NCHP, M); 2.76-2.95 (1H + 2x 1H, multiplet, NCHP, m, 2x CHP, m+M); 2.99 (18H, q, J =7.2 Hz, N(CH$_2$CH$_3$)$_3$); 4.01 (1H, d, J$_{AB}$ = 13.2 Hz, NCH$_A$H$_B$, m); 4.11 (1H, d J$_{AB}$ = 13.2 Hz, NCH$_A$H$_B$, m); 4.21 (d, J$_{AB}$ = 12.9 Hz, NCH$_A$H$_B$, M); 4.44 (1H, d, J$_{AB}$ = 12.9 Hz, NCH$_A$H$_B$, M); 7.05-7.44 (2x 10H, multiplet, CH$_{arom}$). **^{13}C NMR δ (D$_2$O, 75 MHz, ppm):** 8.35 (N(CH$_2$CH$_3$)$_3$); 30.45 (CH$_2$, m); 31.29 (CH$_2$, M); 46.30 (dd, J$_{CP}$ = 122.3 Hz, J$_{CP}$ = 11.5 Hz, CHP, M); 46.50 (N(CH$_2$CH$_3$)$_3$); 49.42 (NCH$_2$, m); 50.46 (NCH$_2$, M); 54.84 (dd, J$_{CP}$ = 128.7 Hz, J$_{CP}$ = 13.3 Hz, NCHP, m); 57.40 (dd, J$_{CP}$ = 130.4 Hz, J$_{CP}$ = 5.8 Hz, NCHP, M); 125.97, 126.52, 128.35, 128.70, 128.87, 129.15, 129.22, 129.33, 129.44, 129.60, 129.70, 129.93, 130.20 (CH$_{arom}$); 131.54 (C$_{q,arom}$, m); 132.22 (C$_{q,arom}$, m) 140.25 (d, J$_{CP}$ = 5.8 Hz, C$_{q,arom}$, m); 141.83 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$, M). **^{31}P NMR δ (D$_2$O, 121 MHz, ppm):** 11.47 (m); 11.78 (M); 19.72 (M); 20.26 (m). **MS m/z (%):** (salt, neg. mode): 384 (100, [M-H]$^-$). (salt, pos. mode): 102 (100); 285 (67) ; 386 (29, [M+H]$^+$); 487 (7, [M+H+Et$_3$N]$^+$); 771 (12, [2M+H]$^+$). **Yield:** 99%.

3.3 Phosphonylation using dialkyl phosphite

To a solution of an aldimine (5 mmol) in methanol (10 ml), 2 equivalents of dimethyl phosphite was added and the resulting mixture was refluxed for 2 to 3 hours shielded from moisture using a CaCl$_2$ tube. After evaporation of the solvent, the residue was dissolved in 10 ml of diethyl ether and added to an equal amount of 1M HCl$_{(aq)}$ in a separatory funnel. The mixture was then shaken very vigorously and the organic phase was discarded. The water phase was washed twice with a small amount of diethyl ether, neutralized using 3M NaOH$_{(aq)}$ and extracted with dichloromethane. The α-aminoalkyl phosphonates are obtained in high purity after drying with MgSO$_4$ and evaporation of the solvent under reduced pressure.

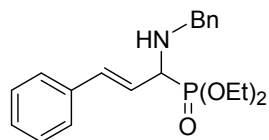**Dimethyl (*2E*)-1-benzylamino-3-phenylprop-2-enyl phosphonate (22b)**

^{1}H NMR δ (300 MHz, ppm): 1.94 (1H, s (br.), NH); 3.65-3.77 (2H, multiplet, CHP, CH$_A$H$_B$N); 3.76 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.80 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.97 (1H, d, J$_{AB}$ = 13.6 Hz, CH$_A$H$_B$Ph); 6.15 (1H, ddd, J$_{AB}$ = 16.0 Hz, J = 8.5 Hz, J$_{HP}$ = 5.8 Hz, =CH); 6.62 (1H, dd, J$_{AB}$ = 16.0 Hz, J = 4.7 Hz, =CHPh); 7.21-7.42 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 51.22 (d, J$_{CP}$ = 16.2 Hz, NCH$_2$); 53.42 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.67 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 57.41 (d, J$_{CP}$ = 156.9 Hz, CHP); 123.82 (d, J$_{CP}$ = 5.8 Hz, =CH); 126.56, 127.17, 128.01, 128.28, 128.45, 128.62 (CH$_{arom}$); 134.50 (d, J$_{CP}$ = 13.9 Hz, =CHPh); 136.24
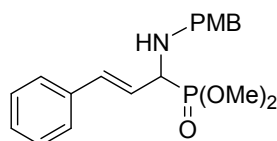
(d, J_{CP} = 2.3 Hz, $C_{q,arom}$); 139.24 ($C_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 26.70. **IR ν (cm^{-1}):** 3305 (NH); 1243 (P=O); 1050, 1028 (P-O). **MS m/z (%):** 332 (100, [M+H]$^+$); 222 (60, [M+H-P(O)(OMe)$_2$]$^+$); **Yield:** 96%. Yellow oil.

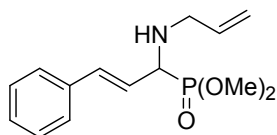## Diethyl (*2E*)-1-benzylamino-3-phenylprop-2-enyl phosphonate (22c)

^{1}H NMR δ (300 MHz, ppm): 1.29 (3H, t, J = 6.9 Hz, CH$_3$); 1.31 (3H, t, J = 6.9 Hz, CH$_3$); 2.28 (1H, s (br.), NH); 3.67 (1H, ddd, J_{HP} = 19.3 Hz, J = 8.5 Hz, J = 0.8 Hz, CHP); 3.75 (1H, d, J_{AB} = 13.6 Hz, C$\underline{H}_A$H$_B$Ph); 3.97 (1H, d, J_{AB} = 13.6 Hz, CH$_A\underline{H}_B$Ph); 4.06-4.25 (4H, multiplet, CH$_2$O); 6.15 (1H, ddd, J_{AB} = 16.0 Hz, J = 8.5 Hz, J_{HP} = 5.8 Hz, =CH); 6.61 (1H, dd, J_{AB} = 16.0 Hz, J = 4.7 Hz, =CHPh); 7.22-7.42 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.28; 16.36; 16.46; 16.54 (CH$_3$); 51.27 (d, J_{CP} = 16.2 Hz, NCH$_2$); 57.72 (d, J_{CP} = 154.6 Hz, CHP); 62.71; 62.82; 62.86; 62.95 (CH$_2$O); 124.19 (d, J_{CP} = 6.9 Hz, =CH); 126.55; 127.13; 127.90; 128.30; 128.42; 128.62 (CH$_{arom}$); 133.49 (d, J_{CP} = 13.8 Hz, =CHPh); 136.41 (d, J_{CP} = 2.3 Hz, $C_{q,arom}$); 139.37 ($C_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 24.42. **IR ν (cm^{-1}):** 3305 (NH); 1243 (P=O); 1050, 1028 (P-O). **MS m/z (%):** 222 (100, [M+H-P(O)(OEt)$_2$]$^+$); 360 (16, [M+H]$^+$). **Yield:** 95%. Yellow oil.

Dimethyl (*2E*)-1-(4-methoxybenzylamino)-3-phenylprop-2-enyl phosphonate (22d)

^{1}H NMR δ (300 MHz, ppm): 1.91 (1H, s (br.), NH); 3.64-3.75 (1H, multiplet, CHP); 3.69 (1H, d, J_{AB} = 13.5 Hz, C$\underline{H}_A$H$_B$Ph); 3.77 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.80 (3H, s, OCH$_3$(Ph)); 3.80 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.91 (1H, d, J_{AB} = 13.2 Hz, CH$_A\underline{H}_B$Ph); 6.14 (1H, ddd, J_{AB} = 16.0 Hz, J = 8.5 Hz, J_{HP} = 5.8 Hz, =CH); 6.61 (1H, dd, J_{AB} = 16.0 Hz, J = 4.7 Hz, =CHPh); 6.83-6.90 (2H, multiplet, CH$_{arom}$); 7.21-7.45 (7H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 50.72 (d, J_{CP} = 17.31 Hz, NCH$_2$); 53.52 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.77 (d, J_{CP} = 6.9 Hz, OCH$_3$); 55.31 (OCH$_3$(Ph)); 57.30 (d, J_{CP} = 155.8 Hz, CHP); 113.92 (=CH$_{o,PMB}$); 123.97 (d, J_{CP} = 6.9 Hz, =CH); 126.66, 128.11, 128.74, 129.62 (CH$_{arom}$); 131.36 ($C_{q,arom,PMB}$); 134.76 (d, J_{CP} = 15.0 Hz, =CHPh); 136.35 (d, J_{CP} = 2.3 Hz, $C_{q,arom}$); 158.87 (OC$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 26.79. **IR ν (cm^{-1}):** 3462 (NH); 1247 (P=O); 1037 (br., P-O). **MS m/z (%):** 362 (100, [M+H]$^+$); 252 (19, [M+H-P(O)(OMe)$_2$]$^+$); **Yield:** 86%. Orange oil.

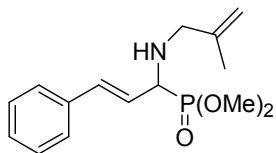## Dimethyl (*2E*)-1-allylamino-3-phenylprop-2-enyl phosphonate (22e)

^{1}H NMR δ (300 MHz, ppm): 1.69 (1H, s (br.), NH); 3.21 (1H, dd, J_{AB} = 14.0 Hz, J = 6.3 Hz, C$\underline{H}_A$H$_B$N); 3.41 (1H, dd, J_{AB} = 14.0 Hz, J = 5.2 Hz, CH$_A\underline{H}_B$N); 3.72-3.84 (7H, multiplet, CHP, OCH$_3$); 5.12-5.22 (2H, multiplet, =CH$_2$); 5.86 (1H, dddd, J = 17.2 Hz, J = 10.3 Hz, J = 6.7 Hz, J = 5.2 Hz, CH$_2$=C$\underline{H}$); 6.10 (1H, ddd, J = 15.8 Hz, J_2 = 8.7 Hz, J_{HP} = 5.8 Hz, PhCH=C$\underline{H}$); 6.62 (1H, dd, J = 16.0 Hz, J = 4.7 Hz, PhC$\underline{H}$=); 7.23-7.42 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 50.09 (d, J_{CP} = 16.2 Hz, CH$_2$N); 53.57 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.73 (d, J_{CP} = 8.1 Hz, OCH$_3$); 57.72 (d, J_{CP} = 156.9 Hz, CHP); 116.96 (=CH$_2$); 123.91 (d, J_{CP} = 6.9 Hz, PhCH=$\underline{C}$H); 126.64; 128.09; 128.72 (CH$_{arom}$); 134.70 (d, J_{CP} = 6.9 Hz, Ph$\underline{C}$H=); 135.97 ($\underline{C}$H=CH$_2$); 136.34 ($C_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 26.77. **MS m/z (%):** 282 (100, [M+H]$^+$). **IR ν**
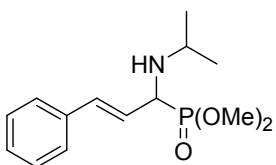
(cm⁻¹): 3308 (NH); 1247 (P=O); 1053, 1033 (P-O). **Mp.:** 54.1°C. **Yield:** 95%. Green solid.

Dimethyl (*2E*)-[1-(2-methylprop-2-enyl)amino]-3-phenylprop-2-enyl phosphonate (22f)

¹H NMR δ (300 MHz, ppm): 1.75 (4H, s (br.), NH + CH₃); 3.16 (1H, d, J_{AB} = 14.3 Hz, NC$\underline{H}$AH_B); 3.29 (1H, d, J_{AB} = 14.3 Hz, NCH$_A\underline{H}_B$); 3.71 (1H, ddd, J_{HP} = 19.5 Hz, J = 8.5 Hz, J = 0.8 Hz, CHP); 3.80 (3H, d, J_{HP} = 9.6 Hz, OCH₃); 3.83 (3H, d, J_{HP} = 9.6 Hz, OCH₃); 4.88 (1H, s, C=C$\underline{H}_A H_B$); 4.90 (1H, s, C=CH$_A\underline{H}_B$); 6.11 (1H, ddd, J = 15.8 Hz, J = 8.5 Hz, J_{HP} = 5.6 Hz, C$\underline{H}$CHP); 6.62 (1H, dd, J = 15.8 Hz, J_{HP} = 4.5 Hz, =C$\underline{H}$Ph); 7.23-7.42 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 20.68 (CH₃); 53.22 (d, J_{CP} = 16.1 Hz, NCH₂); 53.51 (d, J_{CP} = 6.9 Hz, OCH₃); 53.80 (d, J_{CP} = 7.0 Hz, OCH₃); 57.45 (d, J_{CP} = 156.9 Hz, CHP); 111.99 (C=$\underline{C}$H₂); 124.02 (d, J_{CP} = 6.9 Hz, $\underline{C}$HCHP); 126.64 (2 x CH$_{arom}$); 128.05 (CH$_{arom}$); 128.70 (2 x CH$_{arom}$); 134.64 (d, J_{CP} = 13.8 Hz, PhCH); 136.37 (C$_{q,arom}$); 143.03 (=C$_q$). **³¹P NMR δ (121 MHz, ppm):** 26.90. **IR ν (cm⁻¹):** 3460 (NH); 1244 (P=O); 1057 (P-O). **MS m/z (%):** 296.7 (100, [M+H]⁺). **Yield:** 74%. Yellow oil.

Dimethyl (*2E*)-1-isopropylamino-3-phenylprop-2-enyl phosphonate (22h)

¹H NMR δ (300 MHz, ppm): 1.03 (3H, d, J = 6.3 Hz, CH₃); 1.09 (3H, d, J = 6.3 Hz, CH₃); 1.53 (1H, s (br.), NH); 2.95 (1H, septet, J = 6.3 Hz, NCH); 3.78 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.83 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.82 (1H, ddd, J_{HP} = 20.0 Hz, J = 8.5 Hz, J = 1.1 Hz, CHP); 6.12 (1H, ddd, J = 16.0 Hz, J = 8.5 Hz, J_{HP} = 5.8 Hz, PhCH=C$\underline{H}$); 6.61 (1H, dd, J = 16.0 Hz, J_{HP} = 4.7 Hz, =C$\underline{H}$Ph); 7.23-7.42 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 21.56 (CH₃); 23.93 (CH₃)); 46.05 (d, J_{CP} = 16.2 Hz, NCH); 53.44 (d, J_{CP} = 6.9 Hz, OCH₃); 53.89 (d, J_{CP} = 8.1 Hz, OCH₃); 56.26 (d, J_{CP} = 156.9 Hz, CHP); 124.69 (d, J_{CP} = 5.8 Hz, PhCH=$\underline{C}$H); 126.56; 127.92; 128.60 (CH$_{arom}$); 133.84 (d, J_{CP} = 13.9 Hz, Ph$\underline{C}$H=CH); 136.31 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.04. **IR ν (cm⁻¹):** 3316 (NH); 1242 (P=O); 1061, 1033 (P-O). **MS m/z (%):** 174 (100, [M+H-P(O)(OMe)₂]⁺). **Mp.:** 67.3°C. **Yield:** 94%. Yellow solid.

Diethyl (*2E*)-1-(isopropylamino)-3-phenyl-prop-2-enyl phosphonate (22i)
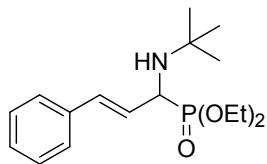See chapter 4, section 3.1 for spectral data. **Yield:** 95%.

Dimethyl (*2E*)-1-(tert-butylamino)-3-phenylprop-2-enyl phosphonate (22j)

¹H NMR δ (300 MHz, ppm): 1.12 (9H, s, CH₃); 1.40 (1H, s (br.), NH); 3.76 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.84 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.90 (1H, dd, J_{HP} = 24.2 Hz, J = 8.0 Hz, CHP); 6.21 (1H, ddd, J_{AB} = 16.0 Hz, J = 8.0 Hz, J_{HP} = 5.8 Hz, PhCH=C$\underline{H}$); 6.63 (1H, dd, J = 16.0 Hz, J = 5.2 Hz, =C$\underline{H}$Ph); 7.21-7.44 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 30.00 (CH₃); 52.18 (NC$_q$, J_{CP} = 15.0 Hz); 53.29 (d, J_{CP} = 6.9 Hz, OCH₃); 53.89 (d, J_{CP} = 158.1 Hz, CHP); 54.43 (d, J_{CP} = 6.9 Hz, OCH₃); 126.45 (d, J_{CP} = 2.3 Hz, CH$_{arom}$); 127.70 (CH$_{arom}$);
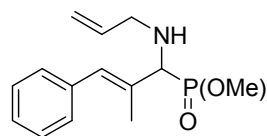
127.96 (d, J_{CP} = 4.6 Hz, PhCH=$\underline{C}$H); 128.59 (CH$_{arom}$); 132.30 (d, J_{CP} = 13.8 Hz, Ph$\underline{C}$H=CH); 136.64 (C$_{q,arom}$); **^{31}P NMR δ (121 MHz, ppm):** 27.02. **IR ν (cm^{-1}):** 3298 (NH); 1240 (P=O); 1060, 1030 (P-O). **MS m/z (%):** 188 (100, [M+H-P(O)(OMe)$_2$]$^+$); 298 (19, [M+H]$^+$). **Mp.:** 54.7°C. **Yield:** 97%. Yellow solid.

Diethyl (*2E*)-1-(tert-butylamino)-3-phenylprop-2-enyl phosphonate (22k)

^{1}H NMR δ (300 MHz, ppm): 1.12 (9H, s, CH$_3$); 1.29 (3H, t, J = 7.2 Hz, CH$_2$$\underline{C}H_3$); 1.32 (3H, t, J = 7.2 Hz, CH$_2$$\underline{C}H_3$); 1.42 (1H, s (br.), NH); 3.86 (1H, ddd, J_{HP} = 24.8 Hz, J = 8.0 Hz, J = 0.8 Hz, CHP); 4.06-4.24 (4H, multiplet, OCH$_2$); 6.21 (1H, ddd, J = 16.0 Hz, J = 8.0 Hz, J_{HP} = 5.8 Hz, =CH); 6.62 (1H, dd, J = 16.0 Hz, J = 5.2 Hz, =$\underline{C}$HPh); 7.21-7.36 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.48 (d, J_{CP} = 5.8 Hz, CH$_2$$\underline{C}H_3$); 16.56 (d, J_{CP} = 5.8 Hz, CH$_2$$\underline{C}H_3$); 30.03 (CH$_3$); 52.08 (NC$_q$, J_{CP} = 13.9 Hz); 54.16 (d, J_{CP} = 155.8 Hz, CHP); 62.51 (d, J_{CP} = 6.9 Hz, OCH$_3$); 63.35 (d, J_{CP} = 6.9 Hz, OCH$_3$); 126.40, 127.56 (CH$_{arom}$); 128.47 (d, J_{CP} = 5.8 Hz, PhCH=$\underline{C}$H); 128.56 (CH$_{arom}$); 132.05 (d, J_{CP} = 12.7 Hz, Ph$\underline{C}$H=CH); 136.84 (d, J_{CP} = 3.5 Hz, C$_{q,arom}$); **^{31}P NMR δ (121 MHz, ppm):** 26.42. **IR ν (cm^{-1}):** 3288 (NH); 1238 (P=O); 1053, 1029 (P-O). **MS m/z (%):** 188 (100, [M+H-P(O)(OEt)$_2$]$^+$); 326 (12, [M+H]$^+$). **Mp.:** 69.6°C. **Yield:** 93%. Yellow solid.

Dimethyl (*2E*)-1-allylamino-2-methyl-3-phenylprop-2-enyl phosphonate (22l)

^{1}H NMR δ (300 MHz, ppm): 1.90 (1H, s (br.), NH); 1.99 (3H, dd, J_{HP} = 3.3 Hz, J = 1.4 Hz, CH$_3$); 3.13 (1H, dd, J_{AB} = 14.0 Hz, J = 6.9 Hz, C$\underline{H}_A$H$_B$N); 3.33 (1H, dd, J_{AB} = 13.8 Hz, J = 5.2 Hz, CH$_A$$\underline{H}_B$N); 3.70 (1H, d, J_{HP} = 21.5 Hz, CHP); 3.78 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.83 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 5.12-5.29 (2H, multiplet, =CH$_2$); 5.81-5.94 (1H, multiplet, =CH); 6.55 (1H, d, J_{HP} = 4.1 Hz, =CHPh); 7.21-7.37 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 15.40 (CH$_3$); 49.86 (d, J_{CP} = 18.5 Hz, NCH$_2$); 53.48 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.65 (d, J_{CP} = 8.1 Hz, OCH$_3$); 62.97 (d, J_{CP} = 153.5 Hz, CHP); 116.99 (=CH$_2$); 126.84, 128.28, 129.07 (CH$_{arom}$); 130.48 (d, J_{CP} = 12.7 Hz, =CHPh); 132.67 (d, J_{CP} = 4.6 Hz, =C$_q$); 136.05 (=CH); 137.28 (d, J_{CP} = 2.3 Hz, C$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 26.98. **IR ν (cm^{-1}):** 3470 (NH); 1248 (P=O); 1039 (br., P-O). **MS m/z (%):** 296 (81, [M+H]$^+$); 186 (100, [M+H-PO(OMe)$_2$]$^+$). **Yield:** 90%. Yellow oil.

Dimethyl 1-allylamino-2-isopentyl-3-phenylprop-2-enyl phosphonate (22m)

Mixture of two isomers: 79% E and 21% Z.

The major isomer is indicated as M, the minor isomer as m whenever possible.
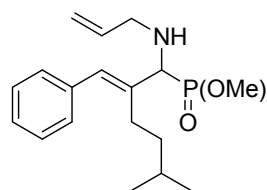
^{1}H NMR δ (300 MHz, ppm): 0.85-0.96 (2x3H, multiplet, CH$_3$, m+M); 1.27-1.49 (2x5H, multiplet, CH$_3$, CH, C$\underline{H}_A$H$_B$, m+M); 1.53-1.71 (2x1H, multiplet, CH$_A$$\underline{H}_B$, m+M); 1.89 (2x1H, s (br.), NH, m+M); 2.11-2.20 (1H, multiplet, C$\underline{H}_A$H$_B$C=, M); 2.22-2.37 (2H, multiplet, C$\underline{H}_A$H$_B$C=, m); 2.50-2.60 (1H, multiplet, CH$_A$$\underline{H}_B$C=, M); 2.84 (1H, dd, J_{AB} = 13.8 Hz, J = 6.3 Hz, NC$\underline{H}_A$H$_B$, m); 3.17 (1H, dd, J_{AB} = 14.0 Hz, J = 5.5 Hz, C$\underline{H}_A$H$_B$N, M); 3.13-3.20 (1H,

multiplet, CH$_A$H̲$_B$N, m); 3.40 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 3.9 Hz, CH$_A$H̲$_B$N, M); 3.66 (1H, d, J$_{HP}$ = 20.6 Hz, CHP, M); 3.77 (2x3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m+M); 3.78 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.83 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 4.25 (1H, d, J$_{HP}$ = 22.6 Hz, CHP, m); 4.83-4.90 (2H, multiplet, =CH$_2$, m); 5.11-5.25 (2H, multiplet, =CH$_2$, M); 5.61-5.74 (1H, multiplet, =CH, m); 5.81-5.94 (1H, multiplet, =CH, M); 6.67 (1H, d, J$_{HP}$ = 5.5 Hz, =CHPh, M); 6.70 (1H, s (br.), =CHPh, m); 7.20-7.36 (2x5H, multiplet, CH$_{arom}$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 13.99 (CH$_3$, M); 14.08 (CH$_3$, m); 22.34 (CH$_3$, M); 22.74 (CH$_3$, m); 27.83 (d, J$_{CP}$ = 2.3 Hz, CH$_2$, M); 28.08 (CH$_2$, m); 30.58 (CH$_2$C=, m); 30.89 (d, J$_{CP}$ = 2.3 Hz, CH$_2$, M); 31.85 (CH, m); 32.00 (CH, M); 49.62 (d, J$_{CP}$ = 16.2 Hz, CH$_2$N, m); 49.84 (d, J$_{CP}$ = 16.2 Hz, CH$_2$N, M); 52.95 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, m); 53.26 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 53.45 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, m); 53.87 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 54.78 (d, J$_{CP}$ = 156.9 Hz, CHP, m); 59.74 (d, J$_{CP}$ = 152.3 Hz, CHP, M); 116.60 (=CH$_2$, m + M); 126.63, 128.18, 128.22, 128.48 (CH$_{arom}$); 128.60 (d, J$_{CP}$ = 13.9 Hz, =CHPh, M); 130.53 (d, J$_{CP}$ = 13.9 Hz, =CHPh, m); 135.75 (=CH, m); 136.24 (=CH, M); 136.42, 137.34, 137.38, 137.43, 137.49 (C$_q$). **^{31}P NMR δ (121 MHz, ppm):** 26.94 (M); 27.64 (m). **IR ν (cm^{-1}):** 3329 (NH); 1246 (P=O); 1052, 1035 (P-O). **MS m/z (%):** 352 (53, [M+H]$^+$); 242 (100, [M+H-PO(OMe)$_2$]$^+$, 100). **Yield:** 88%. Yellow oil.

Dimethyl (*2E*)-1-allylamino-2-chloro-3-phenylprop-2-enyl phosphonate (22n)
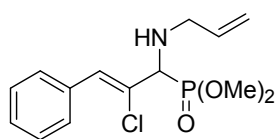
^{1}H NMR δ (300 MHz, ppm): 2.17 (1H, s (br.), NH); 3.14 (1H, d, J$_{AB}$ = 13.5 Hz, NCH̲$_A$H$_B$); 3.38-3.45 (1H, multiplet, NCH$_A$H̲$_B$); 3.81 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.87 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.93 (1H, d, J$_{HP}$ = 24.2 Hz, CHP); 5.08-5.26 (=CH$_2$); 5.80-5.93 (1H, multiplet, =CH); 6.73 (1H, d, JHP = 3.9 Hz, =CHPh); 7.29-7.42 (3H, multiplet, CH$_{arom}$); 7.66-7.69 (2H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 49.41 (d, J$_{CP}$ = 18.5 Hz, NCH$_2$); 53.70 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.98 (d, J$_{CP}$ = 7.0 Hz, OCH$_3$); 62.69 (d, J$_{CP}$ = 162.7 Hz, CHP); 117.57 (=CH$_2$); 128.41, 128.49, 128.57, 128.66, 129.42 (CH$_{arom,}$ =CCl); 129.60 (d, J$_{CP}$ = 13.8 Hz, PhCH=); 134.08 ((C$_{q,arom}$); 135.53 (=CH). **^{31}P NMR δ (121 MHz, ppm):** 23.84. **Yield:** 54%. Yellow oil (purity ~90%).

## Dimethyl (*2E*)-1-allylamino-2-phenylbut-2-enyl phosphonate (E-(22o))
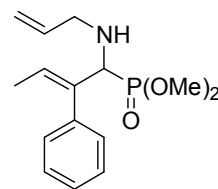
^{1}H NMR δ (300 MHz, ppm): 1.66 (3H, dd, J = 6.6 Hz, J = 5.2 Hz, CH$_3$); 1.84 (1H, s (br.), NH); 3.23 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 6.6 Hz, CH̲$_A$H$_B$N); 3.44 (1H, dd, J$_{AB}$ = 13.6 Hz, J = 5.2 Hz, CH$_A$H̲$_B$N); 3.64 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.66 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.80 (1H, d, J$_{HP}$ = 22.6 Hz, CHP); 5.10-5.22 (2H, multiplet, =CH$_2$); 5.80-5.97 (2H, multiplet, =CH, =C̲HCH$_3$); 7.22-7.40 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 14.79 (d, J$_{CP}$ = 2.3 Hz, CH$_3$); 49.70 (d, J$_{CP}$ = 17.3 Hz, NCH$_2$); 52.88 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.35 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 60.82 (d, J$_{CP}$ = 156.9 Hz, CHP); 116.69 (=CH$_2$); 127.86 (CH$_{arom}$); 127.24 (d, J$_{CP}$ = 10.4 Hz, =C̲HCH$_3$); 127.97 (2 x CH$_{arom}$); 129.01 (2 x CH$_{arom}$); 135.68 (br., =C$_q$); 136.05 (=CH); 138.83 (d, J$_{CP}$ = 3.5 Hz, C$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 26.87. **IR ν (cm^{-1}):** 3469 (NH); 1244 (P=O); 1039 (br., P-O). **MS m/z (%):** 296.3

([M+H]$^+$, 100); 186.2 ([M+H-PO(OMe)$_2$]$^+$, 84). **Chromatography:** Hex/EtOAc (2/8) R$_f$ = 0.20. **Yield:** 52%. Yellow oil.

## Dimethyl (*2Z*)-1-allylamino-2-phenylbut-2-enyl phosphonate (Z-(22o))
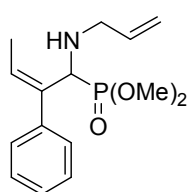
¹H NMR δ (300 MHz, ppm): 1.86 (3H, dd, J = 7.2 Hz, J = 4.7 Hz, CH$_3$); 1.89 (1H, s (br.), NH); 3.00 (1H, dd, J$_{AB}$ = 13.5 Hz, J = 6.9 Hz, CH$_A$H$_B$N); 3.18 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 5.2 Hz, CH$_A$H$_B$N); 3.73 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.79 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 4.29 (1H, d, J$_{HP}$ = 26.4 Hz, CHP); 5.05-5.12 (2H, multiplet, =CH$_2$); 5.71-5.84 (1H, multiplet, =CH); 5.97 (1H, dq, J = 7.2 Hz, J = 4.1 Hz, =CHCH$_3$); 7.20-7.36 (3H, multiplet, CH$_{arom}$); 7.55-7.59 (2H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.34 (CH$_3$); 50.17 (d, J$_{CP}$ = 18.5 Hz, NCH$_2$); 53.35 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$); 53.82 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 54.62 (d, J$_{CP}$ = 160.4 Hz, CHP); 117.11 (=CH$_2$); 127.17 (CH$_{arom}$); 127.25 (2 x CH$_{arom}$); 128.36 (2 x CH$_{arom}$); 130.56 (d, J$_{CP}$ = 11.5 Hz, =CHCH$_3$); 136.14 (=CH); 136.76 (=C$_q$); 140.86 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.40. **IR ν (cm⁻¹):** 3469 (NH); 1246 (P=O); 1058, 1032 (br., P-O). **MS m/z (%):** 296.3 ([M+H]$^+$, 100); 186.2 ([M+H-PO(OMe)$_2$]$^+$, 39). **Chromatography:** Hex/EtOAc (2/8) R$_f$ = 0.24. **Yield:** 10%. Yellow oil.

Dimethyl (*2E*)-1-allylamino-2-benzylbut-2-enyl phosphonate (22p)
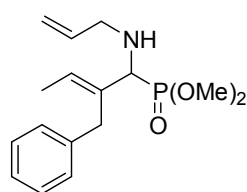
¹H NMR δ (300 MHz, ppm): 1.54 (1H, s (br.), NH); 1.87 (3H, dd, J = 6.3 Hz, J = 5.8 Hz, CH$_3$); 2.68 (1H, dd, J$_{AB}$ = 14.0 Hz, J = 6.6 Hz, NCH$_A$H$_B$); 2.99 (1H, dd, J$_{AB}$ = 14.0 Hz, J = 5.5 Hz, NCH$_A$H$_B$); 3.34-3.40 (1H, multiplet, CH$_A$H$_B$Ph); 3.41 (1H, d, J$_{HP}$ = 21.7 Hz, CHP); 3.68-3.82 (1H, multiplet, CH$_A$H$_B$Ph); 3.73 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.78 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 4.75-7.90 (2H, multiplet, =CH$_2$); 5.49-5.63 (1H, multiplet, =CH); 5.81 (1H, ~quintet, J ≈ 6.3 Hz, =CHCH$_3$); 7.15-7.30 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.15 (CH$_3$); 35.23 (CH$_2$); 49.57 (d, J$_{CP}$ = 16.2 Hz, NCH$_2$); 53.05 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.86 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 58.90 (d, J$_{CP}$ = 154.6 Hz, CHP); 116.32 (=CH$_2$); 124.93 (d, J$_{CP}$ = 11.5 Hz, =CHCH$_3$); 126.25, 128.46, 128.90 (CH$_{arom}$); 133.31 (d, J$_{CP}$ = 3.5 Hz, =C$_q$); 136.09 (=CH); 139.41 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.40. **IR ν (cm⁻¹):** 3321 (NH); 1238 (P=O); 1074, 1026 (P-O). **MS m/z (%):** 310 (100, [M+H]$^+$); 200 (19, [M+H-PO(OMe)$_2$]$^+$). **Mp.:** 78-80°C. **Yield:** 29% (from the corresponding aldehyde). Colourless crystals.

## Dimethyl (*2E*)-1-allylamino-2-(2-phenylethyl)but-2-enyl phosphonate (22q)
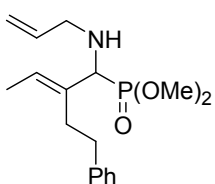
¹H NMR δ (300 MHz, ppm): 1.71 (3H, t, J = 6.05 Hz, CH$_3$); 1.76 (1H, s, NH); 2.28-2.81 (4H, m, CH$_2$CH$_2$); 3.07 (1H, dd, J$_{AB}$ = 14.1 Hz, J = 6.3 Hz, NCH$_A$H$_B$); 3.27 (1H, dd, J$_{AB}$ = 14.1 Hz, J = 5.1 Hz, NCH$_A$H$_B$); 3.50 (1H, d, J$_{HP}$ = 21.5 Hz, CHP); 3.74 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.80 (3H, d, J$_{HP}$ = 10.2 Hz, OCH$_3$); 5.09-5.22 (2H, multiplet, =CH$_2$); 5.66 (1H, dq, J = 6.6 Hz, J = 6.2 Hz, CH$_3$CH); 5.77-5.88 (1H, multiplet, HC=CH$_2$); 7.16-7.32 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 13.43 (CH$_3$); 31.42 (CH$_2$Ph); 34.42 (CCH$_2$); 49.68 (d, J$_{CP}$ = 16.2 Hz, NCH$_2$); 52.90 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.55 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 60.17 (d, J$_{CP}$ = 154.6 Hz, CHP);

116.26 (=$\underline{C}H_2$); 125.16 (d, J_{CP} = 11.5 Hz, $CH_3\underline{C}H$); 125.82 (2 x CH_{arom}); 128.28 (2 x CH_{arom}); 133.73 (d, J_{CP} = 3.5 Hz, H$\underline{C}$=CH_2); 136.29 ($C_{q\,arom}$); 141.97 (=C_q). **^{31}P NMR δ (121 MHz, ppm):** 27.56. **IR ν (cm^{-1}):** 3324 (NH); 1246 (P=O); 1031 (P-O). **MS m/z (%):** 324.2 (100, [M+H]$^+$). **Chromatography:** R_f = 0,32 (Hex/EtOAc 20/80). **Yield:** 44% (from the corresponding aldehyde). Yellow oil.

Dimethyl 3-(2-Nitrophenyl)-1-prop-2-ynylaminoprop-2-enyl phosphonate (22r)

Isolated as the hydrochloride salt.
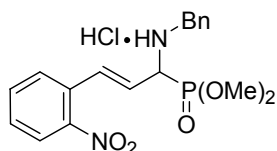
^{1}H NMR δ (300 MHz, ppm): 3.88 (3H, d, J_{HP} = 11.0 Hz, OCH_3); 3.92 (3H, d, J_{HP} = 11.0 Hz, OCH_3); 3.90-3.99 (1H, multiplet, CHP); 4.16 (1H, d, J_{AB} = 13.5 Hz, NC$\underline{H}_AH_B$); 4.75 (1H, dd, J_{AB} = 13.5 Hz, J = 1.7 Hz, NCH$_A\underline{H}_B$); 6.54 (1H, ddd, J = 15.7 Hz, J = 9.9 Hz, J = 5.5 Hz, =C$\underline{H}$CHP); 7.19 (dd, J = 15.7 Hz, J_{HP} = 4.4 Hz, =CHPh); 7.39-7.80 (8H, multiplet, CH_{arom}); 7.97 (1H, dd, J = 8.2 Hz, J = 1.1 Hz, =C$\underline{H}$C$_q$NO$_2$). **^{13}C NMR δ (75 MHz, ppm):** 19.39 (d, J_{CP} = 8.1 Hz, NCH$_2$); 54.09 (d, J_{CP} = 154.6 Hz, CHP); 54.70 (d, J_{CP} = 6.9 Hz, OCH_3); 54.94 (d, J_{CP} = 6.9 Hz, OCH_3); 120.85 (d, J_{CP} = 8.1 Hz, =$\underline{C}$HCHP); 124.87 (=$\underline{C}$HC$_q$NO$_2$); 129.56, 129.73, 129.85, 129.91, 130.75 (CH_{arom}, $C_{q,arom}$); 131.16 (d, J_{CP} = 2.3 Hz, =C_qNO$_2$); 133.97 (CH_{arom}); 136.01 (d, J_{CP} = 12.7 Hz, =CH); 147.53 (C_qNO$_2$). **^{31}P NMR δ (121 MHz, ppm):** 18.28. **Yield:** 77%. Brown solid.

Dimethyl 3-(2-Nitrophenyl)-1-prop-2-ynylaminoprop-2-enyl phosphonate (22s)
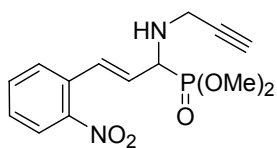
^{1}H NMR δ (300 MHz, ppm): 2.17 (1H, s(br.), NH); 2.31 (1H, t, J = 2.2 Hz, ≡CH); 3.47 (1H, dd, J = 17.2 Hz, J = 2.2 Hz, C$\underline{H}_AH_B$); 3.62 (1H, ddd, J = 17.2 Hz, J = 2.2 Hz, J_{HP} = 2.0 Hz, CH$_A\underline{H}_B$); 3.85 (6H, d, J_{HP} = 10.7 Hz, OCH_3); 4.12 (1H, dd, 1H, J_{HP} = 18.1 Hz, J = 8.3 Hz, CHP); 6.09 (1H, ddd, J = 15.7 Hz, J = 8.3 Hz, J_{HP} = 5.5 Hz, =C$\underline{H}$CHP); 7.21 (1H, dd, J = 16.7 Hz, J_{HP} = 4.7 Hz, =CH); 7.44 (1H, ddd, J = 8.2 Hz, J = 6.4 Hz, J = 2.1 Hz, =C$\underline{H}$CHC$_q$NO$_2$); 7.57-7.65 (2H, multiplet, CH_{arom}); 7.97 (1H, d, J = 8.2 Hz, =C$\underline{H}$C$_q$NO$_2$). **^{13}C NMR δ (75 MHz, ppm):** 36.21 (d, J_{CP} = 17.3 Hz, CH$_2$); 53.64 (d, J_{CP} = 8.1 Hz, OCH_3); 53.74 (d, J_{CP} = 6.9 Hz, OCH_3); 56.50 (d, J_{CP} = 155.8 Hz, CHP); 72.75 (≡CH); 80.65 (≡C_q); 124.63 (=$\underline{C}$HC$_q$NO$_2$); 128.24 (d, J_{CP} = 9.2 Hz, =$\underline{C}$HCHP); 128.62 (=$\underline{C}$HCHC$_q$NO$_2$) 129.00 (d, J_{CP} = 2.3 Hz, =$\underline{C}$HC$_{q,arom}$); 130.71 (d, J_{CP} = 13.9 Hz, =CH); 132.16 (d, J_{CP} = 2.3 Hz, =$C_{q,arom}$); 133.31 (=$\underline{C}$HCHC$_{q,arom}$); 147.66 (C_qNO$_2$). **^{31}P NMR δ (121 MHz, ppm):** 25.70. **IR ν (cm^{-1}):** 1249 (P=O); 1028, 1055 (P-O). **MS: m/z (%):** 325 (21, [M+H]$^+$); 215 (100, [M+H-PO(OMe)$_2$]$^+$). **Mp.:** 87-88°C. **Yield:** 58%.

Dimethyl benzylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22t)
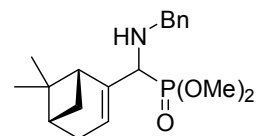
The product was obtained as a mixture of two diastereomeric pairs (ratio: 31/69). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.

^{1}H NMR δ (300 MHz, ppm): 0.90 (3 H, s, CH$_3$, M); 0.93 (3 H, s, CH$_{3,minor}$); 1.19-1.26 (2 x 1 H, multiplet, C$\underline{H}_AH_B$, m+M); 1.31 (2 x

3 H, s, CH$_3$, m+M); 2.08-2.15 (2 x 1 H, multiplet, CH, m+M); 2.18 (2 x 1 H, s (br), NH, m+M); 2.31-2.50 (2 x 4 H, multiplet, CH$_A$H$_B$, CH$_2$CH=, CHC$_q$=, m+M); 3.46 (1H, d, J$_{HP}$ = 21.2 Hz, CHP, m); 3.49 (1H, d, J$_{HP}$ = 20.9 Hz, CHP, M); 3.60 (1 H, d, J$_{AB}$ = 13.2 Hz, CH$_A$H$_B$N, m); 3.63 (1H, d, J$_{AB}$ = 13.2 Hz, CH$_A$H$_B$N, M); 3.70 (2 x 3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m+M); 3.77 (2 x 3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m+M); 3.86 (2 x 1 H, d, J$_{AB}$ = 13.2 Hz, CH$_A$H$_B$N, m+M); 5.56 (2 x 1H, s (br.), =CH, m+M); 7.21-7.41 (2 x 5 H, multiplet, CH$_{arom}$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 21.07 (CH$_3$, M); 21.54 (CH$_3$, m); 26.26 (CH$_3$, m); 26.37 (CH$_3$, M); 31.62 (CH$_2$CH=, m); 31.68 (CH$_2$CH=, M); 32.06 (CH$_2$); 37.85 (C$_q$, m); 38.34 (C$_q$, M); 40.,67 (CH, m); 40.84 (CH, M); 42.95 (CHC$_q$=, M); 43.35 (CHC$_q$=, m); 51.36 (d, J$_{CP}$ = 13.9 Hz CH$_2$N, M); 51.61 (d, J$_{CP}$ = 13.9 Hz, CH$_2$N, m); 52.69 (d, J$_{CP}$ = 6.9 Hz, CH$_3$O, m+M); 52.78 (d, J$_{CP}$ = 6.9 Hz, CH$_3$O, m); 53.44 (d, J$_{CP}$ = 6.9 Hz, CH$_3$O, M); 53.51 (d, J$_{CP}$ = 6.9 Hz CH$_3$O, m); 59.56 (d, J$_{CP}$ = 156.9 Hz, CHP, m); 60.00 (d, J$_{CP}$ = 156.9 Hz, CHP, M); 123.05 (d, J$_{CP}$ = 13.8 Hz, =CH, m); 123.50 (d, J$_{CP}$ = 13.8 Hz, =CH, M); 127.09, 128.33, 128.37 (CH$_{arom}$, m+M); 139.61 (C$_{q,arom}$); 142.16 (d, J$_{CP}$ = 5.8 Hz, =C$_q$, M); 142.34 (d, J$_{CP}$ = 5.8 Hz, =C$_q$, m). **^{31}P NMR δ (121 MHz, ppm):** 26.60 (m); 26.87 (M). **IR ν (cm^{-1}):** 3318 (NH); 1677 (C=C); 1244 (P=O); 1060, 1033 (P-O). **MS m/z (%):** 240 (100, [M+H-P(O)(OMe)$_2$]$^+$); 350 (14, [M+H]$^+$). **Chromatography:** Rf = 0.35 (EtOAc). **Yield:** 80%. Colourless oil.

Diethyl benzylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22u)

See chapter 4, section 3.1 for spectral data. **Yield:** 88%.

Dimethyl allylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22v)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 30/70). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
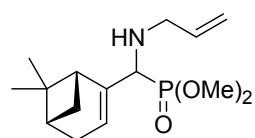

^{1}H NMR δ (300 MHz, ppm): 0.88 (2x3H, s, CH$_3$, m+M); 1.15 (1H, d, J = 8.5 Hz, CH$_A$H$_B$, m); 1.21 (1H, d, J = 8.5 Hz, CH$_A$H$_B$, M); 1.29 (2x3H, s, CH$_3$, m+M); 1.58 (1H, s (br.), NH); 2.06-2.14 (2x 1H, multiplet, C$_q$CHCH$_2$, m+M); 2.27-2.35 (2x 3H, multiplet, CH$_2$CH=, CHC$_q$=, m+M); 2.41-2.48 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 3.11 (2x 1H, dd, J$_{AB}$ = 14.0 Hz, J = 6.9 Hz, NCH$_A$H$_B$, M); 3.28-3.35 (2x 1H, multiplet, NCH$_A$H$_B$, m+M); 3,50 (1H, d, J$_{HP}$ = 21.2 Hz, CHP, M); 3,54 (1H, d, J$_{HP}$ = 20.9 Hz, CHP, m); 3.74 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$, m); 3.75 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$, M); 3.78 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.79 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 5.08-5.30 (2x 2H, multiplet, =CH$_2$, m+M); 5.53 (2x 1H, s (br.), =CH, m+M); 5.76-5.90 (2x 1H, multiplet, CH=CH$_2$, m+M). **^{13}C NMR δ (75 MHz, ppm):** 21.01 (CH$_3$, m); 21.38 (CH$_3$, M); 26.23 (CH$_3$, M); 26.35 (CH$_3$, m); 31.52 (CH$_2$CH=, M); 31.60 (CH$_2$CH=, m); 31.97 (CHCH$_2$CH, m+M); 37.76 (C$_q$(CH$_3$)$_2$, M); 38.23 ((C$_q$(CH$_3$)$_2$, m); 40.63 (CHCH$_2$, M); 40.78 (CHCH$_2$, m); 42.87 (CHC$_q$=, m); 43.33 (CHC$_q$=, M); 49.98 (d, J$_{CP}$ = 17.3 Hz, NCH$_2$, M); 50.08 (d, J$_{CP}$ = 18.5 Hz, NCH$_2$, m); 52.51 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$, m); 52.62 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$, M); 53.38 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, m+M); 59.55 (d, J$_{CP}$ = 156.9 Hz, CHP, M); 59.96 (d, J$_{CP}$ = 156.9 Hz, CHP, m); 116.47 (s (br.), =CH$_2$); 122.57 (d, J$_{CP}$ = 13.9 Hz, =CH, M); 123.05 (d, J$_{CP}$ = 13.9 Hz, =CH, m); 136.18

(C̲H=CH$_2$, m+M); 142.23 (d, J$_{CP}$ = 5.8 Hz, =C$_q$, m); 142.38 (d, J$_{CP}$ = 4.6 Hz, =C$_q$, M). **^{31}P NMR δ (121 MHz, ppm):** 26.76 (m); 27.04 (M). **IR ν (cm^{-1}):** 3466 (NH); 1240 (P=O); 1038 (br., P-O). **MS m/z (%):** 300 (100, [M+H]$^+$); 191 (51, [M+H-PO(OCH$_3$)$_2$]$^+$, 33). **Yield:** 85%. Yellow oil.

## Dimethyl isopropylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22w)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 26/74). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
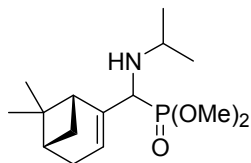
^{1}H NMR δ (300 MHz, ppm): 0.85 (3H, s, CH$_3$, M); 0.87 (3H, s, CH$_3$, m); 0.96 (3H, d, J = 6.1 Hz, CH(C̲H$_3$)$_2$, m); 0.97 (3H, d, J = 6.1 Hz, CH(C̲H$_3$)$_2$, M); 1.03 (3H, d, J = 6.3 Hz, CH(C̲H$_3$)$_2$, M); 1.05 (3H, d, J = 6.3 Hz, CH(C̲H$_3$)$_2$, m); 1.12 (1H, d, J = 8.5 Hz, C̲H$_A$H$_B$, m); 1.20 (1H, d, J = 8.5 Hz, C̲H$_A$H$_B$, M); 1.29 (3H, s, CH$_3$, M); 1.30 (3H, s, CH$_3$, m); 1.44 (1H, s(br), NH); 2.10 (2x 1H, s(br), C$_q$C̲HCH$_2$, m+M); 2.29-2.48 (2x 4H, multiplet, C̲H$_2$CH=, C̲HC$_q$=, CH$_A$H̲$_B$, m+M); 2.81 (1H, septet, J = 6.3 Hz, C̲H(CH$_3$)$_2$); 3.55 (1H, d, J$_{HP}$ = 23.1 Hz, CHP, M); 3.58 (1H, d, J$_{HP}$ = 23.1 Hz, CHP, m); 3.72 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$, m); 3.73 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$, M); 3.80 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.81 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 5.50 (2x 1H, s (br.), =CH, m+M). **^{13}C NMR δ (75 MHz, ppm):** 20.97 (CH$_3$, m); 21.21 (CH$_3$, M); 21.21 (CH(C̲H$_3$)$_2$, m); 21.33 (CH(C̲H$_3$)$_2$, M); 23.82 (CH(C̲H$_3$)$_2$, M); 24.00 (CH(C̲H$_3$)$_2$, m); 26.22 (CH$_3$, M); 26.34 (CH$_3$, m); 31.51 (C̲H$_2$CH=, m+M); 31.84 (CHC̲H$_2$CH, m); 32.04 (CHC̲H$_2$CH, M); 38.00 (C̲$_q$(CH$_3$)$_2$, M); 38.30 ((C̲$_q$(CH$_3$)$_2$, m); 40.62 (C̲HCH$_2$, M); 40.81 (C̲HCH$_2$, m); 43.03 (CHC$_q$=, m); 43.20 (CHC$_q$=, M); 45.70 (d, J$_{CP}$ = 17.3 Hz, C̲H(CH$_3$)$_2$, M); 45.76 (d, J$_{CP}$ = 17.3 Hz, C̲H(CH$_3$)$_2$, m); 52.47 (OCH$_3$, m); 52.60 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$, M); 53.76 (OCH$_3$, m); 53.91 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 58.07 (d, J$_{CP}$ = 159.2 Hz, CHP, M); 58.39 (d, J$_{CP}$ = 156.9 Hz, CHP, m); 122.33 (d, J$_{CP}$ = 15.0 Hz, =CH, M); 122.59 (d, J$_{CP}$ = 16.2 Hz, =CH, m); 142.54 (d, J$_{CP}$ = 5.8 Hz, =C$_q$, m); 142.66 (d, J$_{CP}$ = 3.5 Hz, =C$_q$, M). **^{31}P NMR δ (121 MHz, ppm):** 26.82 (m); 26.96 (M). **IR ν (cm^{-1}):** 3299 (NH); 1252 (P=O); 1038 (br., P-O). **MS m/z (%):** 302 (100, [M+H]$^+$); 193 (33, [M+H-PO(OCH$_3$)$_2$]$^+$, 33). **Yield:** 39%. Yellow oil.

Dimethyl *t*-butylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonate (22x)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 44/56). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
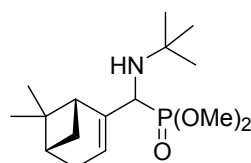
^{1}H NMR δ (300 MHz, ppm): 0.85 (3H, s, CH$_3$, M); 0.86 (3H, s, CH$_3$, m); 1.06 (9H, s, 3x CH$_3$, m); 1.07 (9H, s, 3x CH$_3$, M); 1.16 (1H, d, J = 8.5 Hz, C̲H$_A$H$_B$, m); 1.17 (1H, d, J = 8.5 Hz, C̲H$_A$H$_B$, M); 1.28 (3H, s, CH$_3$, m); 1.30 (3H, s, CH$_3$, M); 1.41 (1H, s(br), NH); 2.07 (2x 1H, s(br), C$_q$C̲HCH$_2$, m+M); 2.27-2.30 (2x 2H, multiplet, C̲H$_2$CH=, m+M); 2.34 (2x 1H, t, J = 5.5 Hz, C̲HC$_q$=, m+M); 2.41-2.47 (2x 1H, multiplet, CH$_A$H̲$_B$, m+M); 3.45 (1H, d, J$_{HP}$ = 24.7 Hz, CHP, m); 3.57 (1H, d, J$_{HP}$ = 25.3 Hz, CHP, M); 3.68 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 3.69 (3H, d, J$_{HP}$ = 10,5 Hz, OCH$_3$, M); 3.82 (6H, d, J$_{HP}$ = 10.2 Hz, 2x OCH$_3$, m); 5.50-5.61 (2x 1H, multiplet, =CH,

m+M). **¹³C NMR δ (75 MHz, ppm):** 21.12 (CH₃, M); 21.43 (CH₃, m); 26.18 (CH₃, M); 26.28 (CH₃, m); 29.62 (3x CH₃, m); 29.79 (3x CH₃, M); 31.57, 31.69, 32.00, 32.44 (CH₂CH=, CH₂); 37.95 (C̲q(CH₃)₂, m+M); 40.46 (C̲HCH₂, M); 40.54 (C̲HCH₂, m); 43.66 (C̲HCH₂CH=, m+M); 45.37 (Cq(CH₃)₃, M+m); 54.77, 51.97, 52.21, 52.31, 54.68, 54.78 (OCH₃, m+M); 55.22 (d, J_{CP} = 161.5 Hz, CHP, m); 55.68 (d, J_{CP} = 161.5 Hz, CHP, M); 120.37 (d, J_{CP} = 12.7 Hz, CH=, m); 121.04 (d, J_{CP} = 13.8 Hz, CH=, M); 144.82 (Cq=, m); 144.93 (CHq=, M). **³¹P NMR δ (121 MHz, ppm):** 26.49 (m); 27.02 (M). **IR ν (cm⁻¹):** 3310 (NH); 1243 (br., P=O); 1037 (br, P-O). **MS m/z (%):** 316 (100, [M+H]⁺). **Mp.:** 56-57°C. **Yield:** 60%. Yellow crystals.

Dimethyl benzylaminofuran-2-ylmethyl phosphonate (22y)
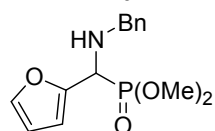
¹H NMR δ (300 MHz, ppm): 2.17 (1H, s (br.), NH); 3.60 (1H, d, J_{AB} = 13.2 Hz, CH₂); 3.63 (3H, d, J_{HP} = 10.7 Hz, CH₃O); 3.81 (3H, d, J_{HP} = 10.5 Hz, CH₃O); 3.87 (1H, d, J_{AB} = 13.2 Hz, CH₂); 4.12 (1H, d, J_{HP} = 22.3 Hz, CHP); 6.37 (2H, multiplet, =CH); 7.22-7.35 (5H, multiplet, CH_arom); 7.45-7.47 (1H, multiplet, CHO_arom). **¹³C NMR δ (75 MHz, ppm):** 51.32 (d, J_{CP} = 16.2 Hz, CH₂); 52.71 (d, J_{CP} = 161.5 Hz, CHP); 53.42 (d, J_{CP} = 6.9 Hz, OCH₃); 53.94 (d̲, J_{CP} = 6.9 Hz, OCH₃); 109.57 (d, J_{CP} = 8.1 Hz, =C̲HCqO); 110.66 (C̲H=CHO); 127.26; 128.42 (CH_arom); 138.86 (C_q,arom)); 142.80 (=CHO); 149.37 (=CqO). **³¹P NMR δ (121 MHz, ppm):** 24.01. **IR ν (cm⁻¹):** 3311, 3470 (NH); 1251 (P=O); 1037 (br., P-O). **MS m/z (%):** 296 (100, [M+H]⁺). **Yield:** 89%. Yellow oil.

Dimethyl allylaminofuran-2-ylmethyl phosphonate (22z)
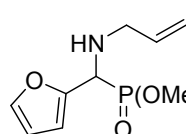
¹H NMR δ (300 MHz, ppm): 2.04 (1H, s (br.), NH̲); 2.95 (1H, dd, J_{AB} = 13.8 Hz, J = 6.7 Hz, CH₂); 3.17 (1H, d, J_{AB} = 13.8 Hz, J = 5.4 Hz, J = 1.4 Hz, CH₂); 3.53 (3H, d, J_{HP} = 10.7 Hz, CH₃O); 3.69 (3H, d, J_{HP} = 10.7 Hz, CH₃O); 4.06 (1H, d, J_{HP} = 22.3 Hz, CHP); 4.96-5.18 (2H, multiplet, =CH₂); 5.68 (1H, dddd, J = 17.1 Hz, J = 10.2 Hz, J = 6.8 Hz, J = 5.5 Hz, CH₂CH̲=); 6.23-6.27 (2H, multiplet, =CH); 7.30-7.32 (1H, multiplet, CHO). **¹³C NMR δ (75 MHz, ppm):** 50.13 (d, J_{CP} = 16.2 Hz, CH₂); 52.80 (d, J_{CP} = 162.7 Hz, CHP); 53.46 (d, J_{CP} = 5.8 Hz, OCH₃); 53.84 (d, J_{CP} = 6.9 Hz, OCH₃); 109.43 (d, J_{CP} = 8.1 Hz, =C̲HCqO); 110.65 (C̲H=CHO); 117.20 (=CH₂); 135.58 (CH₂C̲H=); 142.71 (d, J_{CP} = 2.3 Hz, =CHO); 149.37 (d, J_{CP} = 2.3 Hz, =CqO). **IR ν (cm⁻¹):** 3317 (NH); 1643 (C=C); 1248 (P=O); 1044 (br., P-O). **³¹P NMR δ (121 MHz, ppm):** 24.16. **MS m/z (%):** 246 (100, [M+H]⁺). **Yield:** 89%. Brown oil.

Dimethyl *t*-butylaminofuran-2-ylmethyl phosphonate (22ab)
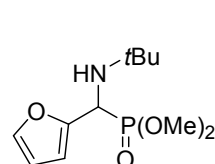
¹H NMR δ (300 MHz, ppm): 1.01 (9H, s, 3x CH₃); 1.71 (1H, s (br.), NH); 3.62 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.85 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 4.26 (1H, d, J_{HP} = 25.6 Hz, CHP); 6.30-6.39 (1H, multiplet, CH=Cq, C̲H=CHO); 7.40 (1H, multiplet, CHO). **¹³C NMR δ (75 MHz, ppm):** 29.47 (3x CH₃); 49.27 (d, J_{CP} = 167.3 Hz, CHP); 51.89 (Cq, d, J_{CP} = 16.2 Hz); 53.34 (d, J_{CP} = 6.9 Hz, OCH₃); 54.79 (d, J_{CP} = 6,9 Hz, OCH₃); 107.96 (d, J_{CP} = 8.0 Hz, C̲H=Cq); 110.99 (d, J_{CP} = 2,3 Hz, C̲H=CHO); 141.95 (d, CHO, J_{CP} = 3.4 Hz); 152.20 (CqO). **³¹P NMR δ (121 MHz, ppm):** 24.27. **IR ν (cm⁻¹):** 3298 (NH); 1246 (P=O); 1064, 1032 (P-O). **MS m/z (%):** 262 (MH⁺, 100); **Mp.:** 41°C. **Yield:** 63%. Yellow crystals.

Dimethyl benzylaminophenylmethyl phosphonate (22ac)
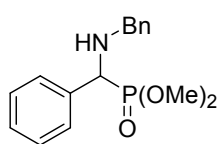
¹H NMR δ (300 MHz, ppm): 2.41 (1H, br. s, NH); 3.54 (3H, d, J_{HP} = 10.5 Hz, CH₃O); 3.74 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.55 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$); 3.82 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$); 4.05 (1H, d, J_{HP} = 20.1 Hz, CHP); 7.22-7.45 (5H, multiplet, CH$_{arom}$); **¹³C NMR δ (75 MHz, ppm):** 51.14 (d, J_{CP} = 17.3 Hz, NCH₂); 53.40 (d, J_{CP} = 5.8 Hz, OCH₃); 53.71 (d, J_{CP} = 6.9 Hz, OCH₃); 59.29 (d, J_{CP} = 154.6 Hz, CHP); 128.02; 128.07; 128.33; 128.39; 128.56; 128.59; 128.63 (CH$_{arom}$); 135.50 (d, J_{CP} = 3.5 Hz, C$_q$); 139.18 (C$_q$CH₂). **IR ν (cm⁻¹):** 3437 (NH); 1230 (P=O); 1034 (br., P-O). **³¹P NMR δ (121 MHz, ppm):** 26.44. **MS m/z (%):** 306 (100, [M+H]⁺). **Yield:** 89%. Colourless oil.

Dimethyl isopropylaminophenylmethyl phosphonate (22ad)
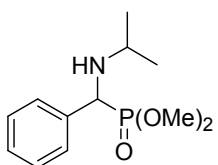
¹H NMR δ (300 MHz, ppm): 1.00 (3H, d, J = 6.1 Hz, CH₃); 1.02 (3H, d, J = 6.3 Hz, CH₃); 1.85 (1H, s (br.), NH); 2.68 (1H, septet, J = 6.3 Hz, NCH); 3.51 (3H, d, J_{HP} = 10.5 Hz, CH₃O); 3.78 (3H, d, J_{HP} = 10.5 Hz, CH₃O); 4.17 (1H, d, J_{HP} = 22.3 Hz, CHP); 7.27-7.43 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 21.31 (CH₃); 24.04 (CH₃); 45.71 (d, J_{CP} =16,2 Hz, NCH); 53,51 (d, J_{CP} = 6.9 Hz, OCH₃); 54.00 (d, J_{CP} = 6.9 Hz, OCH₃); 57.98 (d, J_{CP} = 154.6 Hz, CHP); 127.99, 128.43, 128.51, 128.61 (CH$_{arom}$); 136.29 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.00. **IR ν (cm⁻¹):** 3303 (NH); 1241 (P=O); 1066, 1026 (P-O). **MS m/z (%):** 258 (100, [M+H]⁺). **Mp.:** 72.7 °C. **Yield:** 94%. White solid.

Diethyl isopropylaminophenylmethyl phosphonate (22ae)
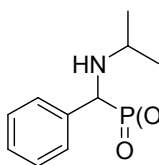
¹H NMR δ (300 MHz, ppm): 0.99 (3H, d, J = 6.1 Hz, CHCH₃); 1.01 (3H, d, J = 6.3 Hz, CHCH₃); 1.11 (3H, t, J = 7.0 Hz, CH₃CH₂); 1.30 (3H, t, J = 7.0 Hz, CH₃CH₂); 1.80 (1H, s (br.), NH); 2.68 (1H, septet, J = 6.2 Hz, NCH); 3.70-3.83 (1H, multiplet, CH₂O); 3.88-4.04 (1H, multiplet, CH₂O); 4.06-4.22 (3H, multiplet, CH₂O, CHP); 7.25-7.42 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.24 (d, J_{CP} = 5.8 Hz, CH₃CH₂); 16.47 (d, J_{CP} = 5.8 Hz, CH₃CH₂); 21.33 (CHCH₃); 24.00 (CHCH₃); 45.74 (d, J_{CP} =16,2 Hz, NCH); 58.30 (d, J_{CP} = 153.5 Hz, CHP); 62.68 (d, J_{CP} = 6.9 Hz, OCH₂); 63.12 (d, J_{CP} = 6.9 Hz, OCH₂); 127.72, 128.42, 128.50 (CH$_{arom}$); 136.63 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.74. **IR ν (cm⁻¹):** 3294 (NH); 1240 (P=O); 1061, 1028 (P-O). **MS m/z (%):** 286 (100, [M+H]⁺). **Mp.:** 36.3 °C. **Yield:** 84%. White solid.

Dimethyl cyclohexyl-isopropylaminomethyl phosphonate (22af)
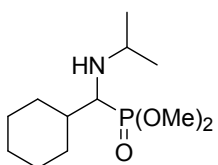
¹H NMR δ (300 MHz, ppm): 0.99 (3H, d, J = 6.3 Hz, CH₃); 1.04 (3H, d, J = 6.1 Hz, CH₃); 1.07-1.46 (6H, multiplet, CHCH₂, 2xCH₂, NH); 1.61-1.87 (6H, multiplet, 3xCH₂); 2.78 (1H, dd, J_{HP} = 16.8 Hz, J = 3.3 Hz, CHP); 2.98 (1H, septet x d, J = 6.1 Hz, J_{HP} = 1.3 Hz, NCH); 3.75 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.78 (3H, d, J_{HP} = 10.5 Hz, OCH₃). **¹³C NMR δ (75 MHz, ppm):** 22.85 (CH₃); 23.36 (CH₃); 26.19, 26.50, 26.68 (3 x CH₂); 28.35 (d, J_{CP} = 3.5 Hz, CH₂); 30.90 (d, J_{CP} = 11.64 Hz, CH₂); 39.62 (d, J_{CP} = 5.8 Hz, CHCH₂); 47.72 (d, J_{CP} = 5.8 Hz, NCH); 52.36 (d, J_{CP} = 8.1 Hz, OCH₃); 52.87 (d, J_{CP} = 8.1 Hz, OCH₃); 57.59 (d, J_{CP} = 144.2 Hz, CHP). **³¹P NMR δ (121 MHz, ppm):**

31.77. **IR ν (cm⁻¹):** 3294; 3309; 3325 (NH); 1243 (P=O); 1067, 1030 (P-O). **MS m/z (%):** 264 (100, [M+H]⁺). **Mp.:** 54.2 °C. **Yield:** 93%. White solid.

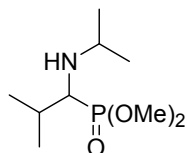### Dimethyl 1-benzylamino-2-methylpropyl phosphonate (22ag)
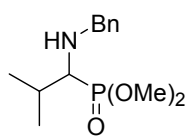
¹H NMR δ (300 MHz, ppm): 1.01 (3H, d, J = 6.9 Hz, CH₃); 1.02 (3H, dd, J = 6.7 Hz, J$_{HP}$ = 1.0 Hz, CH₃); 1.50 (1H, s (br.), NH); 2.05-2.22 (1H, multiplet, CH); 2.78 (1H, dd, J$_{HP}$ = 14.5 Hz, J = 3.7 Hz, CHP); 3.76 (3H, d, J$_{HP}$ = 10.5 Hz, OCH₃); 3.79 (3H, d, J$_{HP}$ = 10.2 Hz, OC$\underline{H}$₃); 3.83 (1H, dd, J$_{AB}$ = 12.6 Hz, J$_{HP}$ = 1.4 Hz, C$\underline{H}$$_AH_B$N); 4.01 (1H, d, J$_{AB}$ = 12.6 Hz, CH$_A$$\underline{H}$$_B$Ph); 7.22-7.38 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 17.92 (d, J$_{CP}$ = 3.5 Hz, CH₃); 20.63 (d, J$_{CP}$ = 12.7 Hz, CH₃); 29.03 (d, J$_{CP}$ = 5.8 Hz, CH); 52.35 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 52.39 (d, J$_{CP}$ = 8.1 Hz, OCH₃); 53.26 (d, J$_{CP}$ = 3.5 Hz, CH₂N); 59.25 (d, J$_{CP}$ = 142.0 Hz, CHP); 127.09; 128.27; 128.44 (CH$_{arom}$); 140.08 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 31.75. **IR ν (cm⁻¹):** 3469 (NH); 1246 (P=O); 1057, 1031 (P-O). **MS m/z (%):** 271 (100, [M+H]⁺). **Yield:** 84%. Colourless oil.

Dimethyl 1-isopropylamino-2-methylpropyl phosphonate (22ah)

¹H NMR δ (300 MHz, ppm): 0.98-1.06 (12H, multiplet, 4xCH₃); 2.02 (1H, multiplet, CH); 2.81 (1H, dd, J$_{HP}$ = 16.5 Hz, J = 3.6 Hz, CHP); 3.00 (1H, septet x d, J = 6.3 Hz, J$_{H-P}$ = 1.4 Hz, NCH); 3.75 (3H, d, J$_{HP}$ = 9.9 Hz, OCH₃); 3.79 (3H, d, J$_{HP}$ = 10.2 Hz, OCH₃). **¹³C NMR δ (75 MHz, ppm):** 17.91 (d, J$_{CP}$ = 2.3 Hz, CH₃); 20.55 (d, J$_{CP}$ = 13.8 Hz, CH₃); 22.72 ($\underline{C}$H₃CHN); 23.45 ($\underline{C}$H₃CHN); 29.26 (d, J$_{CP}$ = 5.8 Hz, CH); 47.51 (d, J$_{CP}$ = 5.8 Hz, NCH); 52.30 (d, J$_{CP}$ = 8.1 Hz, OCH₃); 52.81 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 57.39 (d, J$_{CP}$ = 144.2 Hz, CHP). **IR ν (cm⁻¹):** 1054 (P-O); 1247 (P=O); 1465; 3326 (NH); **³¹P NMR δ (121 MHz, ppm):** 31.84; **MS m/z (%):** 114 (100, [M+H-P(O)(OMe)₂]⁺). **Yield:** 86%. Colourless oil.

3.4 Preparation of monoalkyl aminoalkyl phosphonates

A solution of dialkyl aminoalkyl phosphonate (2 mmol) in 5 ml dry diethyl ether was stirred at room temperature protected from moisture using a CaCl₂ tube. Then, 3 mmol of potassium silanolate (KOTMS) was added in solid form and stirring was continued until precipitation occurred. The precipitate was collected by filtration and washed three times with 2 ml of dry diethyl ether. Finally the powder was dried under vacuum.

Potassium methyl isopropylaminophenylmethyl phosphonates (237a)

¹H NMR δ (D₂O, 300 MHz, ppm): 0.99 (3H, d, J = 6.3 Hz, CH₃); 1.01(3H, d, J = 6.3 Hz, CH₃); 2.71 (1H, septet, J = 6.3 Hz, CH); 3.51(3H, J$_{HP}$ = 10.2 Hz, OCH₃); 4.08 (1H, J$_{HP}$ = 19.8 Hz, CHP); 7.33-7.43 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (D₂O, 75 MHz, ppm):** 20.54 (CH₃); 22.70 (CH₃); 46.30 (d, J$_{CP}$ = 12.7 Hz, CH); 52.44 (d, J$_{CP}$ = 5.8 Hz, OCH₃); 57.84 (d, J$_{CP}$ = 143.1 Hz, CHP); 127.98 (CH$_{arom}$); 129.09 (CH$_{arom}$); 129.17 (CH$_{arom}$); 138.50 (C$_{quat,arom}$). **³¹P NMR δ (D₂O, 121 MHz,**

ppm): 22.32. **IR ν (cm⁻¹):** 3369 (br., NH); 1242, 1214, 1197, 1075 (P-O); 1048 (P-O). **MS m/z (%):** 244 (68, [M-K+2H]⁺); 282 (43, [M+H]⁺); 487 (100, [2M-2K+3H]⁺); 525 (100, [2M-K+2H]⁺); 563 (21, [2M+H]⁺); 844 (13, [3M+H]⁺); 882 (8, [3M+K]⁺). **Mp.:** 204-205°C. **Yield:** 95%. White crystals.

Potassium methyl cyclohexyl-isopropylaminomethyl phosphonates (237c)

¹H NMR δ (D₂O, 300 MHz, ppm): 0.99 (3H, d, J = 6.3 Hz, CH₃); 1.05 (3H, d, J = 6.3 Hz, CH₃); 1.12-2.05 (11H, multiplet, CH$_{2ring}$, C$_{Hring}$); 2.64 (1H, dd, J$_{HP}$ = 16.0 Hz, J = 2.5 Hz, CHP); 3.02 (1H, septet, J = 6.3 Hz, CH); 3.53 (3H, J$_{HP}$ = 10.2 Hz, OCH₃). **¹³C NMR δ (D₂O, 75 MHz, ppm):** 21.29 (CH₃); 22.81 (CH₃); 26.31, 26.83, 27.03, 28.66 (CH$_{2ring}$); 31.03 (d, J$_{CP}$ = 11.5 Hz, CH$_{2ring}$); 40.34 (CH$_{ring}$); 48.14 (NCH); 51.47 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 57.59 (d, J$_{CP}$ = 133.8 Hz, CHP). **³¹P NMR δ (D₂O, 121 MHz, ppm):** 27.81. **IR ν (cm⁻¹):** 3308 (br., NH); 1380, 1194, 1068 (P-O); 1052 (P-O). **MS m/z (%):** 250 (76, [M-K+2H]⁺); 288 (43, [M+H]⁺); 499 (100, [2M-2K+3H]⁺); 537 (70, [2M-K+2H]⁺); 575 (6, [2M+H]⁺); 786 (15, [3M-2K+3H]⁺); 824 (15, [3M-K+2H]⁺). **Yield:** 98%. White crystals (very hydroscopic).

Potassium methyl allylaminofuran-2-ylmethyl phosphonates (237b)

Was formed as an oil, giving a biphasic system with diethyl ether. The solvent was easily decanted and the potassium salts were obtained in pure form after washing three times with ether and drying under vacuum.

¹H NMR δ (D₂O, 300 MHz, ppm): 3.03 (1H, dd, J$_{AB}$ = 14.0 Hz, J = 7.2 Hz, CH$_A$H$_B$); 3.20 (1H, dd, J$_{AB}$ = 14.0 Hz, J = 5.3 Hz, CH$_A$H$_B$); 3.54 (3H, d, J$_{HP}$ = 10.2 Hz, OCH₃); 4.08 (1H, d, J$_{HP}$ = 19.5 Hz, CHP); 5.12-5.19 (2H, multiplet, =CH₂); 5.77-5.90 (1H, multiplet, =CH); 6.38-6.40 (1H, multiplet, =CH$_{ring}$); 6.46-6.48 (1H, multiplet, =CH$_{ring}$); 7.51-7.53 (1H, multiplet, =CHO). **¹³C NMR δ (D₂O, 75 MHz, ppm):** 50,02 (d, J$_{CP}$ = 12.7 Hz); 52.68 (d, J$_{CP}$ = 5.8 Hz, OCH₃); 53.01 (d, J$_{CP}$ = 148.8 Hz, CHP); 109.62 (d, J$_{CP}$ = 6.9 Hz, =CH-C$_q$); 110.12 (=CH$_{ring}$); 117.18 (=CH₂); 135.53 (=CH); 143.07 (d, J$_{CP}$ = 2.3 Hz, =CHO); 151.25 (d, J$_{CP}$ = 4.6 Hz, =C$_q$O). **³¹P NMR δ (D₂O, 121 MHz, ppm):** 19.24. **MS m/z (%):** 232 (13, [M-K+2H]⁺); 270 (67, [M+H]⁺); 308 (100, [M+K]⁺); 463 (10, [2M-2K+3H]⁺); 501 (73, [2M-K+2H]⁺); 539 (59, [M+H]⁺); 577 (22, [2M+K]⁺); 769 (7, [3M-K+2H]⁺); 808 (25 [3M+H]⁺); 846 (23, [3M+K]⁺). **Yield:** 63%. Orange oil.

4 Synthesis of 4-phosphono β-lactams

4.1 Acylation of 1-aminoalkyl phosphonates

To a solution of 5 mmol of 1-aminoalkyl phosphonate in 10 ml of dry THF, a specified amount of base and/or nucleophilic catalyst was added at room temperature under a nitrogen atmosphere. Then a solution of the acid chloride of choice in 2 ml of dry THF was added dropwise using a syringe at room temperature. The reaction mixture was then allowed to react for a

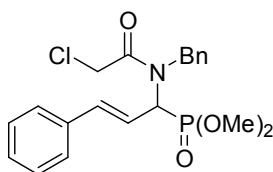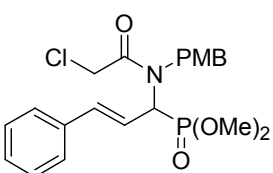specified time at the specified temperature (see Table 8). The reaction mixture was then mixed with a saturated $NaHCO_{3(aq)}$ solution (10 ml) and diethyl ether (10 ml) in a seperatory funnel. The organic phase was collected an the remaining aqueous phase was whashed twice with 5 ml of diethyl ether. The combined organic phases were then mixed with a 1 M $HCl_{(aq)}$ solution (10 ml) in a seperatory funnel. The organic phase was collected and the remaining aqueous phase was washed twice with 5 ml of diethyl ether. The combined organic phases were dried using $MgSO_4$ and the solvent was evaporated under vacuum.

Dimethyl (2*E*)-1-[benzyl(chloroacetyl)amino]-3-phenylprop-2-enyl phosphonate (21b)

¹H NMR δ (300 MHz, ppm): 3.79 (3H, d, J_{HP} = 10.9 Hz, OCH_3); 3.80 (3H, d, J_{HP} = 10.6 Hz, OCH_3); 3.93 (1H, d, J_{AB} = 12.5 Hz, C$\underline{H}_A$H$_B$Cl); 4.01 (1H, d, J_{AB} = 12.5 Hz, CH$_A\underline{H}_B$Cl); 4.87 (1H, d, J_{AB} = 18.2 Hz, NC$\underline{H}_A$H$_B$); 5.05 (1H, d, J_{AB} = 17.8 Hz, NCH$_A\underline{H}_B$); 5.66 (1H, dd, J_{HP} = 20.5 Hz, J = 9.2 Hz, NCHP); 6.18 (1H, multiplet, CH=); 6.76 (1H, dd, J_{trans} = 15.7 Hz, J = 3.0 Hz, PhC$\underline{H}$=); 7.20-7.40 (10H, multiplet, CH_{arom}). **¹³C NMR δ (75 MHz, ppm):** 41.51 (CH_2Cl); 49.78 (N$\underline{C}H_2$); 53.17 (d, J_{CP} = 7.3 Hz, OCH_3); 54.00 (d, J_{CP} = 7.3 Hz, OCH_3); 54.74 (d, J_{CP} = 157.5 Hz, NCHP); 119.03 (=CH); 125.98, 126.68, 126.99, 127.11, 127.71, 128.44, 128.55, 129.02 (CH_{arom}); 135.72; 136.64 ($C_{q,arom}$); 137.32 (d, J_{CP}= 13.4 Hz, =CHPh); 167.38 (d, J_{CP} = 2.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 23.33. **IR ν (cm⁻¹):** 1661 (C=O); 1249 (P=O). **MS m/z (%):** 91(100); 116(18); 207(12); 209(25); 299(39); 301(14). **Chromatography:** Rf = 0.29 (Hex/EtOAc/MeOH 20/78/2). **Yield:** 97%. Yellow oil.

Dimethyl (2*E*)-1-[(4-methoxybenzyl)(chloroacetyl)amino]-3-phenylprop-2-enyl phosphonate (21d)

¹H NMR δ (300 MHz, ppm): 3.76 (3H, s, OCH_3(Ph)); 3.77 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 3.80 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 3.93 (1H, d, J_{AB} = 12.7 Hz, C$\underline{H}_A$H$_B$Cl); 4.04 (1H, d, J_{AB} = 12.7 Hz, CH$_A\underline{H}_B$Cl); 4.79 (1H, d, J_{AB} = 17.6 Hz, NC$\underline{H}_A$H$_B$); 4.96 (1H, d, J_{AB} = 17.6 Hz, NCH$_A\underline{H}_B$); 5.58 (1H, dd, J_{HP} = 20.6 Hz, J = 9.4 Hz, CHP); 6.15-6.29 (1H, multiplet, =CH); 6.73 (1H, dd, J = 15.7 Hz, J_{HP} = 3.0 Hz, =CHPh); 6.85 (2H, d, J = 8.8 Hz, C$\underline{H}C_q$OMe); 7.13-7.33 (7H, multiplet, CH_{arom}). **¹³C NMR δ (75 MHz, ppm):** 41.58 (CH_2Cl); 49.50 (NCH_2); 53.16 (d, J_{CP} = 6.9 Hz, OCH_3); 54.05 (d, J_{CP} = 6.9 Hz, OCH_3); 54.90 (d, J_{CP} = 158.1 Hz, CHP); 55.29 (OCH_3(Ph)); 114.43 ($CH_{arom,PMB}$); 119.14 (=CH); 126.74, 127.38 (CH_{arom}); 128.47 ($CH_2\underline{C}_{q,arom}$); 128.59 ($CH_{arom}$); 135.78 ($C_{q,arom}$); 137.37 (d, J_{CP} = 13.9 Hz, =CHPh); 159 ($OC_{q,arom}$); 167.41 (d, JCP = 3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 23.74. **IR ν (cm⁻¹):** 1663 (C=O, C=C); 1249 (P=O); 1033 (br., P-O). **MS m/z (%):** 229 (100); 436 (60, [M-H]⁻); 338 (21, [M-H+2]⁻). **Chromatography:** Rf = 0.21 (EtOAc). **Yield:** 91%. Orange oil.

Dimethyl (2*E*)-1-[allyl(acetyl)amino]-3-phenylprop-2-enyl phosphonate (255a)

¹H NMR δ (300 MHz, ppm): 2.15 (3H, s, CH₃); 3.77 (3H, d, J_{HP} = 10.7 Hz, OCH₃); 3.79 (3H, d, J_{HP} = 10,7 Hz, OCH₃); 4.10–4.18 (1H, multiplet, NCH$\underline{A}$H$_B$); 4.28-4.36 (1H, multiplet, NCH$_A$H$\underline{B}$); 5.16-5.23 (2H, multiplet, =CH₂); 5.73 (1H, dd, J_{HP} = 20.9 Hz, J = 8.8 Hz, CHP); 5.83-5.94 (1H, multiplet, CH₂C$\underline{H}$=); 6.28 (1H, ddd, J_{trans} = 15.7 Hz, J_{HP} = 8.8 Hz, J = 8.8 Hz, =C$\underline{H}$CHP); 6.83 (1H, dd, J_{trans} = 15.7 Hz, J_{HP} = 2.8 Hz, =CHPh); 7.25-7.39 (5 H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 21.74 (CH₃); 49.33 (NCH₂); 53.13 (d, J_{CP} = 156.9 Hz, CHP); 53.17 (d, J_{CP} = 6.9 Hz, OCH₃); 53.92 (d, J_{CP} = 6.9 Hz, OCH₃); 117.09 (=CH₂); 119.96 (H$\underline{C}$=CHPh); 126.78 (2 x CH$_{arom}$); 128.43 (CH$_{arom}$); 128.73 (2 x CH$_{arom}$); 134.23 (=CH); 136.11 (C$_{q,arom}$); 136.72 (d, J_{CP} = 13.9 Hz, =$\underline{C}$HPh); 171.34 (d, J_{CP} =3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.48. **IR ν (cm⁻¹):** 1651 (C=O, C=C); 1252 (P=O); 1040 (br., P-O). **MS m/z (%):** 324 (100, [M+H]⁺). **Yield:** 78%. Yellow oil.

Dimethyl (2*E*)-1-[allyl(chloroacetyl)amino]-3-phenylprop-2-enyl phosphonate (21e)

¹H NMR δ (300 MHz, ppm): 3.789 (3H, d, J_{HP} = 10.7 Hz, OCH₃); 3.791 (3H, d, J_{HP} = 10,7 Hz, OCH₃); 4.08 (1H, d, J_{AB} = 12.7 Hz, CH$\underline{A}$H$_B$Cl); 4.16 (1H, d, J_{AB} = 12.4 Hz, CH$_A$H$\underline{B}$Cl); 4.19-4.44 (2 H, multiplet, NCH₂); 5.19-5.29 (2H, multiplet, =CH₂); 5.67 (1H, dd, J_{HP} = 21.1 Hz, J = 8.9 Hz, CHP); 5.83-5.94 (1H, multiplet, CH₂C$\underline{H}$=); 6.27 (1H, ddd, J_{trans} = 15.7 Hz, J_{HP} = 8.8 Hz, J = 8.8 Hz, =C$\underline{H}$CHP); 6.79 (1H, dd, J_{trans} = 15.7 Hz, J_{HP} = 2.8 Hz, =CHPh); 7.28-7.39 (5 H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 41.41 (CH₂Cl); 48.48 (NCH₂); 53.22 (d, J_{CP} = 6.9 Hz, OCH₃); 53.79 (d, J_{CP} = 6.4 Hz, OCH₃); 53.84 (d, J_{CP} = 159.9 Hz, CHP); 117.38 (=CH₂); 119.13 (H$\underline{C}$=CHPh); 126.71 (2 x CH$_{arom}$); 128.51 (CH$_{arom}$); 128.69 (2 x CH$_{arom}$); 134.05 (=CH); 135.82 (C$_{q,arom}$); 136.99 (d, J_{CP} = 12.7 Hz, =$\underline{C}$HPh); 167.13 (C=O). **³¹P NMR δ (121 MHz, ppm):** 23.64. **IR ν (cm⁻¹):** 1663 (C=O, C=C); 1251 (P=O); 1033 (P-O). **MS m/z (%):** 225 (100); 248 (18); 358 (13, [M+H]⁺); 360 (4, [M+H+2]⁺). **Chromatography:** Rf = 0.21 (EtOAc/MeOH 99/1). **Yield:** 96%. Yellow oil.

Dimethyl (2*E*)-1-[allyl(chlorobutyryl)amino]-3-phenylprop-2-enyl phosphonate (25b)

¹H NMR δ (300 MHz, ppm): 2,05-2,22 (2H, multiplet, CH₂); 2,46-2,67 (2H, multiplet, CH₂CO); 3,64 (2H, ~t, J = 5,8 Hz, J = 6,3 Hz, CH₂Cl); 3,76 (3H, d, J_{HP} = 10,7 Hz, OCH₃); 3,78 (3H, d, J_{HP} = 10,7 Hz, OCH₃); 4,14-4,37 (2H, multiplet, CH₂N); 5,23-5,16 (2H, multiplet, =CH₂); 5,74 (1H, dd, J_{HP} = 21,0 Hz, J = 8,8 Hz, CHP); 5,92-5,80 (1H, multiplet, =CH); 6,28 (1H, ddd, J = 16,0 Hz, J_{HP} = 8,8 Hz, J = 8,8 Hz, =C$\underline{H}$-CHP); 6,76 (1H, dd, J = 16,0 Hz, J_{HP} = 2,8 Hz, =CHPh); 7,25-7,40 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 27,91 (CH₂); 29,93 ($\underline{C}$H₂C=O); 44,55 (CH₂Cl); 48,45 (CH₂N); 53,00 (J_{CP} = 8,1 Hz, OCH₃); 53,27 (J_{CP} = 156,9 Hz, CHP); 53,73 (J_{CP} = 6,9 Hz, OCH₃); 117,01 (=CH₂); 119,84 (=$\underline{C}$HCHP); 126,66 (2 x CH$_{arom}$); 128,34 (CH$_{arom}$); 128,63 (2 x CH$_{arom}$); 134,18

(<u>C</u>H=CH₂); 135,96 (C$_{quat,arom}$); 136,50 (J$_{CP}$ = 12,7 Hz, =CHPh); 172,38 (C=O). **³¹P NMR δ (121 MHz, ppm):** 24,49. **IR ν (cm⁻¹):** 1651 (br, C=O, C=C); 1249 (P=O); 1030 (br, P-O). **MS m/z (%):** 225 (100); 276 (34, [M+H-P(O)(OMe)₂]⁺); 386 (42, [M+H]⁺); 360 (13, [M+H+2]⁺). **Chromatography:** Rf = 0.28 (EtOAc). **Yield:** 98%.

Dimethyl (2*E*)-1-[(chloroacetyl)(isopropyl)amino]-3-phenyl-prop-2-enyl phosphonate (21f)

¹H NMR δ (300 MHz, ppm): 1.26 (3 H, d, J = 6.5 Hz, CH₃); 1.39 (3 H, d, J = 6.5 Hz, CH₃); 3.71 (3 H, d, J$_{HP}$ = 11.0 Hz, OCH₃); 3.89 (3 H, d, J$_{HP}$ = 11.0 Hz, OCH₃); 4.09-4.27 (4 H, multiplet, CHP, CH, CH₂); 6.47-6.60 (2 H, multiplet, HC=CH); 7.23-7.41 (5 H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 21.03 (CH₃); 21.62 (CH₃); 41.57 (CH₂Cl); 50.90 (NCH); 52.30 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 54.86 (d, J$_{CP}$ = 161.0 Hz, CHP); 54.91 (d, J$_{CP}$ = 5.8 Hz, OCH₃); 121.82 (=CH); 126.80 (2 x CH$_{arom}$); 128.19 (CH$_{arom}$); 128.66 (2 x CH$_{arom}$); 133.97 (d, J$_{CP}$ = 12.1 Hz, =CH-Ph); 136.29 (C$_{q,arom}$); 165.97 (C=O). **³¹P NMR δ (121 MHz, ppm):** 25.86. **IR ν (cm⁻¹):** 1651 (C=O, C=C); 1250 (P=O); 1055 (br., P-O). **MS m/z (%):** 225 (100); 360 (14, [M+H]⁺); 362 (4, [M+H+2]⁺). **Chromatography:** Rf = 0.10 (Hex/EtOAc 20/80). **Yield:** 97%. Yellow oil.

Dimethyl [benzyl(chloroacetyl)amino]furan-2-ylmethyl phosphonate (21h)

¹H NMR δ (300 MHz, ppm): 3.72 (3H, d, J$_{HP}$ = 10.7 Hz, OCH₃); 3.82 (1H, d, J$_{AB}$ = 12.8 Hz, C<u>H</u>$_A$H$_B$Cl); 3.85 (3H, d, J$_{HP}$ = 10.9 Hz, OCH₃); 3.94 (1H, d, J$_{AB}$ = 12.8 Hz, CH$_A$<u>H</u>$_B$Cl); 4.78 (1H, d, J$_{AB}$ = 18.0 Hz, C<u>H</u>$_A$H$_B$N); 5.13 (1H, d, J$_{AB}$ = 18.0 Hz, CH$_A$<u>H</u>$_B$N); 6.24 (1H, dd, J = 2.9 Hz, J = 2.1 Hz, =CH); 6.55 (1H, d, J$_{HP}$ = 22.8 Hz, CHP); 6.68 (1H, d, J = 3.3 Hz, =CHC$_q$); 6.83 (2H, ~d, J ≈ 6.6 Hz, CH$_{arom}$); 7.14-7.28 (3H, multiplet, CH$_{arom}$); 7.31 (1H, d, J = 1.1 Hz, =CHO). **¹³C NMR δ (75 MHz, ppm):** 41.71 (CH₂Cl); 48.00 (d, J$_{CP}$ = 162.7 Hz, CHP); 49.16 (CH₂N); 53.71 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 54.05 (d, J$_{CP}$ = 5.8 Hz, OCH₃); 111.02 (=CH); 113.29 (d, J$_{CP}$ = 3.5 Hz, =<u>C</u>HC$_q$); 125.25 (2 x CH$_{arom}$); 127.35 (CH$_{arom}$); 128.83 (2 x CH$_{arom}$); 136.83 (C$_{q,arom}$); 143.62 (=CHO); 145.42 (d, J$_{CP}$ = 9.2 Hz, =C$_q$); 167.79 (C=O). **³¹P NMR δ (121 MHz, ppm):** 20.84. **IR ν (cm⁻¹):** 1651 (C=O); 1252 (P=O); 1057, 1043 (P-O). **MS m/z (%):** 189 (15); 372 (100, [M+H]⁺); 374 (25, [M+H+2]⁺). **Chromatography:** Rf = 0.26 (Hex/EtOAc 30/70). **Yield:** 99%. Yellow oil.

Dimethyl [benzyl(chlorobutyryl)amino]furan-2-ylmethyl phosphonate (25c)

¹H NMR δ (300 MHz, ppm): 1.92-2.29 (3H, multiplet, CH₂, C<u>H</u>$_A$H$_B$CO); 2.46-2.58 (1H, multiplet, CH$_A$<u>H</u>$_B$CO); 3.47-3.62 (2H, multiplet, CH2Cl); 3.71 (3H, d, J$_{HP}$ = 11.0 Hz, OCH₃); 3.91 (3H, d, J$_{HP}$ = 11.0 Hz, OCH₃); 4.73 (1H, d, J$_{AB}$ = 18.2 Hz, NC<u>H</u>$_A$H$_B$); 5.07 (1H, d, J$_{AB}$ = 18.2 Hz, NCH$_A$<u>H</u>$_B$); 6.21 (1H, dd, J = 3.0 Hz, J = 1.9 Hz, CH=); 6.63 (1H, d, J = 3.0 Hz, =CHC$_q$); 6.66 (1H, d, J$_{HP}$ = 23.1 Hz, CHP); 6.81-6.86 (2H, multiplet, CHarom); 7.10-7.21 (3H, multiplet, Charom); 7.29 (1H, d, J = 1.9 Hz, CHO). **¹³C NMR δ (75 MHz, ppm):** 27.83 (CH₂);

30.26 ($\underline{C}H_2CO$); 44.28 (CH_2Cl); 47.05 (d, J_{CP} = 162.7 Hz, CHP); 49.12 (CH_2N); 53.32 (d, J_{CP} = 6.9 Hz, OCH_3); 53.83 (d, J_{CP} = 5.8 Hz, OCH_3); 110.83 (=CH); 112.79 (d, J_{CP} = 2.3 Hz, =$\underline{C}HC_q$); 125.26, 126.79, 128.42 (Charom); 137.31 (Cq,arom); 143.26 (=CHO); 145.87 (d, J_{CP} = 9.2 Hz, =C_qO); 173.00 (C=O). **³¹P NMR δ (121 MHz, ppm):** 21.70. **IR ν (cm⁻¹):** 1651 (br., C=O, C=C); 1250 (P=O); 1041 (br., P-O). **MS m/z (%):** 400 (100, [M+H]⁺); 402 (35, [M+H+2]⁺). **Chromatography:** Rf = 0.29 (Hex/EtOAc 20/80). **Yield:** 92%. Yellow oil.

Dimethyl [allyl(chloroacetyl)amino]furan-2-ylmethyl phosphonate (21i/36a)

¹H NMR δ (300 MHz, ppm): 3.73 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 3.83 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 4.07 (1H, d, J_{AB} = 12.7 Hz, $C\underline{H}_AH_BCl$); 4.11-4.19 (1H, multiplet, $C\underline{H}_AH_BN$); 4.17 (1H, d, J_{AB} = 12.7 Hz, $CH_A\underline{H}_BCl$); 4.37-4.45 (1H, multiplet, $CH_A\underline{H}_BN$); 4.91-5.01 (2H, multiplet, =CH_2); 5.30-5.43 (1H, multiplet, $C\underline{H}=CH_2$); 6.38 (1H, s (br.), CH=); 6.41 (1H, d, J_{HP} = 26.4 Hz, CHP); 6.70 (1H, d, J = 3.0 Hz, =CHC_q); 7.42 (1H, d, J = 1.7 Hz, =CHO). **¹³C NMR δ (75 MHz, ppm):** 41.37 (CH_2Cl); 47.34 (d, J_{CP} = 162.7 Hz, CHP); 47.88 (CH_2N); 53.63 (d, J_{CP} = 8.1 Hz, OCH_3); 53.80 (d, J_{CP} = 6.9 Hz, OCH_3); 110.94 (=CH); 112.81 (d, J_{CP} = 3.5 Hz, =$\underline{C}HC_q$); 116.31 (=CH_2); 133.12 ($\underline{C}H=CH_2$); 143.49 (=CHO); 145.54 (d, J_{CP} = 10.4 Hz, =C_q); 167.25 (d, J_{CP} = 3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 20.77. **IR ν (cm⁻¹):** 1665 (br., C=O, C=C); 1251 (P=O); 1041 (br., P-O). **MS m/z (%):** 189 (100); 322 (26, [M+H]⁺); 324 (9, [M+H+2]⁺). **Chromatography:** Rf = 0.42 (Hex/EtOAc 20/80). **Yield:** 99%. Yellow oil.

Diethyl [allyl(chloroacetyl)amino]furan-2-ylmethyl phosphonate (21j)

¹H NMR δ (300 MHz, ppm): 1.22 (3H, d, J = 7.2 Hz, CH_3); 1.35 (3H, d, J = 7.2 Hz, CH_3); 3.98-4.23 (7H, multiplet, 2x OCH_2, CH_2Cl, $NC\underline{H}_AH_B$); 4.40-4.49 (1H, multiplet, $NCH_A\underline{H}_B$); 4.87-5.00 (2H, multiplet, =CH_2); 5.27-5.42 (1H, multiplet, $C\underline{H}=CH_2$); 6.33-6.39 (1H, multiplet, CH=); 6.40 (1H, d, J_{HP} = 22.6 Hz, CHP); 6.71 (1H, d, J = 2.8 Hz, =CHC_q); 7.42 (1H, ~d, J = 1.4 Hz, =CHO). **¹³C NMR δ (75 MHz, ppm):** 16.24 (d, J_{CP} = 5.8 Hz, CH_3); 16.42 (d, J_{CP} = 5.8 Hz, CH_3); 41.34 (CH_2Cl); 47.68 (d, J_{CP} = 161.5 Hz, CHP); 47.85 (CH_2N); 63.21 (d, J_{CP} = 6.9 Hz, OCH_2); 63.43 (d, J_{CP} = 6.9 Hz, OCH_2); 110.89 (=CH); 112.72 (d, J_{CP} = 3.5 Hz, =$\underline{C}HC_q$); 116.21 (=CH_2); 133.29 ($\underline{C}H=CH_2$); 143.34 (=CHO); 145.80 (d, J_{CP} = 10.4 Hz, =C_q); 167.19 (d, J_{CP} = 3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 18.12. **IR ν (cm⁻¹):** 1661 (br., C=O, C=C); 1249 (P=O); 1034 (br., P-O). **MS m/z (%):** 217 (100); 350 (20, [M+H]⁺); 352 (7, [M+H+2]⁺). **Yield:** 99%. Yellow oil.

Dimethyl [allyl(chlorobutyryl)amino]furan-2-ylmethyl phosphonate (25d/36b)

¹H NMR δ (300 MHz, ppm): 2.04-2.26 (2H, multiplet, CH_2); 2.45-2.66 (2H, multiplet, CH_2CO); 3.64 (2H, t, J = 6.4 Hz, CH_2Cl); 3.72 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 3.80 (3H, d, J_{HP} = 10.7 Hz, OCH_3); 4.09 (1H, dd (br.), J_{AB} = 18.1 Hz, J = 5.2 Hz, $NC\underline{H}_AH_B$); 4.32 (1H, ddd, J_{AB} = 18.1 Hz,

J = 5.2 Hz, J = 2.2 Hz, NCH$_A$$\underline{H}$$_B$); 4.87-4.99 (2H, multiplet, =CH$_2$) 5.35 (1H, multiplet, =CH); 6.36 (1H, dd, J = 3.3 Hz, J = 1.8 Hz, C$\underline{H}$=CHO); 6.52 (1H, d, J$_{HP}$ = 23.1 Hz, CHP); 6.67 (1H, d, J = 3.3 Hz, CH=C$_q$); 7.41 (1H, d, J = 1.8 Hz, CHO). **^{13}C NMR δ (75 MHz, ppm):** 27.99 (CH$_2$); 30.09 ($\underline{C}$H$_2$CO); 44.54 (CH$_2$Cl); 46.80 (d, J$_{CP}$ = 163.8 Hz, CHP); 47.97 (CH$_2$N); 53.50 (d, J$_{CP}$ = 6,9 Hz, OCH$_3$); 53.84 (d, J$_{CP}$ = 6,9 Hz, OCH$_3$); 110.92 ($\underline{C}$H=CHO); 112.55 (d, J$_{CP}$ = 3.5 Hz, $\underline{C}$H=C$_q$); 116.05 (=CH$_2$); 133.35 (=CH); 143.32 (CHO); 146.14 (d, J$_{CP}$ = 10,4 Hz, C$_q$O); 172.67 (d, J$_{CP}$ = 3.5 Hz, C=O). **^{31}P NMR δ (121 MHz, ppm):** 21.70. **IR ν (cm^{-1}):** 1651 (C=O); 1252 (P=O); 1040 (br., P-O). **MS m/z (%):** 350 (100, [M+H]$^+$); 352 (18, [M+H+2]$^+$). **Chromatography:** Rf = 0.34 (EtOAc). **Yield:** 88%. Yellow oil.

Dimethyl (allylisobutyrylamino)furan-2-ylmethyl phosphonate (36c)

^{1}H NMR δ (300 MHz, ppm): 1.11 (d, 3H, J = 6.6 Hz, CH$_3$); 1.15 (d, 3H, J = 6.6 Hz, CH$_3$); 2.76 (septet, 1H, J = 6.6 Hz, CH); 3.71 (d, 3H, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.79 (d, 3H, J$_{HP}$ = 10.7 Hz, OCH$_3$); 4.08 (dd, 1H, J$_{AB}$ = 18.3 Hz, J = 4.9 Hz, NCH$_A$$\underline{H}$$_B$); 4.35 (ddd, 1H, J$_{AB}$ = 18.3 Hz, J = 4.9 Hz, J = 1.7 Hz NCH$_A$$\underline{H}$$_B$); 4.84 (dd, 1H, J = 17.1 Hz, J$_{gem}$ = 1,1 Hz, =CH$_{cis}$$\underline{H}$$_{trans}$); 4.90 (dd, 1H, J = 10.5 Hz, J = 1.1 Hz, =C$\underline{H}$$_{cis}H_{trans}$); 5.40 (ddt, 1H, J$_{trans}$ = 17.1 Hz, J$_{cis}$ = 10.5 Hz, J = 4.9 Hz, =CH); 6.34 (dd, 1H, J = 3.3 Hz, J = 1.9 Hz, C$\underline{H}$=CHO); 6.58 (d, 1H, J$_{HP}$ = 23.1 Hz, CHP); 6.66 (d (br.), 1H, J$_{vic}$ = 3.3 Hz, CH=C$_q$); 7.39 (d, 1H, J = 1.8 Hz, CHO). **^{13}C NMR δ (75 MHz, ppm):** 19.04 (CH$_3$); 19.97 (CH$_3$); 30.77 (CH); 46.35 (d, CHP, J$_{CP}$ = 162.7 Hz); 47.65 (CH$_2$N); 53.53 (d, OCH$_3$, J$_{CP}$ = 6.9 Hz); 53.81 (d, OCH$_3$, J$_{CP}$ = 6.9 Hz); 110.82 ($\underline{C}$H=CHO); 112.44 (d, $\underline{C}$H=C$_q$, J$_{CP}$ = 3.5 Hz); 115.11 (=CH$_2$); 133.93 (=CH); 143.18 (CHO); 146.22 (d, C$_q$O, J$_{CP}$ = 10.4 Hz); 178.26 (d, C$_q$=O, J$_{CP}$ = 2.3 Hz). **^{31}P NMR δ (121 MHz, ppm):** 22.01. **IR ν (cm^{-1}):** 1652 (C=O); 1222 (P=O); 1044 (P-O). **MS m/z (%):** 316 (100, [M+H]$^+$). **Mp.:** 43-44°C. **Chromatography:** Rf = 0.34 (EtOAc). **Yield:** 88%. Yellow crystals.

Dimethyl [allyl(2,2-dichloro-acetyl)amino]furan-2-ylmethyl phosphonate (36d)

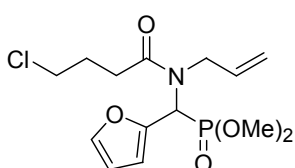**^{1}H NMR δ (300 MHz, ppm):** 3.74 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.84 (3H, d, J$_{HP}$ = 11.0 Hz, OCH$_3$); 4,15 (1H, dd (br.), J$_{AB}$ = 18,7 Hz, J = 5.0 Hz, NC$\underline{H}$$_AH_B$); 4.48 (1H, ddd, J$_{AB}$ = 18.7 Hz, NCH$_A$$\underline{H}$$_B$); J = 4.1 Hz, J = 2.0 Hz, 4.91-5.07 (2H, multiplet, =CH$_2$); 5.45 (1H, multiplet, =CH); 6.25 (1H, s, CHCl$_2$); 6.36 (1H, d, J$_{HP}$ = 22.6 Hz, CHP); 6.38 (1H, dd, J$_{vic,CH=Cq}$ = 3.1 Hz, J$_2$ = 2.1 Hz, C$\underline{H}$=CHO); 6.73 (1H, d, J$_{vic}$ = 3.1 Hz, CH=C$_q$); 7.43 (1H, d, J = 1.4 Hz, CHO); **^{13}C NMR δ (75 MHz, ppm):** 47.75 (CH$_2$N); 48.13 (d, CHP, J$_{CP}$ = 161.5 Hz); 53.70 (d, OCH$_3$, J$_{CP}$ = 6.9 Hz); 53.98 (d, OCH$_3$, J$_{CP}$ = 5.8 Hz); 64.20 (CHCl$_2$); 111.00 ($\underline{C}$H=CHO); 113.25 (d, $\underline{C}$H=C$_q$, J$_{CP}$ = 3.4 Hz); 116.47 (=CH$_2$); 132.80 (=CH); 143.77 (CHO); 144.97 (d, C$_q$O, J$_{CP}$ = 9.2 Hz); 164.80 (d, C$_q$=O, J$_{CP}$ = 3.5 Hz). **^{31}P NMR δ (121 MHz, ppm):** 20.20. **IR ν (cm^{-1}):** 1672 (C=O); 1261 (P=O); 1053, 1040 (P-O). **MS m/z (%):** 356 (100, [M+H]$^+$); 358 (68, [M+H+2]$^+$); 360 (11, [M+H+4]$^+$). **Mp.:** 59-60°C. **Chromatography:** Rf = 0.31 (Hex/EtOAc 40/60). **Yield:** 96%. Yellow Crystals.

4.2 One-pot phosphonylation of *N*-acyliminium ions

4.2.1 General procedure

5 Mmol of imine was dissolved in 10 ml of THF in a round bottom flask under a nitrogen atmosphere at temperature T. Then, 0.57 g (1 eq., 5 mmol) of chloroacetyl chloride was added dropwise using a syringe. The mixture was stirred for t minutes at temperature T before 1 eq. (5 mmol) of trimethyl or triethyl phosphite was added. Then the mixture was heated very fast and refluxed for 2 more hours using a single tube cooler. CAUTION: during this reaction, methyl chloride is liberated from the reaction mixture. Therefore, the reaction should be performed in a properly working hood. Finally, the solvent was removed under reduced pressure and the *N*-chloroacetyl aminoalkyl phosphonates could be obtained in pure form after column chromatography. (Parameters t and T are given for each individual derivative in the section below).

Dimethyl (2*E*)-1-[(chloroacetyl)anilino]-3-phenylprop-2-enyl phosphonate (21a)

Procedure: T = 0°C; t = 10 minutes.

¹H NMR δ (300 MHz, ppm): 3.77 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.78 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$); 3.82 (2H, s, CH$_2$Cl); 5.59 (1H, dd, J_{HP} = 19.4 Hz, J = 9.8 Hz, CHP); 6.09 (1H, J = 15.8 Hz, J = 9.7 Hz, J_{HP} = 6.3 Hz, =CH); 66.76 (1H, J = 15.8 Hz, J_{HP} = 3.0 Hz, =CH); 7.22-7.51 (10 H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 42.09 (CH$_2$Cl); 52.89 (d, J_{CP} = 8.1 Hz, OCH$_3$); 53.98 (d, J_{CP} = 6.9 Hz, OCH$_3$); 57.70 (d, J_{CP} = 158.0 Hz, CHP); 119.34 (d, J_{CP} = 2.3 Hz, =CH); 126.82, 128.50, 128.64, 129.56, 129.72, 129.86 (CH$_{arom}$); 135.82 (C$_{q,arom}$); 137.24 (d, J_{CP} = 13.9 Hz, =CHPh); 138.49 (C$_{q,arom}$); 166.02 (d, J_{CP} = 2.3 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 23.57. **IR ν (cm⁻¹):** 1677, 1663 (C=O, C=C); 1259 (P=O); 1047, 1023 (P-O). **MS m/z (%):** 225 (100); 284 (34); 394 (31, [M+H]⁺); 396 (11, [M+H+2]⁺). **Chromatography:** Rf = 0.25 (Hex/EtOAc 20/80). **Mp.:** 91-92°C. **Yield:** 43%. Brown crystals.

Dimethyl (2*E*)-1-[benzyl(chloroacetyl)amino]-3-phenylprop-2-enyl phosphonate (21b)

Procedure: T = -40°C; t = 10 minutes. **Yield:** 55%. Yellow oil. Spectral data can be found in chapter 4, section 4.1.

Diethyl (2*E*)-1-[benzyl(chloroacetyl)amino]-3-phenylprop-2-enyl phosphonate (21c)

Procedure: T = -40°C; t = 10 minutes.
¹H NMR δ (300 MHz, ppm): 1.27 (3H, t, J = 6.9 Hz, CH$_3$); 1.32 (3H, t, J = 6.9 Hz, CH$_3$); 3.88 (1H, d, J_{AB} = 12.7 Hz, CH$_A$H$_B$Cl); 3.98 (1H, d, J_{AB} = 12.7 Hz, CH$_A$H$_B$Cl); 4.06-4.23 (4H, multiplet, OCH$_2$); 4.88 (1H, d, J_{AB} = 18.2 Hz, CH$_A$H$_B$Ph); 5.10 (1H, d, J_{AB} =

18.2 Hz, CH$_A$<u>H$_B$</u>Ph); 5.73 (1H, dd, J$_{HP}$ = 20.6 Hz, J = 9.2 Hz, CHP); 6.09-6.20 (1H, multiplet, =CH); 6.77 (1H, dd, J = 16.0 Hz, J$_{HP}$ = 2.8 Hz); 7.16-7.32 (10 H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.48 (CH$_3$); 16.53 (CH$_3$); 41.61 (CH$_2$Cl); 49.62 (CH$_2$Ph); 54.86 (d, J$_{CP}$ = 156.3 Hz, CHP); 62.84 (d, J$_{CP}$ = 6.4 Hz, OCH$_2$); 63.42 (d, J$_{CP}$ = 5.8 Hz, OCH$_2$); 119.43 (=CH); 126.03 (CH$_{arom}$); 126.69 (CH$_{arom}$); 127.69 (CH$_{arom}$); 128.25 (CH$_{arom}$); 128.44 (CH$_{arom}$); 128.62 (CH$_{arom}$); 129.05 (CH$_{arom}$); 135.93 (C$_{q,arom}$); 137.03 (C$_{q,arom}$); 137.15 (d, J$_{CP}$ = 13.3 Hz, =CH); 167.44 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 20.99. **IR ν (cm^{-1}):** 1665 (C=O; C=C); 1248 (P=O); 1050 (P-O). **MS m/z (%):** 253 (100); 436 (53, [M+H]$^+$); 438 (15, [M+H+2]$^+$). **Chromatography:** Rf = 0.33 (Hex/EtOAc/MeOH 78/20/2). **Yield:** 46%. Yellow oil.

Dimethyl (2*E*)-1-[benzyl(chlorobutyryl)amino]-3-phenylprop-2-enyl-phosphonate (25a)

Procedure: T = -40°C; t = 10 minutes.

^{1}H NMR δ (300 MHz, ppm): 2.01-2.21 (2H, multiplet, CH$_2$); 2.30-2.62 (2H, multiplet, CH$_2$CO); 3.42-3.60 (2H, multiplet, CH$_2$Cl); 3.76 (3H, d, J$_{HP}$ = 11.0 Hz, OCH$_3$); 3.79 (3H, J$_{HP}$ = 10.7 Hz, OCH$_3$); 4.82 (1H, d, J$_{AB}$ = 17.9 Hz, C<u>H$_A$</u>H$_B$Ph); 4.99 (1H, d, J$_{AB}$ = 17.9 Hz, CH$_A$<u>H$_B$</u>Ph); 5.71 (1H, dd, J$_{HP}$ = 20.6 Hz, J = 9.4 Hz, CHP); 6.12-6.23 (1H, multiplet, =CH); 6.72 (1H, dd, J = 15.7 Hz, J$_{HP}$ = 3.0 Hz); 7.14-7.36 (10 H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 28.00 (CH$_2$); 30.22 (CH$_2$CO); 44.45 (CH$_2$Cl); 49.91 (NCH$_2$); 53.04 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.97 (d, J$_{CP}$ =6.9 Hz, OCH$_3$); 54.41 (d, J$_{CP}$ = 156.3 Hz, CHP); 119.96 (=CH); 126.21, 126.72, 127.12, 127.44, 127.74, 128.36, 128.60, 128.87 (CH$_{arom}$); 136.00 (C$_{q,arom}$); 136.95 (d, J$_{CP}$ = 13.9 Hz, =CH); 137.37 (C$_{q,arom}$); 162.83 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 24.49. **IR ν (cm^{-1}):** 1668 (C=O; C=C); 1250 (P=O); 1030 (br., P-O). **MS m/z (%):** 436 (100, [M+H]$^+$); 438 (34, [M+H+2]$^+$). **Chromatography:** Rf = 0.22 (EtOAc). **Yield:** 38%. Yellow oil.

Dimethyl (2*E*)-1-[allyl(chloroacetyl)amino]-3-phenylprop-2-enyl-phosphonate (21e)

Procedure: T = 20°C; t = 20 minutes. **Yield:** 41%. Spectral data can be found in chapter 4, section 4.1.

Dimethyl (2*E*)-1-[allyl(chlorobutyryl)amino]-3-phenylprop-2-enyl-phosphonate (25b)

Procedure: T = rt; t = 10 minutes. **Yield:** 45%. Spectral data can be found in chapter 4, section 4.1.

Dimethyl (2*E*)-1-[(chloroacetyl)isopropylamino]-3-phenylprop-2-enyl phosphonate (21f)
Dimethyl 3-[(chloroacetyl)isopropylamino]-1-phenylprop-2-enyl phosphonate (267a)

Procedure: T = -20°C; t = 10 minutes. **Yield:** 27%. Yellow oil. Spectral data can be found in chapter, section 4.1.

The corresponding 1,4-adduct could be recovered from the reaction mixture in 8% yield using colum chromatography:

¹H NMR δ (300 MHz, ppm): 1.10 (3H, d, J = 8.3 Hz, CH₃); 1.12 (3H, d, J = 7.2 Hz, CH₃); 3.07 (3H, d, J$_{HP}$ = 10.7 Hz, OCH₃); 3.72 (3H, d, J$_{HP}$ = 10.7 Hz, OCH₃); 3.99 (1H, dd, J$_{HP}$ = 24.9 Hz, J = 9.2 Hz, CHP); 4.10 (2H, s, CH₂Cl); 4.35-4.75 (1H, multiplet, CHN); 5.95-6.07 (1H, multiplet, =CH); 6.24 (1H, dd, J$_{trans}$ = 13.8 Hz, J$_{HP}$ = 4.1 Hz, =CHN); 7.30-7.40 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 19.89 (CH₃); 20.00 (CH₃); 42.32 (CH₂Cl); 46.07 (d, J$_{CP}$ = 146.5 Hz, CHP); 46.94 (CHN); 53.25 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 53.83 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 127.93, 128.73, 128.82, 129.12 (CH$_{arom}$, =CH); 134.31 (C$_{q,arom}$); 165.71 (C=O).). **³¹P NMR δ (121 MHz, ppm):** 26.61. **IR ν (cm⁻¹):** 1668, 1647 (C=O, C=C); 1252 (P=O); 1032 (P-O). **MS m/z (%):** 250 (23); 284 (15); 360 (100, [M+H]⁺); 362 (34, [M+H+2]⁺). **Chromatography:** Rf = 0.19 (Hex/EtOAc 20/80). **Yield:** 8%. Yellow oil.

Dimethyl (chloroacetyl)anilinofuran-2-ylmethyl phosphonate (21g)

Procedure: T = 0°C; t = 10 minutes.

¹H NMR δ (300 MHz, ppm): 3.73 (3H, d, J$_{HP}$ = 3.7 Hz, OCH₃); 3.81 (3H, d, J$_{HP}$ = 11.0 Hz, OCH₃); 3.81 (2H, s, CH₂Cl); 6.26-6.28 (1H, multiplet, =CH); 6.35-6.36 (1H, multiplet, =C$\underline{H}$C$_q$O); 6.57 (1H, d, J$_{HP}$ = 22.6 Hz, CHP); 7.28-7.39 (6H, multiplet, CH$_{arom}$, =CHO). **¹³C NMR δ (75 MHz, ppm):** 42.23 (CH₂Cl); 50.46 (d, J$_{CP}$ = 163.8 Hz, CHP); 53.28 (d, J$_{CP}$ = 8.1 Hz, OCH₃); 53.96 (d, J$_{CP}$ = 5.8 Hz, OCH₃); 110.82 (=CH); 113.47 (d, J$_{CP}$ = 2.3 Hz, =CHC$_q$O); 129.23 (CH$_{arom}$); 129.44 (CH$_{arom}$); 137.63 (C$_{q,arom}$); 143.23 (=CHO); 145.32 (d, J$_{CP}$ = 9.2 Hz, =C$_q$O); 166.32 (C=O). **³¹P NMR δ (121 MHz, ppm):** 20.55. **IR ν (cm⁻¹):** 1677 (C=O); 1238 (br., P=O); 1035 (br., P-O). **MS m/z (%):** 358 (100, [M+H]⁺); 360 (33, [M+H+2]⁺). **Chromatography:** Rf = 0.24 (Hex/EtOAc 70/30). **Yield:** 35%. Brown oil.

Dimethyl [benzyl(chloroacetyl)amino]furan-2-ylmethyl phosphonate (21h)

Procedure: T = 0°C; t = 10 minutes. **Yield:** 57%. Spectral data can be found in chapter 4, section 4.1.

Dimethyl [allyl(chloroacetyl)amino]furan-2-ylmethyl phosphonate (21i/36a)

Procedure: T = 0°C; t = 10 minutes. **Yield:** 43%. Spectral data can be found in chapter 4, section 4.1.

Diethyl [benzyl(chloroacetyl)amino]phenylmethyl phosphonate (21k)
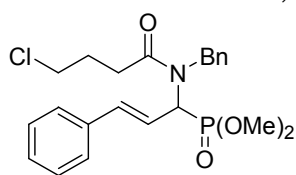
Procedure: T = 20°C; t = 30 minutes.

¹H NMR δ (300 MHz, ppm): 1.12 (3H, t, J = 7.2 Hz, CH₃); 1.31 (3H, t, J = 7.2 Hz, CH₃); 3.79 (1H, d, J$_{AB}$ = 12.7 Hz, C$\underline{H}$$_AH_B$Cl); 3.90 (1H, d, J$_{AB}$ = 12.7 Hz, CH$_A$$\underline{H}$$_B$Cl); 3.91-4.21 (4H, multiplet, OCH₂); 4.83 (1H, d, J$_{AB}$ = 18.2 Hz, C$\underline{H}$$_AH_B$N); 5.08 (1H, d, J$_{AB}$ = 18.2 Hz,

CH$_A$H$_B$N); 6.35 (1H, d, J$_{HP}$ = 22.6 Hz, CHP); 6.77-6.79 (2H, multiplet, CH$_{arom}$); 7.10-7.12 (2H, multiplet, CH$_{arom}$); 7.23-7.29 (4H, multiplet, CH$_{arom}$); 7.62-7.65 (2H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.16 (CH$_3$); 16.33 (CH$_3$); 41.81 (CH$_2$Cl); 49.34 (CH$_2$N); 54.53 (d, J$_{CP}$ = 158.1 Hz; CHP); 62.75, 63.23, 63.31 (OCH$_2$); 125.64, 127.20, 128.34, 128.56, 128.81, 130.41, 130.51 (CH$_{arom}$); 132.99 (C$_{q,arom}$); 136.77 (C$_{q,arom}$); 167.87 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 20.45. **IR ν (cm^{-1}):** 1663 (C=O); 1251 (P=O); 1040 (br., P-O). **Chromatography :** Rf = 0.39 (Hex/EtOAc 80/20). **Yield:** 39%. Yellow oil.

4.2.2 Side products

N-benzyl-2-chloro-*N*-(2-methylprop-1-enyl) acetamide (265)

This is the major component of the reaction mixture using the general procedure described above (T = -40°C, t = 10 minutes) with imine **19ah**. However, the same product was obtained without adding trimethyl phosphite, but using the following procedure: 0.81 g (5 mmol) of imine **19ah** was dissolved in 10 ml of dry THF in a round bottom flask under a nitrogen atmosphere at room temperature. Then, 0.57 g (5 mmol) of chloroacetyl chloride was added dropwise using a syringe. The mixture was stirred for 30 minutes at room temperature and then refluxed for 2 more hours. Finally, the solvent was removed under reduced pressure and the enamide could be recovered as white crystals.

^{1}H NMR δ (300 MHz, ppm): 1.40 (3H, d, J = 1.2 Hz, CH$_3$); 1.68 (3H, d, J = 1.2 Hz, CH$_3$); 4.03 (2H, s, CH$_2$Cl); 4.61 (2H, s, CH$_2$N); 5.79-5.81 (1H, multiplet, =CH); 7.25-7.31 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 17.34 (CH$_3$); 21.74 (CH$_3$); 42.23 (CH$_2$Cl); 51.37 (CH$_2$N); 121.98 (=CH); 127.49 (CH$_{arom}$); 128.39 (2 x CH$_{arom}$); 128.80 (2 x CH$_{arom}$); 136.41 (C$_{q,arom}$); 138.73 (=C$_q$); 166.42 (C=O). **IR ν (cm^{-1}):** 1661 (br. C=O, C=C). **MS m/z (%):** 238 (100, [M+H]$^+$); 240 (39, [M+H+2]$^+$). **Mp.:** 96-97°C. **Yield:** 95%. White crystals.

N-benzyl-2-chloro-*N*-{[(1*R*,5*R*)-6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-ylidene]methyl} acetamide (266)

Formed as an undesired side product from imine **19u** using the general procedure (T = 20°C; t = 45 minutes).

^{1}H NMR δ (300 MHz, ppm): 0.62 (3H, s, CH$_3$); 1.24 (3H, s, CH$_3$); 1.34 (1H, d, J = 8.5 Hz, CH$_A$H$_B$); 2.31 (1H, ddd, J = 6.6 Hz, J = 5.8 Hz, J = 5.5 Hz, CH-CH=); 2.45 (1H, ddd, J = 8.8 Hz, J = 5.5 Hz, J = 5.5 Hz, CH$_A$H$_B$); 2.63 (1H, dd, J = 5.5 Hz, J = 5.8 Hz, CH-C$_{quat}$=); 4.00 (1H, d, J$_{AB}$ = 13.2 Hz, CH$_A$H$_B$Cl); 4.09 (1H, d, J$_{AB}$ = 13.2 Hz, CH$_A$H$_B$Cl); 4.54 (1H, d, J$_{AB}$ = 14.1 Hz, CH$_A$H$_B$N); 4.66 (1H, d, J$_{AB}$ = 14.1 Hz, CH$_A$H$_B$N); 5.82 (1H, s, =CHN); 5.99 (1H, d, J = 8.5 Hz, =CH-C$_{quat}$); 6.43 (1H, dd, J = 8.5 Hz, J = 6.6 Hz, =CH-CH); 7.22-7.33 (5H, m, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 22.03 (CH$_3$); 25.88 (CH$_3$); 35.96 (CH$_2$); 41.97 (CH$_2$Cl);

43.27 ($\underline{C}$H-CH=); 44.66 ($\underline{C}$H-C$_{quat}$=); 44.80 (C$_{quat}$); 51.91 (CH$_2$N); 119.69 (=CHN); 123.70 (=CH-$\underline{C}$$_{quat}$); 127.51 (CH$_{arom}$); 128.36 (2xCH$_{arom}$); 128.88 (2xCH$_{arom}$); 136.56 (C$_{quat,arom}$); 140.99 (=$\underline{C}$H-CH); 145.93 (=C$_{quat}$); 166.36 (C=O). **IR ν (cm⁻¹):** 1671 (C=O); 1639 (C=C). **MS m/z (%):** 316 (100, M⁺+H); 318 (31, M⁺+H+2). **Chromatography:** Rf = 0.80 (Hex/EtOAc 60/40). **Yield:** 44%.
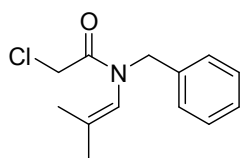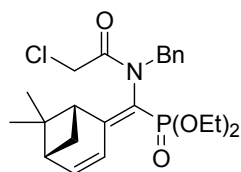
Dimethyl benzylamino[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methylphosphonate

Formed as an undesired side product from imine **19u** using the general procedure (T = 20°C; t = 45 minutes). Mixture of two diastereomers (ratio 47:53). Spectral data can be found in chapter 4, section 3.3.

4.2.3 Preparation of 3-imino-1-phenylpropyl phosphonates

To a mixture of 2.7 mmol of diethyl (3-oxo-1-phenyl-propyl) phosphonate **217** (see chapter 4, section 3.2.5) in 7 ml of dry dichloromethane, 1 equivalent of amine (or 1.1 equivalent in case a volatile amine is used) wass added together with 2 equivalents of MgSO$_4$. The resulting mixture was stirred for 14 hours at room temperature. The corresponding imines were obtained after filtration of the solids and evaporation of the solvent under reduced pressure.

Diethyl 3-(isopropylimino)-1-phenylpropyl phosphonate (216a)

¹H NMR δ (300 MHz, ppm): 0.96 (3H, d, J = 6.3 Hz, CHC$\underline{H}$$_3$); 1.04 (3H, d, J = 6.3 Hz, CHC$\underline{H}$$_3$); 1.12 (3H, t, J = 7.2 Hz, CH$_3$); 1.27 (3H, t, J = 7.2 Hz, CH$_3$); 2.82-3.04 (2H, multiplet, CH$_2$); 3.14 (1H, septet, J = 6.3 Hz, NCH); 3.41 (1H, ddd, J$_{HP}$ = 22.5 Hz, J = 10.5 Hz, J = 5.4 Hz, CHP); 3.72-4.12 (4H, multiplet, OCH$_2$); 7.21-7.39 (5H, multiplet, CH$_{arom}$); 7.48 (1H, t, J = 4.8 Hz, N=CH). **¹³C NMR δ (75 MHz, ppm):** 16.26 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.40 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 23.85 (CH$\underline{C}$H$_3$); 23.88 (CH$\underline{C}$H$_3$); 35.63 (d, J$_{CP}$ = 2.3 Hz, CH$_2$); 41.99 (d, J$_{CP}$ = 138.5 Hz, CHP); 61.09 (NCH); 61.98 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 62.65 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 127.23 (d, J$_{CP}$ = 2.3 Hz, CH$_p$); 128.43 (d, J$_{CP}$ = 2.3 Hz, CH$_m$); 129.46 (d, J$_{CP}$ = 6.9 Hz, CH$_o$); 135.20 (d, J$_{CP}$ = 6.9 Hz, C$_q$); 159.01 (d, J$_{CP}$ = 17.3 Hz, N=CH). **³¹P NMR δ (121 MHz, ppm):** 28.13. **IR ν (cm⁻¹):** 1666 (N=C); 1245 (P=O); 1054, 1027 (P-O). **MS m/z (%):** 312 (100, [M+H]⁺). **Yield:** 87%. Orange oil.
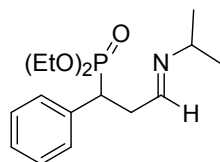
Diethyl 3-(allylimino)-1-phenylpropyl phosphonate (216c)

¹H NMR δ (300 MHz, ppm): 1.11 (3H, t, J = 7.2 Hz, CH$_3$); 1.28 (3H, t, J = 7.2 Hz, CH$_3$); 2.89-3.11 (2H, multiplet, CH$_2$); 3.41 (1H, ddd, J$_{HP}$ = 22.2 Hz, J = 10.2 Hz, J = 5.2 Hz, CHP); 3.71-4.14 (6H, multiplet, OCH$_2$, NCH$_2$); 4.85-5.02 (2H, multiplet, =CH$_2$); 5.76-5.90 (1H, multiplet, =CH); 7.24-7.38 (5H, multiplet, CH$_{arom}$); 7.54 (1H, t, J = 4.7 Hz, N=CH). **¹³C NMR δ (75 MHz, ppm):** 15.72 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 15.87 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 35.40 (CH$_2$); 40.97 (d, J$_{CP}$ = 138.5 Hz, CHP); 61.38 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 62.12 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 62.45 (NCH$_2$); 114.99 (=CH$_2$); 126.76 (CH$_p$); 127.96 (CH$_m$); 128.85 (d, J$_{CP}$ = 6.9 Hz,
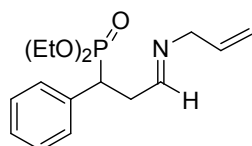
CH$_o$); 134.85 (d, J$_{CP}$ = 6.9 Hz, C$_q$); 135.05 (=CH); 162.33 (d, J$_{CP}$ = 16.2 Hz, N=CH). **31P NMR δ (121 MHz, ppm):** 28.19. **IR ν (cm^{-1}):** 1667 (N=C); 1245 (P=O); 1054, 1028 (P-O). **MS m/z (%):** 310 (100, [M+H]$^+$). **Yield:** 92%. Yellow oil.

Diethyl 3-(benzylimino)-1-phenylpropyl phosphonate (216d)
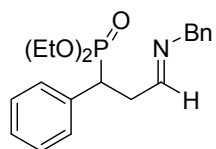
1H NMR δ (300 MHz, ppm): 1.11 (3H, t, J = 7.2 Hz, CH$_3$); 1.26 (3H, t, J = 7.2 Hz, CH$_3$); 2.89-3.09 (2H, multiplet, CH$_2$); 3.41 (1H, ddd, J$_{HP}$ = 22.4 Hz, J = 9.9 Hz, J = 5.5 Hz, CHP); 3.69-4.09 (4H, multiplet, OCH$_2$); 4.45 (2H, s, NCH$_2$); 7.18-7.43 (10H, multiplet, CH$_{arom}$); 7.64 (1H, t, J = 4.7 Hz, N=CH). **13C NMR δ (75 MHz, ppm):** 16.30 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.44 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 35.93 (d, J$_{CP}$ = 2.3 Hz, CH$_2$); 40.70 (d, J$_{CP}$ = 139.6 Hz, CHP); 62.06 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 62.75 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 64.77 (NCH$_2$); 126.80 (CH$_{arom}$); 127.31 (d, J$_{CP}$ = 3.5 Hz, CH$_p$); 127.69 (CH$_{arom}$); 128.34 (CH$_{arom}$); 128.60 (d, J$_{CP}$ = 2.3 Hz, CH$_m$); 129.50 (d, J$_{CP}$ = 6.9 Hz, CH$_o$); 135.38 (d, J$_{CP}$ = 6.9 Hz, C$_q$); 138.95 (C$_{q,arom}$); 163.11 (d, J$_{CP}$ = 17.3 Hz, N=CH). **31P NMR δ (121 MHz, ppm):** 28.21. **IR ν (cm^{-1}):** 1665 (N=C); 1243 (P=O); 1053, 1028 (P-O). **MS m/z (%):** 360 (100, [M+H]$^+$). **Yield:** 96%. Yellow oil.

4.2.4 Preparation of 3-(chloroacetylalkylamino)-1-phenylprop-2-enyl phosphonates (267b-d)

A mixture of 2.4 mmol of imine and 7 ml of dry THF was stirred at room temperature under a nitrogen atmosphere. Then, 2.4 mmol of chloroacetyl chloride in 2 ml of dry THF was added dropwise using a syringe. After stirring for 10 more minutes at room temperature, 1 equivalent of triethyl amine was added resulting in immediate precipitation of ammonium salts. After stirring for 1 hour at room temperature, the mixture was poured into 10 ml of a saturated NaHCO$_{3(aq)}$ solution and extracted with 10 ml of diethyl ether. The remaining water phase was extracted two times more with 5 ml of diethyl ether. The combined organic phases were dried using MgSO$_4$. The enamides were obtained in reasonable purity (80-90%) after filtration of the solids and evaporation of the solvent under reduced pressure. Further purification was performed using column chromatography.

Diethyl 3-(chloroacetylisopropylamino)-1-phenylprop-2-enyl phosphonate (267b)
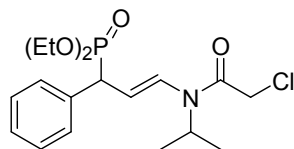
1H NMR δ (300 MHz, ppm): 1.08-1.14 (4H, multiplet, CH$_3$); 1.16 (3H, t, J = 7.2 Hz, CH$_3$); 1.28 (3H, t, J = 7.2 Hz, CH$_3$); 3.75-4.16 (5H, multiplet, OCH$_2$, CHP); 4.10 (2H, s, CH$_2$Cl); 4.70 (1H, septet (br.), J = 6.3 Hz, NCH); 6.03 (1H, ddd, J = 13.8 Hz, J = 8.8 Hz, J$_{HP}$ = 8.8 Hz, =CH); 6.22 (1H, dd, J = 13.8 Hz, J$_{HP}$ = 4.1 Hz, =CHN); 7.26-7.41 (5H, multiplet, CH$_{arom}$). **13C NMR δ (75 MHz, ppm):** 16.28 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.42 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 19.81 (CH$\underline{C}$H$_3$); 19.92 (CH$\underline{C}$H$_3$); 42.38 (CH$_2$Cl); 46.43 (d, J$_{CP}$ = 138.5 Hz, CHP); 46.93 (NCH); 62.42 (d, J$_{CP}$ = 6.9 Hz,

OCH$_2$); 63.06 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 127.45 (d, J$_{CP}$ = 15.0 Hz, =CHN); 127.69 (d, J$_{CP}$ = 3.5 Hz, =CH); 128.73, 128.80, 128.89 (CH$_{arom}$); 134.65 (d, J$_{CP}$ = 6.9 Hz, C$_{q,arom}$); 165.67 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 24.29. **IR ν (cm^{-1}):** 1678 (C=O); 1654 (C=C); 1247 (P=O); 1029 (br., P-O). **MS m/z (%):** 388 (100, [M+H]$^+$); 390 (32, [M+H+2]$^+$). **Mp.:** 76-78°C. **Chromatography:** Rf = 0.27 (EtOAc). **Yield:** 45%. Yellow crystals.

Spectral data of the corresponding dimethyl phosphonate **267a** can be found in chapter 4, section 4.2.1.

Diethyl 3-(allylchloroacetylamino)-1-phenylprop-2-enyl phosphonate (267c)

The product was found as a mixture of two rotamers (ratio 37:63). From the (H,H) coupling constants it was found that **267c** was exclusively formed in the (*E*)-geometry. Peaks of the Major rotamer are indicated as 'M'. Also most peaks of the minor 'm' isomer are indicated below.
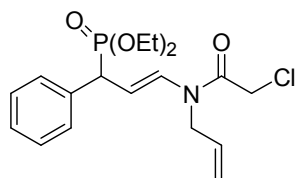
^{1}H NMR δ (300 MHz, ppm): 1.13 (3H, t, J = 7.2 Hz, CH$_3$, M); 1.26 (3H, t, J = 7.2 Hz, CH$_3$, M); 3.66-4.15 (2x5H, multiplet, OCH$_2$, CHP, m + M); 4.11 (2H, s, CH$_2$Cl, m); 4.17 (2H, s, CH$_2$Cl, M); 4.25-4.32 (2x2H, multiplet, NCH$_2$, m+M); 5.11-5.26 (2x2H, multiplet, =CH$_2$, m + M); 5.42-5.51 (1H, multiplet, =CH, m); 5.55 (1H, ddd, J = 13.5 Hz, J = 9.1 Hz, J$_{HP}$ = 9.1 Hz, =CH, M); 5.70-5.91 (2x1H, multiplet, C$\underline{H}$=CH$_2$, m+M); 6.75 (1H, dd, J = 13.5 Hz, J$_{HP}$ = 3.9 Hz, =CHN, M); 7.22-7.42 (2x5+2H, multiplet, CH$_{arom}$, m +M, =CHN, m). **^{13}C NMR δ (75 MHz, ppm):** 16.37 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.54 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 41.23 (CH$_2$Cl, M); 41.57 (CH$_2$Cl, m); 46.42 (NCH$_2$, M); 46.52 (d, J$_{CP}$ = 139.6 Hz, CHP, M); 46.79 (d, J$_{CP}$ = 140.8 Hz, CHP, m); 47.72 (NCH$_2$, m); 62.27 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$, m); 62.58 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$, M); 63.00 (d, J$_{CP}$ = 8.1 Hz, OCH$_2$, M); 108.46 (d, J$_{CP}$ = 8.1 Hz, =CH, m); 110.24 (d, J$_{CP}$ = 9.2 Hz, =CH, M); 117.15 (CH=$\underline{C}$H$_2$, m); 117.24 (CH=$\underline{C}$H$_2$, M); 127.365, 127.59, 128.81, 128.95, 129.04 (CH$_{arom}$, m+M); 129.15 (d, J$_{CP}$ = 15.0 Hz, =CHN, m); 129.80 (d, J$_{CP}$ = 13.9 Hz, =CHN, M); 131.35 ($\underline{C}$H=CH$_2$, m); 131.41 ($\underline{C}$H=CH$_2$, M); 135.74 (d, J$_{CP}$ = 5.8 Hz, $\underline{C}$$_q$CHP, M); 136.40 (d, J$_{CP}$ = 5.8 Hz, $\underline{C}$$_q$CHP, M); 164.97 (C=O, m); 165.16 (C=O, M). **^{31}P NMR δ (121 MHz, ppm):** 25.09 (M); 25.51 (m). **IR ν (cm^{-1}):** 1679 (C=O); 1650 (C=C); 1240 (P=O); 1053, 1028 (P-O). **MS m/z (%):** 386 (100, [M+H]$^+$); 388 (28, [M+H]$^+$+2). **Chromatography:** Rf = 0.23 (EtOAc). **Yield:** 31%. Yellow oil.

Diethyl 3-(benzylchloroacetylamino)-1-phenylprop-2-enyl phosphonate (267d)

The product was found as a mixture of two rotamers (ratio 29:71). From the (H,H) coupling constants it was found that **267d** was exclusively formed in the (*E*)-geometry. Peaks of the Major rotamer are indicated as 'M'. Also most peaks of the minor 'm' isomer are indicated below.
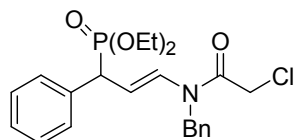
^{1}H NMR δ (300 MHz, ppm): 1.07 (3H, t, J = 7.2 Hz, CH$_3$, M); 1.17 (3H, t, J = 7.2 Hz, CH$_3$, M); 3.62-4.05 (5H, multiplet, OCH$_2$, CHP, m + M); 4.07 (2H, s, CH$_2$Cl, m); 4.24 (2H, s, CH$_2$Cl, M); 4.89 (2H, s (br.), NCH$_2$, M); 4.92 (2H, s (br.),

NCH$_2$, m); 5.38-5.45 (1H, multiplet, =CH, m); 5.51 (1H, ddd, J = 13.8 Hz, J = 9.4 Hz, J$_{HP}$ = 9.4 Hz, =CH); 6.75 (1H, dd, J = 13.8 Hz, J$_{HP}$ = 3.9 Hz, =CHN, M); 7.15-7.39 (10H, multiplet, CH$_{arom}$); 7.50 (1H, dd, J = 14.5 Hz, J$_{HP}$ = 3.6 Hz, =CHN, m). **^{13}C NMR δ (75 MHz, ppm):** 16.22 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.38 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 41.24 (CH$_2$Cl, M); 41.68 (CH$_2$Cl, m); 46.27 (d, J$_{CP}$ = 139.1 Hz, CHP, M); 46.53 (d, J$_{CP}$ = 139.1 Hz, CHP, m); 47.33 (NCH$_2$, M); 48.92 (NCH$_2$, m); 62.22 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$, m); 62.49 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$, M); 62.86 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$, M); 108.94 (d, J$_{CP}$ = 9.2 Hz, =CH, m); 111.24 (d, J$_{CP}$ = 8.1 Hz, =CH, M); 127.15, 127.34, 128.65, 128.79, 128.88 (CH$_{arom}$, m + M); 129.12 (br., =CHN, m); 129.68 (d, J$_{CP}$ = 15.0 Hz, =CHN, M); 135.20 (C$_{q,arom}$, m); 135.52 (d, J$_{CP}$ = 6.9 Hz, C$_q$CHP, M); 136.05 (C$_{q,arom}$, M); 165.41 (C=O, m); 165.52 (C=O, M). **^{31}P NMR δ (121 MHz, ppm):** 24.83 (M); 25.35 (m). **Chromatography:** Rf = 0.25 (EtOAc). **Yield:** 29%. Purity: ~90%. Yellow oil.

4.3 Synthesis of 4-phosphono β-lactams

4.3.1 Typical procedure for the synthesis of 4-phosphono-β-lactams 23

Using NaH as a base

0.24 g (6 mmol, 1.2 equiv.) of a NaH emulsion in mineral oil was washed three times with petroleum ether to remove the oil and then 15 ml of dry THF was added. Then 5 mmol of the corresponding *N*-chloroacetyl aminoalkyl phosphonate **21** in 5 ml of dry THF was added dropwise and the resulting mixture was refluxed for two or three hours, protected from moisture using a CaCl$_2$ tube. After cooling, the mixture was poured into 25 ml of water and extracted with 20 ml of diethyl ether. The remaining water phase was then washed two times with 10 ml of diethyl ether. The combined organic phases were dried using MgSO$_4$, and after filtration, the solvent was removed under reduced pressure.

Using LiHMDS as a base

A solution of 5 mmol of the *N*-chloroacetyl aminoalkyl phosphonate **21** in 15 ml of dry THF was stirred at room temperature under a nitrogen atmosphere. Then, 5.5 ml of LiHMDS (1.0 M in hexane) was added dropwise using a syringe. Stirring was continued for 1 h at room temperature and the mixture was poured into 20 ml of 0.5 M HCl$_{(aq)}$ and extracted with 15 ml of diethyl ether. The remaining water phase was then washed two times with 10 ml of diethyl ether. The combined organic phases were dried with MgSO$_4$, and after filtration the solvent was removed under reduced pressure.

Dimethyl 4-oxo-1-phenyl-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23a)
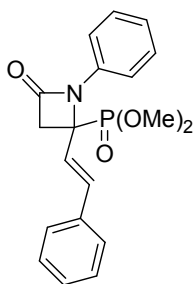
¹H NMR δ (300 MHz, ppm): 3.20 (1H, dd, J$_{AB}$ = 15.3 Hz, J$_{HP}$ = 5.8 Hz, C$\underline{H}$$_AH_B$); 3.63 (1H, dd, J$_{AB}$ = 15.3 Hz, J$_{HP}$ = 8.0 Hz, CH$_A$$\underline{H}$$_B$); 3.74 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.82 (3H, d, J$_{HP}$ = 11.6 Hz, OCH$_3$); 6.59 (1H, dd, J$_{trans}$ = 16.2 Hz, J$_{HP}$ = 9.4 Hz, =CH); 6.84 (1H, dd, J$_{trans}$ = 16.2 Hz, J$_{HP}$ = 2.8 Hz, =C$\underline{H}$Ph); 7.11 (1H, td, J = 7.4 Hz, J = 1.1 Hz, CH$_{para,PhN}$); 7.24-7.39 (7H, multiplet, CH$_{arom}$); 7.80 (2H, d, J = 8.0 Hz, CH$_{ortho,PhN}$). **¹³C NMR δ (75 MHz, ppm):** 49.42 (CH$_2$); 53.51 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 54.43 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 59.82 (d, J$_{CP}$ = 168.5 Hz, C$_q$P); 118.08 (2 x CH$_{ortho,PhN}$); 122.21 (d, J$_{CP}$ = 6.9 Hz, =CH); 124.45 (CH$_{para,PhN}$); 126.80 (2 x CH$_{arom}$); 128.65 (CH$_{arom}$); 128.71 (2 x CH$_{arom}$); 129.06 (2 x CH$_{arom}$); 134.25 (d, J$_{CP}$ = 9.2 Hz, =$\underline{C}$HPh); 135.38 (C$_{q,arom}$); 137.40 (C$_{q,arom}$); 163.41 (d, J$_{CP}$ = 8.1 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.19. **IR ν (cm⁻¹):** 1760 (C=O); 1253 (P=O); 1059, 1032 (P-O). **MS m/z (%):** 358 (100, [M+H]⁺). **Chromatography:** Rf = 0.21 (EtOAc). **Yield:** 90%. Orange oil.

Dimethyl 1-benzyl-4-oxo-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23b)

¹H NMR δ (300 MHz, ppm): 3.08 (1H, dd, C$\underline{H}$$_AH_BCO, J_{AB}$ = 14.6 Hz, J$_{HP}$ = 5.8 Hz); 3.47 (1H, dd, CH$_A$$\underline{H}$$_BCO, J_{AB}$ = 14.6 Hz, J$_{HP}$ = 8.3 Hz); 3.75 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.76 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 4.39 (1H, d, J$_{AB}$ = 15.3 Hz, C$\underline{H}$$_AH_B$Ph); 4.74 (1H, d, J$_{AB}$ = 15.3 Hz, CH$_A$$\underline{H}$$_B$Ph); 6.18 (1H, dd, J = 16.2 Hz, J$_{HP}$ = 8.5 Hz, =CH); 6.52 (1H, dd, J = 16.2 Hz, J$_{HP}$ = 3.3 Hz, =CHPh); 7.08-7.44 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 45.84 (CH$_2$Ph); 47.87 (CH$_2$CO); 53.52, 53.62, 53.85, 53.94 (OCH$_3$); 59.34 (d, J$_{CP}$ = 167.3 Hz, C$_q$P); 122.74 (d, J$_{CP}$ = 6.9 Hz, =CH); 126.58 (2 x CH$_{arom}$); 127.70 (CH$_{arom}$); 128.41 (CH$_{arom}$); 128.56 (2 x CH$_{arom}$); 128.92 (2 x CH$_{arom}$) 128.94 (2 x CH$_{arom}$); 134.20 (d, J$_{CP}$ = 9.2 Hz, =CHPh); 135.40 (C$_{q,arom}$); 136.70 (C$_{q,arom}$); 166.06 (d, J$_{CP}$ = 6.9 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.01. **IR ν (cm⁻¹):** 1754 (C=O); 1252 (P=O); 1056, 1022 (P-O). **MS m/z (%):** 372 (100, [M+H]⁺). **Mp.:** 115-116°C. **Chromatography:** Rf = 0.24 (Hex/EtOAc/MeOH 20/78/2). **Yield:** 75%. Colourless crystals.

Diethyl 1-benzyl-4-oxo-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23c)

¹H NMR δ (300 MHz, ppm): 1.31 (6H, t, J = 7.2 Hz, CH$_3$); 3.07 (1H, dd, J$_{AB}$ = 14.6 Hz, J$_{HP}$ = 5.8 Hz, C$\underline{H}$$_AH_B$CO); 3.47 (1H, dd, J$_{AB}$ = 14.6 Hz, J$_{HP}$ = 8.3 Hz, CH$_A$$\underline{H}$$_B$CO); 4.04-4.24 (4H, multiplet, OCH$_2$); 4.39 (1H, d, J$_{AB}$ = 15.1 Hz, C$\underline{H}$$_AH_B$Ph); 4,77 (1H, d, J$_{AB}$ = 15.1 Hz, CH$_A$$\underline{H}$$_B$Ph); 6,19 (1H, dd, J$_{trans}$ = 16.2 Hz, J$_{HP}$ = 8.3 Hz, =CH); 6.50 (1H, dd, J$_{trans}$ = 16.2 Hz, J$_{HP}$ = 3.6 Hz, =CHPh); 7.07-7.44 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.58 (CH$_3$); 45.81 (CH$_2$Ph); 47.81 (CH$_2$CO); 59.47 (d, J$_{CP}$ = 166.7 Hz, C$_{quat}$P); 63.13 (d, J$_{CP}$ = 7.5 Hz, OCH$_2$); 63.43 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 123.07 (d, J$_{CP}$ = 6.3 Hz, =CH); 126.57 (CH$_{arom}$); 127.68 (CH$_{arom}$); 128.35 (CH$_{arom}$); 128.61 (CH$_{arom}$); 128.94 (CH$_{arom}$); 132.34 (d, J$_{CP}$ = 9.2 Hz, =$\underline{C}$HPh); 135.60 (C$_{quat,arom}$); 136.96 (C$_{quat,arom}$); 166.21 (d,

J_{CP} = 7.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 21.70. **IR ν (cm⁻¹):** 1760 (C=O); 1249 (P=O); 1050, 1024 (P-O). **MS m/z (%):** 400 (100, [M+H]⁺). **Chromatography:** Rf = 0.31 (Hex/EtOAc/MeOH 20/78/2). **Yield:** 92%. Yellow oil.

Dimethyl 1-(4-methoxybenzyl)-4-oxo-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23d)

¹H NMR δ (300 MHz, ppm): 3.06 (1H, dd, C$\underline{H}_A$H$_B$CO, J_{AB} = 14.6 Hz, J_{HP} = 5.8 Hz); 3.45 (1H, dd, CH$_A$$\underline{H}_B$CO, J_{AB} = 14.6 Hz, J_{HP} = 8.0 Hz); 3.76 (3H, d, J_{HP} = 10.7 Hz, OCH₃); 3.77 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.78 (3H, s, OCH₃(Ph)); 4.32 (1H, d, J_{AB} = 15.1 Hz, C$\underline{H}_A$H$_B$Ph); 4.69 (1H, d, J_{AB} = 15.1 Hz, CH$_A$$\underline{H}_B$Ph); 6.16 (1H, dd, J = 16.2 Hz, J_{HP} = 8.8 Hz, =CH); 6.53 (1H, dd, J = 16.2 Hz, J_{HP} = 3.3 Hz, =CHPh); 6.84-6.90 (2H, multiplet, CH$_{arom}$); 7.11-7.38 (7H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 45.32 (CH₂Ph); 47.87 (CH₂CO); 53.61 (d, J_{CP} = 8.1 Hz, OCH₃); 53.97 (d, J_{CP} = 8.6 Hz, OCH₃); 55.30 (OCH₃(Ph)); 59.28 (d, J_{CP} = 167.3 Hz, C$_q$P); 113.99 (2x CH$_{arom}$); 122.88 (d, J_{CP} = 6.9 Hz, =CH); 126.63, 128.44, 128.59 (CH$_{arom}$); 128.74 (CH₂C$_{q,arom}$); 130.39 (CH$_{arom}$); 134.08 (d, J_{CP} = 9.2 Hz, =CHPh); 135.40 (C$_{q,arom}$); 159.19 (OC$_{q,arom}$); 166.00 (d, J_{CP} = 8.1 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.06. **IR ν (cm⁻¹):** 1756 (C=O); 1248 (P=O); 1036 (br., P-O). **MS m/z (%):** 402 (100, [M+H]⁺). **Chromatography:** Rf = 0.18 (EtOAc). **Yield:** 39%. Orange oil.

Dimethyl 1-allyl-4-oxo-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23e)

¹H NMR δ (300 MHz, ppm): 3.07 (1H, dd, J_{AB} = 14.6 Hz, J_{HP} = 5.8 Hz, C$\underline{H}_A$H$_B$C=O); 3.44 (1H, dd, J_{AB} = 14.6 Hz, J_{HP} = 8.0 Hz, CH$_A$$\underline{H}_B$C=O); 3.83 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.85 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.88-4.12 (2H, multiplet, CH₂N); 5.24 (1H, dd, J_{cis} = 10.2 Hz, J = 1.1 Hz, =C$\underline{H}_A$H$_B$); 5.31 (1H, dd, J_{trans} = 17.1 Hz, J = 1.4 Hz, =CH$_A$$\underline{H}_B$); 6.03-5.91 (1H, multiplet, C$\underline{H}$=CH₂); 6.47 (1H, dd, J_{trans} = 16.2 Hz, J_{HP} = 8.3 Hz, =CH); 6.79 (1H, dd, J_{trans} = 16.2 Hz, J_{HP} = 3.6 Hz, =CHPh); 7.27-7.42 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 44.97 (CH₂N); 47.85 (CH₂C=O); 53.79 (d, J_{CP} = 7.5 Hz, OCH₃); 54.07 (d, J_{CP} = 6.9 Hz, OCH₃); 58.88 (d, J_{CP} = 167.3 Hz, C$_q$-P); 118.35 (=CH₂); 123.02 (d, J_{CP} = 6.9 Hz, =CH); 126.81 (2 x CH$_{arom}$); 128.68 (CH$_{arom}$); 128.84 (2 x CH$_{arom}$); 132.57 ($\underline{C}$H=CH₂); 134.18 (d, J_{CP} = 9.2 Hz, =$\underline{C}$HPh); 135.62 (d, J_{CP} = 1.7 Hz, C$_{q,arom}$); 165.97 (d, J_{CP} = 7.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.23. **IR ν (cm⁻¹):** 1760 (C=O); 1253 (P=O); 1053, 1031 (P-O). **MS m/z (%):** 322 (100, [M+H]⁺). **Chromatography:** Rf = 0.23 (EtOAc). **Yield:** 62%. Yellow oil.

Dimethyl 1-isopropyl-4-oxo-2-[(*E*)-2-phenylethenyl]-2-azetidinyl phosphonate (23f)

¹H NMR δ (300 MHz, ppm): 1.43 (3H, d, J = 6.9 Hz, CH₃); 1,45 (3H, d, J = 6.9 Hz, CH₃); 2.96 (1H, dd, J_{AB} = 14.6 Hz, J_{HP} = 5.5 Hz, C$\underline{H}_A$H$_B$); 3.32 (1H, dd, J_{AB} = 14.6 Hz, J_{HP} = 7.7 Hz, CH$_A$$\underline{H}_B$); 3.59 (1H, septet, J = 6.9 Hz, CH); 3.81 (3H, d, J_{HP} = 9.1 Hz, OCH₃); 3.85 (3H, d, J_{HP} = 9.4 Hz, OCH₃); 6.43 (1H, dd, J_{trans} = 16.2 Hz, J_{HP} = 10.2 Hz,
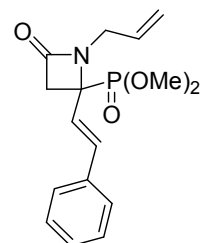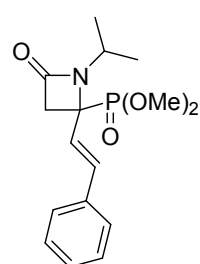
=CH); 6.84 (1H, dd, J_{trans} = 16.1 Hz, J_{HP} = 3.0 Hz, =CHPh); 7.26-7.42 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 20.87 (CH$_3$); 22.14 (CH$_3$); 47.13 (CH$_2$); 47.49 (CH); 53.83 (d, J_{CP} = 7.2 Hz, OCH$_3$); 53.92 (d, J_{CP} = 7.2 Hz, OCH$_3$); 58.06 (d, J_{CP} = 167.9 Hz, C$_{quat}$); 123.41 (d, J_{CP} = 8.1 Hz, =CH); 126.79 (2 x CH$_{arom}$); 128.70 (CH$_{arom}$); 128.86 (2 x CH$_{arom}$); 134.33 (d, J_{CP} = 9.2 Hz, =CHPh); 135.66 (C$_{q,arom}$); 165.39 (d, J_{CP} = 8.1 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 24.75. **IR ν (cm⁻¹):** 1752 (C=O); 1252 (P=O); 1055, 1031 (P-O). **MS m/z (%):** 324 (100, [M+H]⁺). **Chromatography:** Rf = 0.22 (EtOAc). **Yield:** 85%. Yellow oil.

Dimethyl 1-phenyl-2-furan-2-yl-4-oxo-2-azetidinyl phosphonate (23g)
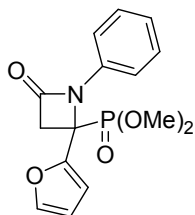
¹H NMR δ (270 MHz, ppm): 3.60 (1H, dd, J_{AB} = 9.2 Hz, J_{HP} = 2.6 Hz, CH$_A$H$_B$C=O); 3.65 (1H, dd, J_{AB} = 9.2 Hz, J_{HP} = 4.3Hz, CH$_A$H$_B$C=O); 3.74 (3H, d, J_{HP} = 10.6 Hz, OCH$_3$); 3,80 (3H, d, J_{HP} = 10.9 Hz, OCH$_3$); 6.39 (1H, dd, J = 1.7 Hz, J = 2.0 Hz, =CH) ; 6.88 (1H, d, J = 3.3Hz, =CH); 7.03-7.08 (1H, CH$_{arom}$); 7.23-7.34 (2H, multiplet, CH$_{arom}$); 7.42 (1H, d, J = 1.0 Hz, =CHO); 7.64 (1H, multiplet, CH$_{arom}$); 7.66 (1H, multiplet, CH$_{arom}$). **¹³C NMR δ (68 MHz, ppm):** 47.56 (d, J_{CP} = 2.4 Hz, CH$_2$C=O); 53.66 (d, J_{CP} = 7.3 Hz, OCH$_3$); 54.52 (d, J_{CP} = 7.3 Hz, OCH$_3$); 55.91 (d, J_{CP} = 172.1 Hz, NC$_q$P); 110.91 (=CH); 112.54 (=CH); 117.79 (2x); 124.49; 128.91 (2x) (CH$_{arom}$) ; 137.36 (C$_{q,arom}$) ; 143.66 (=CHO) ; 146.44 (d, J_{CP} = 20.8 Hz, =C$_q$O) ; 163.77 (d, J_{CP} = 7.4 Hz, C=O). **³¹P NMR δ (109 MHz, ppm):** 21.80. **IR ν (cm⁻¹):** 1762 (C=O) ; 1260 (P=O). **MS^{EI} m/z (%):** 322(3); 205(20); 204(66); 203(40); 174(100); 173(61); 171(95); 120(11); 110(30); 96(37); 95(43); 94(35); 77(62). **Chromatography:** Rf = 0.26 (Hex/EtOAc 20/80). **Yield:** 89%. Yellow oil.

Dimethyl 1-benzyl-2-furan-2-yl-4-oxo-2-azetidinyl phosphonate (23h)
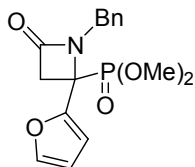
¹H NMR δ (270 MHz, ppm): 3.48 (1H, dd, J_{AB} = 14,5 Hz, J_{HP} = 7.9 Hz, CH$_A$H$_B$C=O); 3.56 (1H, dd, J_{AB} = 14.5 Hz, J_{HP} = 5.9 Hz, CH$_A$H$_B$C=O); 3.68 (6H, d, J_{HP} = 10.9 Hz, OCH$_3$); 4.42 (2H, s, CH$_2$Ph); 6,28 (1H, t, J = 1,7 Hz, =CH); 6.59 (1H, dd, J = 1,7 Hz, J = 1,0 Hz, =CH); 7.15-7.21 (5H, multiplet, CH$_{arom}$); 7.30 (1H, s, =CHO). **¹³C NMR δ (68 MHz, ppm):** 45.89 (CH$_2$Ph); 46.07 (CH$_2$); 53.54 (d, J_{CP} = 8.6 Hz, OCH$_3$); 53.84 (d, J_{CP} = 7.3 Hz, OCH$_3$); 54.75 (d, J_{CP} = 173.4 Hz, NC$_q$P); 110.83 (=CH); 111.93 (=CH); 127.24, 128.19 (2x), 128.44 (2x) (CH$_{arom}$); 135.83 (C$_{q,arom}$); 143.34 (=CHO); 146.79 (d, J_{CP} = 19.5 Hz, =C$_q$O); 166.21 (d, J_{CP} = 8.6 Hz, C=O). **³¹P NMR δ (109 MHz, ppm):** 21.36. **IR ν (cm⁻¹):** 1754 (C=O); 1261 (P=O). **MS^{EI} m/z (%):** 337(6); 231(21); 228(17); 227(100); 203(14); 173(12); 94(10); 93(10); 91(59); 65(9). **Chromatography:** Rf = 0.29 (Hex/EtOAc 20/80). **Yield:** 99%. Yellow oil.

Dimethyl 1-allyl-2-furan-2-yl-4-oxo-2-azetidinyl phosphonate (23i)
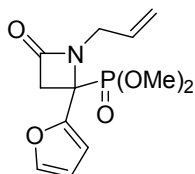
¹H NMR δ (300 MHz, ppm): 3.46 (1H, dd, J_{AB} = 14.7 Hz, J_{HP} = 7.8 Hz, CH$_A$H$_B$C=O); 3.53 (1H, dd, J_{AB} = 14.7 Hz, J_{HP} = 6.1 Hz, CH$_A$H$_B$C=O); 3.79 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.79-3.86 (1H, multiplet, CH$_A$H$_B$N); 3.86 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.95 (1H, dd, J_{AB} = 16.0 Hz, J = 5.8 Hz, CH$_A$H$_B$N); 5.06 (1H, dd, J_{cis} = 10.2 Hz, J = 1.4 Hz, =CH$_A$H$_B$); 5.12 (1H, dd, J_{trans} = 17.1 Hz, J = 1.4 Hz, =CH$_A$H$_B$); 5.76-5.63 (1H, multiplet, CH=CH$_2$); 6.40-6.42 (1H, multiplet, =CH); 6.69-6.70 (1H, multiplet,

=C<u>H</u>C$_q$); 7.46-7.47 (1H, multiplet, =C<u>H</u>O). **^{13}C NMR δ (75 MHz, ppm):** 44.33 (CH$_2$N); 46.14 (d, J$_{CP}$ = 2.3 Hz, CH$_2$); 53.71 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 54.12 (d, J$_{CP}$ = 5.8 Hz, OCH$_3$); 54.64 (d, J$_{CP}$ = 174.2 Hz, C$_q$P); 111.03 (<u>C</u>H=CH); 111.76 (d, J$_{CP}$ = 2.3 Hz, <u>C</u>H=C$_q$); 117.78 (=CH$_2$); 131.66 (<u>C</u>H=CH$_2$); 143.35 (=CHO); 147.28 (d, J$_{CP}$ = 18.5 Hz, O-<u>C</u>=CH); 166.03 (d, J$_{CP}$ = 8.1 Hz, C=O). **^{31}P NMR δ (121 MHz, ppm):** 22.06. **IR ν (cm^{-1}):** 1764 (C=O); 1645 (C=C); 1260 (P=O); 1055, 1036 (P-O). **MS m/z (%):** 203 (100); 286 (24, [M+H]$^+$). **Chromatography:** Rf = 0.20 (Hex/EtOAc 20/80). **Yield:** 55%. Orange oil.

Dimethyl 1-benzyl-4-oxo-2-phenyl-2-azetidinyl phosphonate (23j)
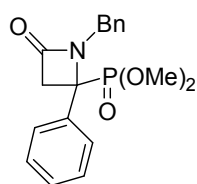
^{1}H NMR δ (270 MHz, ppm): 3.24 (1H, dd, J$_{AB}$ = 14.8 Hz, J$_{HP}$ = 6.3 Hz, C<u>H</u>$_A$H$_B$C=O); 3.60 (3H, d, J$_{HP}$ = 9.6 Hz, OCH$_3$); 3.63 (1H, dd, J$_{AB}$ = 14.8 Hz, J$_{HP}$ = 6.3 Hz, CH$_A$<u>H</u>$_B$C=O) ; 3.64 (3H, d, J$_{HP}$ = 9.6 Hz, OCH$_3$) ; 4.60 (1H, d, J$_{AB}$ = 15.5 Hz, NC<u>H</u>$_A$H$_B$); 4.74 (1H, d, J$_{AB}$ = 15.5 Hz, NCH$_A$<u>H</u>$_B$); 7.17-7.41 (10H, multiplet, CH$_{arom}$). **^{13}C NMR δ (68 MHz, ppm):** 47.04 (N<u>C</u>H$_2$); 48.52 (<u>C</u>H$_2$C=O); 53.53 (d, J$_{CP}$ = 7.3 Hz, OCH$_3$); 53.95 (d, J$_{CP}$ = 6.1 Hz, OCH$_3$); 61.28 (d, J$_{CP}$ = 163.5 Hz, C$_q$); 127.17, 127.24, 127.42, 128.35, 128.43 (2x), 128.50 (2x) (CH$_{arom}$); 135.50 (d, J$_{CP}$ = 8.6 Hz, C$_{q,arom}$); 136.55 (C$_{q,arom}$); 167.19 (C=O, J$_{CP}$ = 7.3 Hz). **^{31}P NMR δ (109 MHz, ppm):** 23.84. **IR ν (cm^{-1}):** 1759 (C=O) ; 1251 (P=O). **MS^{EI} m/z (%):** 346(5); 240(27); 236(100); 103(15); 92(16); 91(76); 77(12); 65(12). **Chromatography:** Rf = 0.23 (Hex/EtOAc 70/30). **Yield:** 92%. Yellow oil.

4.3.2 Hydrogenation of diethyl 1-benzyl-4-oxo-2-(2-phenylethyl)-2-azetidinyl phosphonate (273)

A heterogeneous mixture of 1.5 mmol lactam **23c** and Pd/C (10 mol% Pd) in ethanol was stirred for 14 h under a 4 bar H$_2$ atmosphere. The catalyst was then removed by filtration over celite® and the solvent was evaporated under reduced pressure.
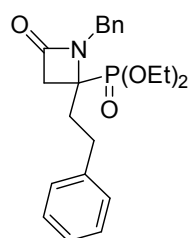
^{1}H NMR δ (300 MHz, ppm): 1.33 (6H, t, J = 7.2 Hz, CH$_3$); 1.92-2.18 (2H, multiplet, CH$_2$Ph); 2.26 (1H, ~td, J ≈ 12 Hz, J = 5.2 Hz, C<u>H</u>$_A$H$_B$C$_q$); 2.51 (1H, ~td, J ≈ 12 Hz, J = 5.2 Hz, CH$_A$<u>H</u>$_B$C$_q$); 2.98 (1H, dd, J$_{AB}$ = 14.9 Hz, J = 6.2 Hz, C<u>H</u>$_A$H$_B$CO); 3.18 (1H, dd, J$_{AB}$ = 14.9 Hz, J = 8.5 Hz, CH$_A$<u>H</u>$_B$CO); 4.04-4.21 (4H, multiplet, OCH$_2$); 4.25 (1H, d, J$_{AB}$ = 15.1 Hz, C<u>H</u>$_A$H$_B$Ph); 4,73 (1H, d, J$_{AB}$ = 15.1 Hz, CH$_A$<u>H</u>$_B$Ph); 6.70-6.82 (2H, multiplet, CH$_{arom}$); 7.05-7.49 (8H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.54 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 16.62 (d, J$_{CP}$ = 5.8 Hz, CH$_3$); 29.12 (d, J$_{CP}$ = 9.2 Hz, CH$_2$Ph); 32.83 (d, J$_{CP}$ = 9.2 Hz, <u>C</u>H$_2$C$_q$); 43.12 (<u>C</u>H$_2$CO); 45.41 (CH$_2$Ph); 58.42 (d, J$_{CP}$ = 163.8 Hz, C$_{quat}$P); 62.64 (d, J$_{CP}$ = 8.1 Hz, OCH$_2$); 63.01 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 126.07, 127.78, 128.18, 128.34, 128.73, 129.03 (CH$_{arom}$); 136.59 (C$_{q,Bn}$); 140.50 (C$_{q,Ph}$); 166.13 (d, J$_{CP}$ = 6.9 Hz, C=O). **^{31}P NMR δ (121 MHz, ppm):** 24.46. **IR ν (cm^{-1}):** 1757 (C=O); 1245 (P=O); 1043, 1021 (P-O). **MS m/z (%):** 402 (83, [M+H]$^+$); 264 (100, [M+H-P(O)(OEt)$_2$]$^+$). **Yield:** 91%. Yellow oil.

4.3.3 Preparation of dimethyl 1-allyl-6-oxo-2-((*E*)-phenylethenyl)piperidin-2-yl phosphonate (24)

A solution of *N*-chlorobutyryl aminoalkenyl phosphonate **25b** (1.51 g, 3.92 mmol) in dry THF (15 ml) was cooled to -78°C and 5.75 ml LiHMDS (1.0 M solution in hexane) was added dropwise using a syringe. The mixture was stirred for 5 minutes at -78°C and was then allowed to warm up to room temperature. Stirring was continued for 1 h. Then, the mixture was poured into 20 ml of 0.5 M HCl(aq) and 15 ml of diethyl ether. After vigorously mixing both phases, the organic phase was collected. The aqueous phase was washed twice with 10 ml of diethyl ether. The combined organic phases are dried using MgSO$_4$. A brown oil was obtained after filtration of the solids and evaporation of the solvent under reduced pressure. δ-lactam **24** could be obtained in pure form after column chromatography.
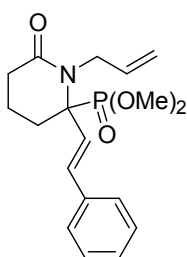
¹H NMR δ (300 MHz, ppm): 1.72-1.98 (2H, multiplet, CH$_2$); 2.06-2.21 (1H, multiplet, CH$_A$H$_B$); 2.34-2.53 (3H, multiplet, CH$_2$CO, CH$_A$H$_B$); 3.81 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.83 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 4.23-4.29 (2H, multiplet, NCH$_2$); 5.10-5.18 (2H, multiplet, =CH$_2$); 5.90-6.03 (1H, multiplet, HC=CH$_2$); 6.33 (1H, dd, J = 16.2 Hz, J$_{HP}$ = 10.2 Hz, =CH); 6.63 (1H, dd, J = 16.2 Hz, J$_{HP}$ = 3.5 Hz, =CHPh); 7.24-7.39 (5H, multiplet, =CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.86 (d, J$_{CP}$ = 5.8 Hz); 32.22 (CH$_2$); 32.47 (CH$_2$); 48.78 (NCH$_2$); 53.10 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 54.24 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 65.81 (d, J$_{CP}$ =156.9 Hz, C$_q$P); 115.91 (=CH$_2$); 126.63 (2 x CH$_{arom}$); 126.75 (=CH); 128.29, 128.75 (3x CH$_{arom}$); 132.62 (d, J$_{CP}$ = 10.4 Hz, =CHPh); 134.98 (HC=CH$_2$); 135.93 (C$_{q,arom}$); 171.34 (d, J$_{CP}$ = 3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 25.93. **IR ν (cm⁻¹):** 1646 (C=O); 1245 (P=O); 1046, 1028 (P-O). **MS m/z (%):** 350 (100, [M+H]+); 240 (51, [M+H-PO(OMe)$_2$]⁺). **Chromatography:** Rf = 0.14 (EtOAc). **Yield:** 15%. Yellow oil.

4.4 Origin of the regioselectivity towards four-membered phosphono lactams

4.4.1 Preparation of benzylbut-2-enylideneamine (19o)

An equimolar mixture of crotonaldehyde (0.10 mol) and benzylamine was stirred at 0°C and 3.02 g of solid KOH (0.036 mol) was added. The mixture was stirred for 10 minutes at 0°C and 20 minutes at room temperature and was then filtered over MgSO$_4$. The resulting oil was distilled immediately (bp. 50°C, 0.02 mbar) and the distillate was collected in a flask at -5°C (ice/salt bath). The product was highly unstable at ambient temperatures and should be used immediately or should be kept at -32°C for short periods.
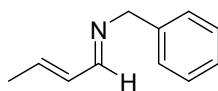
¹H NMR δ (300 MHz, ppm): 1.88 (3H, d, J = 5.2 Hz, CH₃); 4.61 (2H, s, NCH₂); 6.12-6.34 (2H, multiplet, HC=CH); 7.20-7.35 (5H, multiplet, CH$_{arom}$); 7.94 (1H, d, J = 8.2 Hz, N=CH). **¹³C NMR δ (75 MHz, ppm):** 18.48 (CH₃); 65.04 (NCH₂); 127.00, 128.08, 128.57 (CH$_{arom}$); 132.29 (=CH); 139.63 (C$_{q,arom}$); 140.77 (=CH); 163.45 (C=N). **IR ν (cm⁻¹):** 1655 (C=N); 1626 (C=C). **Yield:** 32%.

4.4.2 Preparation of dimethyl (*2E*)-1-(benzylchloroacetylamino)but-2-enyl phosphonate (21q)

A solution of imine **19o** (10 mmol) in dry THF (15 ml) was stirred at -40°C under a nitrogen atmosphere. Chloroacetyl chloride (10 mmol in 3 ml of dry THF) was added dropwise using a syringe and the mixture was stirred for 10 minutes at -40°C. Then triethyl phosphite (10 mmol in 3 ml of dry THF) was added and the mixture was refluxed for 2 h. Finally the solvent was evaporated under reduced pressure. The final mixture mainly consisted of vinyl phosphate **259b** and enamide **278**. Using column chromatography, the desired (chloroacetyl-benzyl-amino)-but-2-enyl phosphonate **21q** could be obtained in only 9% yield next to the corresponding 1,4-adduct **277** in 5% yield.

Dimethyl (*2E*)-1-(benzylchloroacetylamino)but-2-enyl phosphonate (21q)
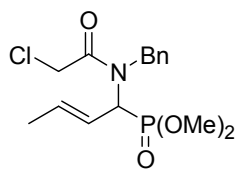
¹H NMR δ (300 MHz, ppm): 1.63-1.67 (3H, multiplet, CH₃); 3.75 (1 H, d, J$_{HP}$ = 11.3 Hz, OCH₃); 3.79 (1 H, d, J$_{HP}$ = 11.3 Hz, OCH₃); 3.86 (1 H, d, J = 11.7 Hz, CH$_A$H$_B$Cl); 3.96 (1 H, d, J = 11.7 Hz, CH$_A$H$_B$Cl); 4.78 (1H, d, J = 17.9 Hz, CH$_A$H$_B$Ph); 4.92 (1H, d, J = 17.9 Hz, CH$_A$H$_B$Ph); 5.44-5.59 (1 H, multiplet, =CH); 5.90-6.01 (1 H, multiplet, =CH-CH₃); 7.13-7.43 (5 H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 18.09 (CH₃); 41.61 (CH₂Cl); 49.51 (CH₂Ph); 53.07 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 53.86 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 54.24 (d, J$_{CP}$ = 156.9 Hz, CHP); 120.99 (=CH); 126.03 (2 x CH$_{arom}$); 127.68 (CH$_{arom}$); 128.95 (2 x CH$_{arom}$); 135.28 (d, J$_{CP}$ = 12.7 Hz, =CH-CH₃); 136.92 (C$_{q,arom}$); 167.42 (C=O). **³¹P NMR δ (121 MHz, ppm):** 24.49. **IR ν (cm⁻¹):** 1661 (C=O); 1606 (C=C); 1250 (P=O); 1032 (P-O). **MS m/z (%):** 346 (74 [M+H]⁺); 236 (100, [M+H-P(O)(OMe)₂]⁺. **Chromatography:** R$_f$ = 0.25 (EtOAc). **Yield:** 9%. Yellow oil.

Dimethyl 3-(benzylchloroacetylamino]-1-methylprop-2-enyl phosphonate (277)
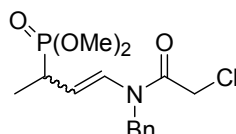
¹H NMR δ (300 MHz, ppm): 1.26 (3H +3H, dd, J$_{HP}$ = 18.2 Hz, J = 7.2 Hz, CH₃, m+M); 2.55-2.78 (1H + 1H, multiplet, CHP, m+M); 3.58-3.67 (6H + 6H, multiplet, OCH₃, m+M); 4.09 (2H, s, CH₂Cl, m); 4.30 (2H, s, CH₂Cl, M); 4.81-4.95 (2H + 2H, multiplet, CH₂Ph, m+M); 5.02-5.10 (1H, multiplet, =CH, m); 5.14 (1H, ddd, J = 14.0 Hz, J = 8.8 Hz, J$_{HP}$ ≈ 7.0 Hz, =CH, M); 6.66 (1H, dd, J = 14.0 Hz, J$_{HP}$ = 5.0 Hz, =CHN, M); 7.15-7.46 (5H + 5H + 1H, multiplet, CH$_{arom}$, m+M, =CHN, m).

¹³C NMR δ (75 MHz, ppm): 14.31 (CH₃, J_{CP} = 5.8 Hz); 33.03 (d, J_{CP} = 141.9 Hz, CHP, M); 33.15 (d, J_{CP} = 141.9 Hz, CHP, m); 41.36 (CH₂Cl, M); 41.82 (CH₂Cl, m); 47.19 (CH₂Ph, M); 41.82 (CH₂Ph, m); 52.77, 52.90, 53.00 (OCH₃, m+M); 109.88 (d, J_{CP} = 9,2 Hz, =CH, m); 112.29 (d, J_{CP} = 10.4 Hz, =CH, M); 125.58, 127.03, 127.26, 127.73, 127.92, 128.11, 128.57 (CH_{arom}, m+M, =CHN, m); 128.71 (=CHN, M); 128.86, 129.03 (CH_{arom}, m+M); 135.21 (C_{q,arom}, m); 136.05 (C_{q,arom}, M); 165.46 (C=O). **³¹P NMR δ (121 MHz, ppm):** 32.07 (M); 32.59 (m). **IR ν (cm⁻¹):** 1678, 1652 (C=C, C=O); 1242 (P=O); 1056, 1031 (P-O). **MS m/z (%):** 346 (100, [M+H]⁺); 236 (17, [M+H+P(O)(OMe)₂]⁺). **Chromatography:** Rf = 0.16 (EtOAc). **Yield:** 5%. Yellow oil.

4.4.3 Preparation of diethyl [benzylchloroacetylamino][(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl phosphonate (21p)
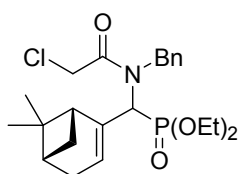
To a mixture of aminoalkenyl phosphonate **22u** (5 mmol), triethyl amine (5.5 mmol) and dry THF (10 ml), chloroacetyl chloride (7.5 mmol in 2 ml of dry THF) was added. The mixture was stirred for 30 minutes at room temperature, protected from moisture using a CaCl₂ tube. Then, the mixture was poured into 15 ml of a saturated NaHCO₃₍aq₎ solution and was extracted with 15 ml of diethyl ether. The remaining aqueous phase was extracted two times more with 5 ml of diethyl ether. The combined organic phase were dried using MgSO₄. After filtration of the solids and evaporation of the solvent under reduced pressure, the *N*-chloroacetyl aminoalkenyl phosphonate **21p** was obtained as a mixture of two diastereomers (crude yield: 89%; ratio 44:56). Both isomers could be separated using column chromatography.

Major isomer:
¹H NMR δ (300 MHz, ppm): 0.86 (3H, s, CH₃); 1.10 (1H, d, J = 8.5 Hz, C<u>H</u>ₐH_B); 1.17 (3H, t, J = 7.0 Hz, CH₂C<u>H</u>₃); 1.25 (3H, s, CH₃); 1.29 (3H, t, J = 7.0 Hz, CH₂C<u>H</u>₃); 2.05-2,10 (1H, multiplet, C<u>H</u>CH₂); 2,25 (1H, ~t, J = 5,0 Hz, C<u>H</u>C_{quat}=); 2,32-2,58 (3H, multiplet, CHₐ<u>H</u>_B & CH₂); 3.88 (2H, s, CH₂Cl); 3.92-4,01 (2H, multiplet, OCH₂); 4.08-4.22 (2H, multiplet, OCH₂); 4.59 (1H, d, J_{AB} = 17.9 Hz, C<u>H</u>ₐH_BN); 4.86 (1H, d, J_{AB} = 17.9 Hz, CHₐ<u>H</u>_BN); 5.40-5.50 (1H, multiplet, CHP); 5.97 (1H, s (br.), CH=); 7.24-7.37 (5H, multiplet, CH_{arom}). **¹³C NMR δ (75 MHz, ppm):** 16.15 (d, J_{CP} = 5.8 Hz, CH₂<u>C</u>H₃); 16.36 (d, J_{CP} = 5.8 Hz, CH₂<u>C</u>H₃); 21.33 (CH₃); 26.03 (CH₃); 31.64, 31.70 (CH₂ & <u>C</u>H₂CH=); 37.97 (C_q); 40.08 (<u>C</u>HCH₂); 41.51 (CH₂Cl); 45.21 (<u>C</u>HC_q=, J_{CP} = 9.2 Hz); 50.02 (CH₂N); 56,15 (CHP, J_{CP} = 154.6 Hz); 61,73 (OCH₂, J_{CP} = 6.9 Hz); 63.06 (d, J_{CP} = 5.8 Hz, OCH₂); 126.01 (2 x CH_{arom} + CH=); 127.43 (CH_{arom}); 128.79 (2 x CH_{arom}); 136.94 (C_{q,arom}); 139.69 (=C_q); 168.41 (CO). **³¹P NMR δ (121 MHz, ppm):** 20.77. **IR ν (cm⁻¹):** 1663 (C=O); 1606 (C=C); 1249 (P=O); 1050, 1029 (P-O). **MS m/z (%):** 454 (100, M+H]⁺). **Chromatography:** R_f = 0.22 (Hex/EtOAc 40/60). **Yield:** 18%. Pale yellow oil.
Minor isomer:

¹H NMR δ (300 MHz, ppm): 0.63 (1H, d, J = 8.8 Hz, CH$_A$H$_B$); 0.88 (3H, s, CH$_3$); 1.23-1.32 (9H, multiplet, 2 x CH$_2$CH$_3$, CH$_3$); 1.93-2.04 (1H, multiplet, CHCH$_2$); 2.10 (1H, ~t, J = 5.5 Hz, CHC$_q$=); 2,.15-2.27 (3H, multiplet, CH$_A$H$_B$ & CH$_2$); 3.88 (2H, s, CH$_2$Cl); 4.03-4.18 (4H, multiplet, OCH$_2$); 4.78 (2H, s, CH$_2$N); 5.46 (1H, d (br.), J$_{HP}$ = 21.2 Hz, CHP); 6.19 (1H, s (br.), CH=); 7.14-7.35 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.27, 16.31, 16.35 (CH$_2$CH$_3$); 20.92 (CH$_3$); 26.11 (CH$_3$); 31.48 (CH$_2$); 31.83 (CH$_2$CH=); 38.20 (C$_q$); 40.00 (CHCH$_2$); 41.90 (CH$_2$Cl); 45.75 (d, J$_{CP}$ = 12,7 Hz, CHC$_q$=); 48.69 (CH$_2$N); 55.48 (d, J$_{CP}$ = 156.9 Hz, CHP); 62.19 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 62.68 (d, J$_{CP}$ = 6.9 Hz, OCH$_2$); 125.78 (2 x CH$_{arom}$); 127.04 (d, J$_{CP}$ = 5.8 Hz, =CH); 127.34 (CH$_{arom}$); 128.83 (2 x CH$_{arom}$); 137.08 (C$_{q,arom}$); 139.15 (=C$_q$); 168.52 (d, J$_{CP}$ = 3.5 Hz, CO). **³¹P NMR δ (121 MHz, ppm):** 20.46. **IR ν (cm⁻¹):** 1663 (C=O); 1606 (C=C); 1251 (P=O); 1046, 1029 (P-O). **MS m/z (%):** 454 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.29 (Hex/EtOAc 40/60). **Yield:** 14%. Pale yellow oil.

4.4.4 Preparation of diethyl [1-benzyl-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-4-oxo-azetidin-2-yl] phosphonate (23l)

0.08 g (2.0 mmol) of a NaH emulsion in mineral oil was washed three times with petroleum ether. Then, 5 ml of dry THF was added and the suspension was stirred at room temperature under a nitrogen atmosphere. A solution of 0.74 g (1.6 mmol) of *N*-chloroacetyl aminoalkenyl phosphonate **21p** as a single diastereomer in 5 ml of dry THF was added dropwise using a syringe. The mixture was refluxed for 3 h. After cooling, the mixture was poured in 25 ml of water and extracted with 20 ml of diethyl ether. The remaining water phase was then washed two times with 10 ml of diethyl ether. The combined organic phases were dried with MgSO$_4$, and after filtration the solvent was removed under reduced pressure. The 4-phosphono β-lactam **23l** could be obtained in pure form as a mixture of diastereomers (ratio: 41/59) using column chromatography.
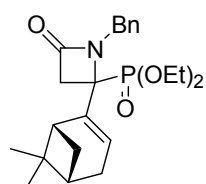
¹H NMR δ (300 MHz, ppm): 0.71 (3H, s, CH$_3$, m); 0.77-0.81 (1H, multiplet, CHCH$_A$H$_B$CH, m); 0.79 (3H, s, CH$_3$, M); 1.02 (1H, d, J = 8.8 Hz, CHCH$_A$H$_B$CH, M); 1.14 (3H, s, CH$_3$, m); 1.23 (3H, s, CH$_3$, M); 1.25-1.34 (2x 6H, multiplet, CH$_2$CH$_3$, m+M); 1.87-2.03 (2x 1H, multiplet, CH, m+M); 2.12-2.41 (2x 4H, multiplet, CHC$_q$=, CH$_2$, CHCH$_A$H$_B$CH, m+M); 2.83 (1H, dd, J$_{AB}$ = 14.7 Hz, J = 5.5 Hz, CH$_A$CH$_B$CO, m); 2.90 (1H, dd, J$_{AB}$ = 14.7 Hz, J = 6.3 Hz, CH$_A$H$_B$CO, M); 3.253 (1H, dd, J$_{AB}$ = 14.7 Hz, J = 8.5 Hz, CH$_A$H$_B$CO, M); 3.257 (1H, dd, J$_{AB}$ = 14.9 Hz, J = 7.2 Hz, CH$_A$H$_B$CO, m); 3.89-4.22 (2x 4H, multiplet, OCH$_2$, m+M); 4.34 (1H, d, J$_{AB}$ = 15.5 Hz, NCH$_A$H$_B$, m); 4.45 (1H, d, J$_{AB}$ = 15.8 Hz, NCH$_A$H$_B$, M); 4.52 (1H, d, J$_{AB}$ = 15.5 Hz, NCH$_A$H$_B$, M); 4.58 (1H, d, J$_{AB}$ = 15.8 Hz, NCH$_A$H$_B$, M); 5.61-5.67 (1H, multiplet, =CH, M); 5.90-5.95 (1H, multiplet, =CH, m); 7.20-7.37 (2x 5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 16.46 (d, J$_{CP}$ = 5.8 Hz, CH$_2$CH$_3$); 16.60 (d, J$_{CP}$ = 5.8 Hz, CH$_2$CH$_3$); 20.79 (CH$_3$, m); 21.25 (CH$_3$, M); 25.92 (CH$_3$, m); 26.09 (CH$_3$, M); 31.25, 31.60, 31.64, 31.75 (CH$_2$, CHCH$_2$CH, m+M); 37.60 (C$_q$, M); 37.68 (C$_q$, m); 40.03 (CH, M); 40.23 (CH, m); 41.87

(d, J_{CP} = 5.8 Hz, CH<u>C</u>$_q$=, m); 43.29 (d, J_{CP} = 3.5 Hz, CH<u>C</u>$_q$=, M); 44.81 (<u>C</u>H$_2$CO, M); 44.91 (<u>C</u>H$_2$CO, m); 46.42 (N<u>C</u>H$_2$, m); 46.82 (N<u>C</u>H$_2$, M); 60.33 (d, J_{CP} = 166.1 Hz, <u>C</u>$_q$P, m); 60.95 (d, J_{CP} = 165.0 Hz, <u>C</u>$_q$P, M); 62.46, 62.55, 62.67, 62.82, 62.94, 63.04 (O<u>C</u>H$_2$, m+M); 123.45 (d, J_{CP} = 9.2 Hz, =<u>C</u>H, M); 124.99 (d, J_{CP} = 5.8 Hz, =<u>C</u>H, m); 127.27, 127.42, 128.29, 128.37, 128.84, 129.71, 130.54 (<u>C</u>H$_{arom}$, m+M); 136.67 (<u>C</u>$_{q,arom}$, m); 136.98 (<u>C</u>$_{q,arom}$, M); 141.29 (d, J_{CP} = 8.1 Hz, =<u>C</u>$_q$, m); 142.16 (d, J_{CP} = 6.9 Hz, =<u>C</u>$_q$, M); 167.41 (d, J_{CP} = 6.9 Hz, <u>C</u>=O, M). **^{31}P NMR δ (121 MHz, ppm):** 21.86 (M); 22.00 (m). **IR ν (cm^{-1}):** 1760 (C=O); 1673 (C=C); 1247 (P=O); 1046, 1024 (P-O). **MS m/z (%):** 418 (100, M+H]$^+$). **Chromatography:** Rf = 0.37 (EtOAc). **Yield:** 25%. Yellow oil.

Also a side product, originating from the unreacted allyl anion, could be recovered during column chromatography:

Diethyl [benzyl(2-chloroacetyl)amino](6,6-dimethyl-bicyclo[3.1.1]hept-2-ylidene)methyl phosphonate (281)
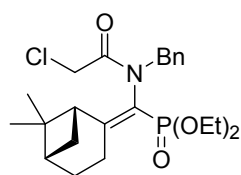
^{1}H NMR δ (300 MHz, ppm): 0.33 (3H, s, CH$_3$); 0.84 (3H, s, CH3); 1.23-1.30 (1H, multiplet, CHC<u>H</u>$_A$H$_B$CH); 1.327 (3H, t, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); 1.331 (3H, t, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); 1.81-2.04 (3H, multiplet, C<u>H</u>C<u>H</u>$_2$); 2.23-2.35 (1H, multiplet, CHCH$_A$<u>H</u>$_B$CH); 2.67 (1H, t, J = 4.4 Hz, C<u>H</u>C$_q$=); 2.72-2.98 (2H, multiplet, CH$_2$C$_q$=); 3.98 (1H, d, J_{AB} = 14.0 Hz, C<u>H</u>$_A$H$_B$Cl); 4.00-4.15 (4H, multiplet, OCH$_2$); 4.17 (1H, d, J_{AB} = 14.0 Hz, CH$_A$<u>H</u>$_B$Cl); 4.19 (1H, d, J_{AB} = 14.6 Hz, NC<u>H</u>$_A$H$_B$); 5.10 (1H, d, J_{AB} = 14.6 Hz, NCH$_A$<u>H</u>$_B$); 7.19-7.45 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 16.54 (d, J_{CP} = 6.9 Hz, CH$_2$<u>C</u>H$_3$); 21.60 (CH3); 21.94 (d, J_{CP} = 3.5 Hz, <u>C</u>H$_2$C$_q$=); 23.38 (CH$_2$); 25.16 (CH$_3$); 26.71 (CH<u>C</u>H$_2$CH); 40.00 (CH); 40.29 (C$_q$); 42.56 (<u>C</u>H$_2$Cl); 47.03 (d, J_{CP} = 12.7 Hz, <u>C</u>HC$_q$=); 53.10 (N<u>C</u>H$_2$); 62.15 (d, J_{CP} = 6.9 Hz, O<u>C</u>H$_2$); 62.23 (d, J_{CP} = 5.8 Hz, O<u>C</u>H$_2$); 122.51 (d, J_{CP} = 215.8 Hz, =<u>C</u>$_q$P); 127.68, 128.49 (CH$_{arom}$); 128.92 (=<u>C</u>$_q$); 129.77 (CH$_{arom}$); 136.75 (<u>C</u>$_{q,arom}$); 167.79 (d, J_{CP} = 11.5 Hz, <u>C</u>=O). **^{31}P NMR δ (121 MHz, ppm):** 12.95. **IR ν (cm^{-1}):** 1674 (C=O); 1236 (P=O); 1049, 1023 (P-O). **MS m/z (%):** 454 (100, [M+H]+); 456 (36 [M+H+2]$^+$). **Chromatography:** Rf = 0.40 (EtOAc). **Yield:** 10%. Yellow oil.

4.4.5 Dimethyl (*2E*)-[acetylisopropylamino]-3-phenylprop-2-enyl phosphonate (255b)

To a solution of aminoalkenyl phosphonate **22h** (6.64 mmol) in dry THF (15 ml), 1.05 g (13.28 mmol) of pyridine and 0.16 g (1.33 mmol) of DMAP was added. The mixture was stirred at room temperature under a nitrogen atmosphere. Then, 0.78 g (9.96 mmol) of acetyl chloride in 5 ml of THF was added using a syringe. The mixture was stirred for 1 h at room temperature and one more hour at reflux temperature. Finally the reaction mixture was washed with a saturated solution of NaHCO$_{3(aq)}$ and a 0.5 M solution of HCl$_{(aq)}$ consecutively. The resulting organic phase was dried using MgSO$_4$ and evaporated to obtain **255b** in 66% yield as yellow crystals.
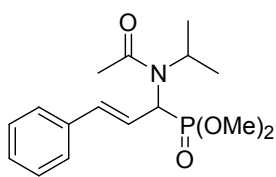
¹H NMR δ (300 MHz, ppm): 1.21 (3H, d, J = 6.6 Hz, CH₃); 1.35 (3H, d, J = 6.6 Hz, CH₃); 2.19 (3H, s, CH₃CO); 3.69 (3H, d, J_{HP} = 10.6 Hz, OCH₃); 3.89 (3H, d, J_{HP} = 10.6 Hz, OCH₃); 3.96-4.34 (2H, multiplet, CHP, NCH); 6.49-6.62 (2H, multiplet, HC=CH); 7.21-7.40 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 20.95 (CH₃); 21.74 (CH₃); 21.92 (CH₃CO); 50.55 (NCH); 51.97 (d, J_{CP} = 6.9 Hz, OCH₃); 53.00 (d, J_{CP} = 161.5 Hz, CHP); 54.80 (d, J_{CP} = 5.8 Hz, OCH₃); 122.94 (d, J_{CP} = 2.3 Hz, =CH); 126.66 (2 x CH$_{arom}$); 127.96 (CH$_{arom}$); 128.54 (2 x CH$_{arom}$); 133.56 (d, J_{CP} = 12.7 Hz, =CHPh); 136.39 (C$_{q,arom}$); 169.77 (CO). **³¹P NMR δ (121 MHz, ppm):** 26.55. **IR ν (cm⁻¹):** 1639 (br., C=O, C=C); 1230 (br., P=O); 1049, 1030 (P-O). **MS m/z (%):** 326 [M+H]⁺. **Mp.:** 51-52°C. **Yield:** 66%. Yellow crystals.

4.4.6 Anion trapping experiment with H⁺

0.10 g (2.5 mmol) of a sodium hydride suspension in mineral oil was washed three times with petroleum ether to remove the mineral oil. Then 2 ml of dry THF was added to the sodium hydride and the mixture was cooled to -78°C under a nitrogen atmosphere. Then, 0.68 g of **255b** (2.1 mmol in 6 ml of THF) was added dropwise using a syringe. The mixture was kept at -78°C for 10 minutes and was then allowed to warm up to room temperature over a 2 h period. After adding water and 1N HCl$_{(aq)}$ for neutralization, the reaction mixture was extracted with ether. After drying with MgSO₄ and evaporation of the solvent, 0.61 g of a mixture was obtained consisting of starting material **255b** (13%) and isomer **287** (87%), which could be obtained in pure form after flash chromatography. From the ³J_{CP} and the ³J_{HP} coupling constants, an *E* geometry of the double bond can be concluded.

Dimethyl (acetylisopropylamino)-3-phenylprop-1-enyl phosphonate (287)
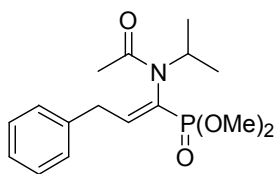
¹H NMR δ (300 MHz, ppm): 1.26 (3H, d, J = 6.7 Hz, CH₃); 1.37 (3H, d, J = 6.7 Hz, CH₃); 1.98 (3H, s, CH₃CO); 3.55 (2H, ddd, J_{AB} = 16.2 Hz, J = 7.4 Hz, J_{HP} = 3.3 Hz, CH₂); 3.80 (6H, d, J_{HP} = 10.7 Hz, OCH₃); 4.26 (1H, septet, J = 6.7 Hz, NCH); 6.98 (1H, dt, J_{HP} = 13.2 Hz, J = 7.4 Hz, =CH); 7.16-7.43 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 19.51 (CH₃); 20.41 (CH₃); 23.12 (CH₃CO); 34.48 (d, J_{CP} = 13.8 Hz, CH₂); 50.63 (NCH); 52.95 (d, J_{CP} = 6.9 Hz, OCH₃); 53.03 (d, J_{CP} = 5.8 Hz, OCH₃); 126.97 (CH$_{arom}$); 128.33 (CH$_{arom}$); 128.95 (CH$_{arom}$); 131.49 (d, J_{CP} = 214.6 Hz, C$_q$P); 136.66 (C$_{q,arom}$); 148.07 (d, J_{CP} = 27.7 Hz, =CH); 170.41 (CO). **³¹P NMR δ (121 MHz, ppm):** 15.69. **IR ν (cm⁻¹):** 1659 (br., C=O, C=C); 1251 (P=O); 1050, 1029 (P-O). **MS m/z (%):** 326 (100, [M+H]⁺). **Chromatography:** Rf = 0.17 (EtOAc/MeOH 98/2). **Yield:** 42%. Yellow oil.

5 Synthesis of 2-phosphono pyrroles

5.1 Preparation of α-alkyl crotonaldehydes

5.1.1 Preparation of but-2-enylidene-cyclohexylamine (19p)

A solution of crotonaldehyde (0.143 mol) in benzene (14.3 ml) was added dropwise to a mixture of cyclohexyl amine (0.30 mol) and potassium carbonate (43 mmol) at -15°C. After the addition was complete, the mixture was stirred for 1 h at 0°C and 2.5 h at room temperature. Distillation of the mixture at 10 mbar gave a major fraction (bp. 55-57°C) which on redistillation at 42 mbar gave the pure imine (bp. 95-100°C).
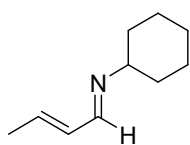
¹H NMR δ (300 MHz, ppm): 0.97-1.95 (10H, multiplet, 5x CH_2); 1.87 (3H, d, J = 5.2 Hz, CH_3); 2.90-2.99 (1H, multiplet, NCH); 6.06-6.27 (2H, multiplet, HC=CH); 7.86 (1H, d, J = 7.7 Hz, N=CH). **¹³C NMR δ (75 MHz, ppm):** 18.38 (CH_3); 24.91 (2x CH_2); 25.64 (CH_2); 34.50 (2x CH_2); 69.49 (CHN); 132.49 (=CH); 139.82 (=$CHCH_3$); 160.42 (N=CH). **IR ν (cm⁻¹):** 1656 (C=N); 1625 (C=C). **Yield:** 42%.

5.1.2 Alkylation of but-2-enylidene-cyclohexylamine (19p)

A mixture of diisopropyl amine (20 mmol) and HMPA (20 mmol) in 40 ml of dry THF was stirred at 0°C under a nitrogen atmosphere. Butyl lithium (8.4 ml of a 2.5 M solution in hexane) was added dropwise using a syringe. After stirring for 15 minutes, imine **19p** (20 mmol in 10 ml of dry THF) was added dropwise using a syringe. Stirring was continued for 15 minutes and then, the mixture was cooled to -78°C. After stirring for 30 minutes at -78°C, the alkyl bromide (21.4 mmol in 5 ml of THF) wass added dropwise using a syringe. Stirring was continued for 4 h before the reaction was quenched using 20 ml of a saturated $NH_4Cl_{(aq)}$ solution at -78°C. The intermediate imine was then extracted with 40 ml of diethyl ether. The remaining water phase was extracted two times more with 10 ml of diethyl ether. Then 20 ml of a NaOAc/HOAC buffer mixture (12.5 ml HOAc, 12.5 ml H_2O, 5.4 g NaOAc) was added to the combined organic phases. The resulting biphasic system was stirred vigorously for 1 h at room temperature. Then, the organic phase was collected, washed with 10 ml of a 0.5 M $HCl_{(aq)}$ solution and three times with 10 ml of a saturated $NaHCO_{3(aq)}$ solution and dried using $MgSO_4$. The corresponding aldehyde was then obtained in reasonable purity after filtration of the solids and evaporation of the solvent under reduced pressure. No further purification was performed at this stage and the crude mixture was used immediately for conversion to the corresponding aminoalkenyl phosphonate **22p,q**.

5.2 Benzylation of α-aminoalkenyl phosphonates

To a roundbottom flask, 3.1 mmol of α-aminoalkenyl phosphonate **22** was added together with 3 g of K_2CO_3, 0.23 g (1.5 mmol) of NaI and 4 ml of acetone. Then 0.79 g (4.65 mmol) of benzyl bromide was added and the mixture was refluxed during 5 to 10 h. The course of the reaction was conveniently monitored using ^{31}P NMR spectra directly from the reaction mixture. After complete conversion of the starting material, the solids were removed by filtration and the solvent by evaporation under reduced pressure. The corresponding *N*-benzyl α-aminoalkenyl phosphonate **32** can be obtained in pure form as a pale yellow oil using column chromatography over silica gel using a hexane, ethyl acetate mixture as a mobile phase.

Dimethyl *(2E)*-1-(allylbenzylamino)-3-phenylprop-2-enyl phosphonate (32a)
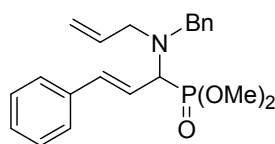
¹H NMR δ (300 MHz, ppm): 3.10 (1H, dd, J_{AB} = 14.0 Hz, J = 7.7 Hz, CH̱AHB); 3.51 (1H, d, J_{AB} = 13.8 Hz, CH̱AHBPh); 3.63-3.68 (1H, multiplet, CHAH̱B); 3.68 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.85 (3H, d, J_{HP} = 10.7 Hz, OCH₃); 3.85 (1H, dd, J_{HP} = 24.2 Hz, J = 9.1 Hz, CHP); 4.22 (dd, J_{AB} = 13.8 Hz, J = 1.9 Hz, CHAH̱BPh); 5.19-5.29 (2H, multiplet, =CH₂); 5.79-5.93 (1H, multiplet, CH̱=CH₂); 6.37 (1H, ddd, J = 16.7 Hz, J = 9.1 Hz, J_{HP} = 6.3 Hz, =CH); 6.60 (1H, J = 15.7 Hz, J_{HP} = 3.03 Hz, =CHPh); 7.20-7.45 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 52.65 (d, J_{CP} = 6.9 Hz, OCH₃); 53.68 (d, J_{CP} = 6.9 Hz, OCH₃); 54.25 (d, J_{CP} = 6.9 Hz, CH₂); 55.16 (d, J_{CP} = 8.4 Hz, CH₂Ph); 59.45 (d, J_{CP} = 160.4 Hz, CHP); 117.66 (=CH₂); 119.75 (=CH); 126.67, 127.05, 128.12, 128.33, 128.51, 128.65, 128.77, 129.03 (CH$_{arom}$); 136.28 (C$_{q,arom}$); 136.39 (C̱H=CH₂); 136.96 (d, J_{CP} = 6.9 Hz, =CHPh); 139.40 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.11. **IR ν (cm⁻¹):** 1642, 1601 (C=C); 1243 (P=O); 1039 (br., P-O). **MS m/z (%):** 262 (13); 372 (100, [M+H]⁺). **Chromatography:** R_f = 0.26 (Hex/EtOAc 40/60). **Yield:** 61%. Pale yellow oil.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-methyl-3-phenylprop-2-enyl phosphonate (32b)
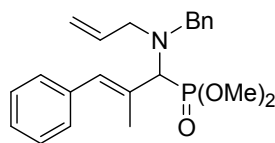
¹H NMR δ (300 MHz, ppm): 2.07 (3H, s, CH₃); 3.25 (1H, dd, J_{AB} = 14.2 Hz, J = 7.4 Hz, NCH̱AHB); 3.62-3.70 (1H, multiplet, NCHAH̱B); 3.72 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 3.72-3.86 (2H, multiplet, CHP, CH̱AHBPh); 3.84 (3H, d, J_{HP} = 10.5 Hz, OCH₃); 4.18 (1H, dd, J_{AB} = 13.8 Hz, J_{HP} = 2.5 Hz, CHAH̱BPh); 5.15-5.26 (2H, multiplet, =CH₂); 5.79-5.92 (1H, multiplet, =CH); 6.66 (1H, s (br.), =CHPh); 7.20-7.39 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 18.63 (d, J_{CP} = 6.9 Hz, CH₃); 52.86 (d, J_{CP} = 8.1 Hz, OCH₃); 52.98 (d, J_{CP} = 6.9 Hz, OCH₃); 63.92 (d, J_{CP} = 153.5 Hz, CHP); 117.83 (=CH₂); 126.82, 127.02, 128.21, 128.28, 128.88, 129.12 (CH$_{arom}$); 131.95 (d, J_{CP} = 4.6 Hz, =C$_q$); 132.38 (d, J_{CP} = 11.5 Hz, =CHPh); 136.49 (=CH); 137.40 (=C$_{q,arom}$); 139.80 (CH₂C̱$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.35. **IR ν (cm⁻¹):** 1247 (P=O); 1037 (br., P-O). **MS m/z (%):** 386 (100, [M+H]⁺). **Chromatography:** R_f = 0.26 (Hex/EtOAc 60/40). **Yield:** 50%.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-benzylbut-2-enyl phosphonate (32c)
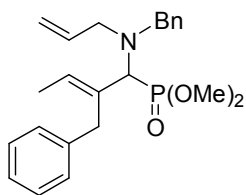
¹H NMR δ (300 MHz, ppm): 1.83 (3H, d, J = 6.6 Hz, CH₃); 3.20 (1H, d, J$_{AB}$ = 14.9 Hz, C$_q$CH$_A$H$_B$C$_q$); 3.34-3.39 (2H, multiplet, NCH₂CH=); 3.46 (3H, d, J$_{HP}$ = 10.5 Hz, OCH₃); 3.53 (1H, d, J$_{HP}$ = 20.6 Hz, CHP); 3.66 (3H, d, J$_{HP}$ = 10.5 Hz, OCH₃); 3.68-3.74 (1H, multiplet, C$_q$CH$_A$H$_B$C$_q$); 3.86-3.88 (2H, multiplet, NCH₂); 5.05-5.16 (2H, multiplet, =CH₂); 5.73 (1H, dxdxt, J = 17.3 Hz, J = 10.2 Hz, J = 6.5 Hz, =CH); 6.27 (1H, q, J = 6.6 Hz, =CHCH₃); 6.92 (2H, d, J = 6.6 Hz, CH$_{arom}$); 7.10-7.39 (8H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.44 (CH₃); 35.74 (d, J$_{CP}$ = 11.5 Hz, C$_q$CH₂C$_q$); 51.81 (d, J$_{CP}$ = 6.9 Hz, OMe); 52.65 (d, J$_{CP}$ = 6.9 Hz, OMe); 54.20 (d, J$_{CP}$ = 3.5 Hz, NCH₂CH=); 54.91 (s (br.), NCH₂); 58.41 (d, J$_{CP}$ = 140.8 Hz, CHP); 117.63 (=CH₂); 126.06, 126.98 (CH$_{arom}$); 127.72 (d, J$_{CP}$ = 5.8 Hz, =CHCH₃); 128.29, 128.81, 129.22 (CH$_{arom}$); 133.22 (d, J$_{CP}$ = 10.4 Hz, =C$_q$); 137.16 (=CH); 139.45 (=C$_q$CH₂C$_{q,arom}$); 140.29 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 28.84. **IR ν (cm⁻¹):** 1236 (P=O); 1053, 1030 (P-O). **MS m/z (%):** 400 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.45 (Hex/EtOAc 50/50). **Yield:** 50%. Yellow oil.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-isopentyl-3-phenylprop-2-enyl phosphonate (*E*-(32d))
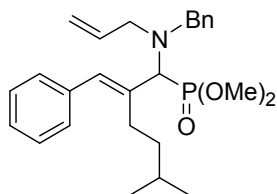
¹H NMR δ (300 MHz, ppm): 0.83-0.88 (3H, multiplet, CH₃); 1.12-1.35 (6H, multiplet, CH₃, CH₂, CH); 2.05-2.17 (1H, multiplet, CH$_A$H$_B$C$_q$=); 2.40-2.49 (1H, multiplet, CH$_A$H$_B$C$_q$=); 3.42-3.57 (2H, multiplet, NCH₂); 3.75 (3H, d, J$_{HP}$ = 10.5 Hz, OCH₃); 3.83 (1H, d, J$_{HP}$ = 21.5 Hz, CHP); 3.87 (3H, d, J$_{HP}$ = 10.5 Hz, OCH₃); 3.96 (1H, d, J$_{AB}$ = 13.5 Hz, CH$_A$H$_B$Ph); 4.04 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 3.9 Hz, CH$_A$H$_B$Ph); 5.15-5.28 (2H, multiplet, =CH₂); 5.77-5.90 (1H, multiplet, =CH); 7.12 (1H, s (br.), =CHPh); 7.21-7.35 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.07 (CH₃), 22.37 (CH₃); 28.02 (CH₂); 31.27 (d, J$_{CP}$ = 10.4 Hz, CH₂C$_q$=); 31.81 (CH); 52.05 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 53.11 (d, J$_{CP}$ = 6.9 Hz, OCH₃); 54.25 (d, J$_{CP}$ = 4.6 Hz, NCH₂); 55.08 (d, J$_{CP}$ = 4.6 Hz, NCH₂Ph); 58.72 (d, J$_{CP}$ = 144.2 Hz, CHP); 117.68 (=CH₂); 126.65, 126.97, 128.17, 128.20, 128.74, 129.10 (CH$_{arom}$); 131.36 (d, J$_{CP}$ = 5.8 Hz, =CHPh); 136.96 (=CH); 137.15 (d, J$_{CP}$ = 8.1 Hz, =C$_q$); 137.68 (C$_{q,arom}$); 139.96 (CH₂C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 28.72 **IR ν (cm⁻¹):** 1247 (P=O); 1058, 1029 (P-O); **MS m/z (%):** 442 (100, [M+H]⁺); 332 (32, [M+H-PO(OMe)₂]⁺). **Chromatography:** R$_f$ = 0.50 (Hex/EtOAc 50/50). **Yield:** 34%. Yellow oil.

Dimethyl *(2Z)*-1-(allylbenzylamino)-2-isopentyl-3-phenylprop-2-enyl phosphonate (*Z*-(32d))
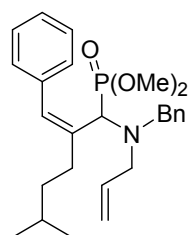
¹H NMR δ (300 MHz, ppm): 0.84-0.96 (3H, multiplet, CH₃); 1.32-1.46 (4H, multiplet, CH₃, CH); 1.61-1.72 (2H, multiplet, CH₂); 2.40-2.63 (2H, multiplet, CH₂C$_q$=); 3.05 (1H, dd, J$_{AB}$ = 14.3 Hz, J = 7.4 Hz, NCH$_A$H$_B$); 3.47-3.57 (1H, multiplet, NCH$_A$CH$_B$); 3.55 (1H, d, J$_{AB}$ = 14.0 Hz, CH$_A$H$_B$Ph); 3.69 (3H, d, J$_{HP}$ = 10.7 Hz, OCH₃); 3.71 (3H, d, J$_{HP}$ = 10.7 Hz, OCH₃); 4.05 (1H, dd, J$_{AB}$ = 14.0 Hz,

J_{HP} = 1.9 Hz, CH$_A$H$_B$Ph); 4.54 (1H, d, J_{HP} = 24.8 Hz, CHP); 4.71-4.87 (2H, multiplet, =CH$_2$); 5.52-5.65 (1H, multiplet, =CH); 6.70 (1H, s (br.), =CHPh); 7.07-7.35 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.22 (CH$_3$); 22.84 (CH$_3$); 28.60 (CH$_2$); 32.01 (CH); 33.54 (CH$_2$C$_q$=); 52.55 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.08 (d, J_{CP} = 6.9 Hz, OCH$_3$); 54.74 (d, J_{CP} = 8.1 Hz, NCH$_2$); 55.55 (d, J_{CP} = 8.1 Hz, NCH$_2$Ph); 56.82 (d, J_{CP} = 156.9 Hz, CHP); 117.28 (=CH$_2$); 126.69, 126.69, 128.06, 128.37, 128.44, 128.89 (CH$_{arom}$); 131.05 (d, J_{CP} = 13.9 Hz, =CHPh); 135.83 (=CH); 136.99 (=C$_q$); 137.92 (C$_{q,arom}$); 139.93 (CH$_2$C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.79. **IR ν$_{max}$ (cm⁻¹):** 1249 (P=O); 1059, 1031 (P-O). **MS: m/z (%):** 442 (100, [M+H]⁺); 332 (19, [M+H-PO(OMe)$_2$]⁺). **Chromatography:** R$_f$ = 0.58 (Hex/EtOAc 50/50). **Yield:** 11%. Yellow oil.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-phenylbut-2-enyl phosphonate (32e)
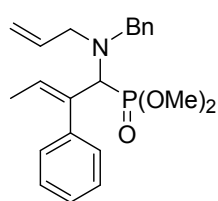
¹H NMR δ (300 MHz, ppm): 1.69 (3H, d, J = 6.3 Hz, CH$_3$); 2.95 (1H, dd, J_{AB} = 13.9 Hz, J = 7.6 Hz, NCH$_A$H$_B$); 3.43 (1H, d, J_{AB} = 13.5 Hz, CH$_A$H$_B$Ph); 3.44-3.51 (1H, multiplet, NCH$_A$H$_B$); 3.70 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.82 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 4.03 (1H, d, J_{HP} = 24.5 Hz, CHP); 4.02-4.08 (1H, multiplet, CH$_A$H$_B$Ph); 4.84-5.01 (2H, multiplet, =CH$_2$); 5.60-5.74 (1H, multiplet, =CH); 6.41 (1H, qd, J = 6.8 Hz, J_{HP} = 1.7 Hz, =CHCH$_3$); 7.04-7.36 (10H, multiplet, =CH). **¹³C NMR δ (75 MHz, ppm):** 15.10 (CH$_3$); 52.63 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.27 (d, J_{CP} = 6.9 Hz, OCH$_3$); 54.35 (d, J_{CP} = 6.9 Hz, NCH$_2$); 55.27 (d, J_{CP} = 6.9 Hz, CH$_2$Ph); 60.81 (d, J_{CP} = 156.9 Hz, CHP); 117.58 (=CH$_2$); 126.76, 127.95, 128.13, 128.95 (CH$_{arom}$); 129.09 (d, J_{CP} = 4.6 Hz, =CHCH$_3$); 134.12 (d, J_{CP} = 8.1 Hz, =C$_q$); 136.47 (=CH); 139.43 (CH$_2$C$_{q,arom}$); 141.51 (d, J_{CP} = 13.9 Hz, C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 27.19. **IR (cm⁻¹) ν$_{max}$:** 1246 (P=O); 1057, 1036 (P-O). **MS: m/z (%):** 386 (100, [M+H]⁺); 276 (10, [M+H-PO(OMe)$_2$]⁺). **Chromatography:** R$_f$ = 0.30 (Hex/EtOAc 50/50). **Yield:** 25%. Yellow oil. - The minor *(2Z)*-isomer could not be obtained in pure form.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-(2-phenylethyl)but-2-enyl phosphonate (32f)
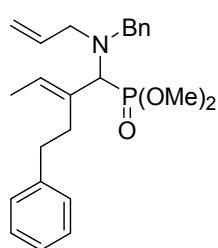
¹H NMR δ (300 MHz, ppm): 1.64 (3H, d, J = 6.8 Hz, CH$_3$); 2.23-2.33 (1H, multiplet, CH$_A$H$_B$Ph); 2.47-2.57 (3H, multiplet, CH$_2$CH$_A$H$_B$Ph); 3.32 (1H, dd, J_{AB} = 13.8 Hz, J = 6.1 Hz, NCH$_A$H$_B$CH); 3.44 (1H, ddd, J_{AB} = 13.8 Hz, J = 6.6 Hz, J = 4.3 Hz, NCH$_A$H$_B$CH); 3.65-3.81 (2H, multiplet, CHP, NCH$_A$H$_B$Ph); 3.68 (3H, d, J_{HP} = 10.6 Hz, OCH$_3$); 3.83 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.92 (1H, dd, J_{AB} = 13.8 Hz, J = 1.1 Hz, NCH$_A$H$_B$Ph); 5.11-5.25 (2H, multiplet, =CH$_2$); 5.79 (1H, ddt, J = 16.6 Hz, J = 10.5 Hz, J = 6.5 Hz, NCH$_2$CH); 6.05 (1H, q, J = 6.8 Hz, CH$_3$CH); 7.10-7.38 (10H, multiplet, CH$_{arom}$). **¹³C NMR (75 MHz, ppm) δ:** 13.69 (CH$_3$); 32.95 (d, J_{CP} = 10.7 Hz, CH$_2$Ph); 34.58 (CCH$_2$); 52.10 (d, J_{CP} = 8.1 Hz, OCH$_3$); 52.87 (d, J_{CP} = 7.0 Hz, OCH$_3$); 54.09 (d, J_{CP} = 4.6 Hz, NCH$_2$CH); 54.84 (d, J_{CP} = 3.4 Hz, NCH$_2$Ph); 59.23 (d, J_{CP} = 143.1 Hz, CHP); 117.76 (C=CH$_2$); 125.89 (CH$_{arom}$); 126.98 (CH$_{arom}$); 127.38 (d, J_{CP} = 5.8 Hz, CH$_3$CH); 128.29 (2 x CH$_{arom}$); 128.38 (2 x CH$_{arom}$); 128.52 (2 x CH$_{arom}$); 129.10 (2 x CH$_{arom}$); 133.48 (d, J_{CP} = 8.0 Hz, HC=CH$_2$); 137.12

(C$_{q,arom}$); 140.17 (C$_{q,arom}$); 141.97 (=C$_q$). **^{31}P NMR (121 MHz, ppm) δ:** 29.01 **IR ν (cm^{-1}):** 1241 (P=O); 1028 (P-O). **MS: m/z (%):** 414 (100, [M+H]$^+$). **Chromatography:** R$_f$ = 0.41 (Hex/EtOAc 40/60). **Yield:** 92%. Yellow oil.

Dimethyl *(2E)*-1-[benzyl(2-methylprop-2-enyl)amino]-3-phenylprop-2-enyl phosphonate (32g)
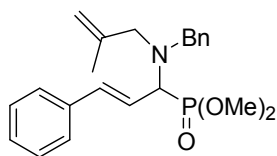
^{1}H NMR δ (300 MHz, ppm): 1.79 (3H, s, CH$_3$); 3.02 (1H, d, J$_{AB}$ = 12.7 Hz, NCH$_A$H$_B$Ph); 3.47 (1H, d, J$_{AB}$ = 13.8 Hz, NCH$_A$H$_B$C); 3.51 (1H, d, J$_{AB}$ = 12.7 Hz, NCH$_A$H$_B$Ph); 3.68 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$); 3.82 (3H, d, J$_{HP}$ = 10.7 Hz, OCH$_3$); 3.82 (1H, dd, J$_{HP}$ = 23.7 Hz, J = 9.8 Hz, CHP); 4.22 (1H, dd, J$_{AB}$ = 13.8 Hz, J = 2.2 Hz, NCH$_A$H$_B$C); 4.91 (1H, s, C=CH$_A$H$_B$); 4.98 (1H, s, C=CH$_A$H$_B$); 6.38 (1H, ddd, J = 15.7 Hz, J = 9.8 Hz, J$_{HP}$ = 6.3 Hz, CHCHP); 6.70 (1H, dd, J$_{HP}$ = 3.0 Hz, J = 15.7 Hz, PhCH); 7.22-7.45 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 20.64 (CH$_3$); 52.85 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 53.31 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 55.14 (d, J$_{CP}$ = 6.9 Hz, NCH$_2$C); 57.84 (d, J$_{CP}$ = 8.1 Hz, NCH$_2$Ph); 59.01 (d, J$_{CP}$ = 160.4 Hz, CHP); 113.63 (C=CH$_2$); 119.74 (CHCHP); 126.75 (2 x CH$_{arom}$); 127.10 (CH$_{arom}$); 128.22 (CH$_{arom}$); 128.40 (2 x CH$_{arom}$); 128.75 (2 x CH$_{arom}$); 128.84 (2 x CH$_{arom}$); 136.40 (C$_{q arom}$); 137.28 (d, J$_{CP}$ = 15.0 Hz, PhCH); 139.57 (C$_{q arom}$); 143.53 (C=CH$_2$). **^{31}P NMR δ (121 MHz, ppm):** 27.48 **IR ν (cm^{-1}):** 1246 (P=O); 1029 (P-O). **MS: m/z (%):** 386 (100, [M+H]$^+$). **Chromatography:** R$_f$ = 0.47 (Hex/EtOAc 40/60). **Mp. (°C):** 78.5. **Yield:** 86%. Yellow crystals.

Dimethyl (allylbenzylamino)[(1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl]methyl phosphonates (32h)

The product was obtained as a mixture of two diastereomeric pairs (ratio: 31/69). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
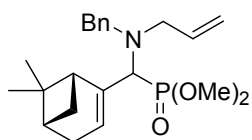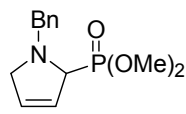
^{1}H NMR δ (300 MHz, ppm): 0.89 (3H, s, CH$_3$, m); 0.92 (3H, s, CH$_3$, M); 1.22 (1H, d, J = 8.5 Hz, CH$_A$H$_B$, m+M); 1.29 (2x3H, s (br.), CH$_3$, m+M); 2.06-2.14 (2x 1H, multiplet, C$_q$CHCH$_2$, m+M); 2.29-2.36 (3+2H, multiplet, CH$_2$CH=, m+M, CHC$_q$=, M); 2.39-2.48 (2+1H, multiplet, CH$_A$H$_B$, m+M, CHC$_q$=, m); 3.07 (2x 1H, dd, J$_{AB}$ = 14.0 Hz, J = 7.2 Hz, NCH$_A$H$_B$, m+M); 3.54-3.66 (2x 2H, multiplet, NCH$_A$H$_B$, CHP m+M); 3,64 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m); 3.67 (3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, M); 3.81 (2x3H, d, J$_{HP}$ = 10.5 Hz, OCH$_3$, m+M); 5.08-5.26 (2x 2H, multiplet, =CH$_2$, m+M); 5.56 (1H, s (br.), =CH, m); 5.71-5.87 (2+1H, multiplet, =CH, M, CH=CH$_2$, m+M); 7.20-7.36 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 21.32 (CH$_3$, m); 21.59 (CH$_3$, M); 26.42 (CH$_3$, m); 26.46 (CH$_3$, M); 31.74 (br.), 31.88 (CH$_2$CH=, CHCH$_2$CH, m+M); 37.82 (C$_q$(CH$_3$)$_2$, m); 38.00 (C$_q$(CH$_3$)$_2$, M); 40.26 (CHCH$_2$, m); 40.31 (CHCH$_2$, M); 45.84 (d, J$_{CP}$ = 4.6 Hz, CHC$_q$=, m); 46.60 (d, J$_{CP}$ = 9.2 Hz, CHC$_q$=, M); 51.85 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, m); 51.94 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 53.01 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, M); 53.24 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$, m); 54.31 (d, J$_{CP}$ = 6.9 Hz, NCH$_2$, m); 54.40 (d, J$_{CP}$ = 6.9 Hz, NCH$_2$, m); 55.24 (d (br.), J$_{CP}$ = 6.9 Hz, NCH$_2$Ph, m+M); 60.40 (d, J$_{CP}$ = 154.6 Hz, CHP, M); 60.57 (d, J$_{CP}$ = 156.9 Hz, CHP, m); 117.41 (=CH$_2$, m); 117.46 (=CH$_2$, M); 125.70 (d, J$_{CP}$ = 9.2 Hz, =CH, M); 126.04 (d, J$_{CP}$ = 13.9 Hz, =CH, m); 126.85 (br.), 128.15, 128.93 (CH$_{arom}$, m+M); 136.90 (CH=CH$_2$, m); 137.00 (CH=CH$_2$, M); 139.86 (C$_{q,arom}$, m);

139.95 ($C_{q,arom}$, M); 140.21 (d, J_{CP} = 5.8 Hz, =C_q, m); 140.66 (d, J_{CP} = 5.8 Hz, =C_q, M). **³¹P NMR δ (121 MHz, ppm):** 27.16 (m); 27.50 (M). **IR ν (cm⁻¹):** 1247 (P=O); 1060, 1036 (br., P-O). **MS m/z (%):** 390 (100, [M+H]⁺). **Chromatography:** Rf = 0.37 (Hex/EtOAc 40/60). **Yield:** 66%. Yellow oil.
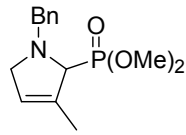
5.3 Ring closure to 2-phosphono 3-pyrrolines

To an ovendry roundbottom flask, 0.34 mmol of aminoalkenyl phosphonate **32** was added together with 4 ml of dry dichloromethane. The solution was stirred under a nitrogen atmosphere and 14.4 mg (5 mol%) of Grubbs' second generation catalyst **302** was added. The reaction mixture was then stirred for 3 – 5 hours at room temperature, depending on the derivative used. The course of the reaction was conveniently monitored using ³¹P NMR spectra of samples directly from the reaction mixture. Only in case of phosphonate **32e**, complete conversion to pyrroline **31e** needed 3 h at reflux temperature. The reaction mixture was then poured into a seperatory funnel containing 5 ml of 1N HCl$_{(aq)}$. After vigorous shaking and phase separation, the organic layer was removed from the funnel. The remaining aqueous layer was washed twice with 2 ml of dichloromethane, then neutralized until slightly basic and extracted twice with 4 ml of dichloromethane. The combined organic phases were dried using MgSO₄. The corresponding pyrrolines **31** were obtained as clear, colourless oils after filtration and evaporation of the solvent.

Dimethyl 1-benzyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (31a)

¹H NMR δ (300 MHz, ppm): 3.29-3.43 (1H, multiplet, C$\underline{H}_A$H$_B$); 3.65 (1H, d, J_{AB} = 13.5 Hz, C$\underline{H}_A$H$_B$Ph); 3.71-3.80 (1H, multiplet, CH$_A\underline{H}_B$); 3.80 (3H, d, J_{HP} = 10.2 Hz, OCH₃); 3.83 (3H, d, J_{HP} = 10.2 Hz, OCH₃); 4.09-4.16 (1H, multiplet, CHP); 5.74-5.92 (1H, multiplet, =C$\underline{H}$CH₂); 5.87-5.92 (1H, multiplet, =C$\underline{H}$CH); 7.22-7.38 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 53.08 (d, J_{CP} = 8.1 Hz, OCH₃); 53.70 (d, J_{CP} = 6.9 Hz, OCH₃); 60.10 (d, J_{CP} = 5.8 Hz, CH₂); 60.53 (d, J_{CP} = 8.1 Hz, CH₂Ph); 68.36 (d, J_{CP} = 176.5 Hz, CHP); 124.00 (d, J_{CP} = 5.8 Hz, =$\underline{C}$HCH₂); 127.00 (CH$_{arom}$); 128.30 (2 x CH$_{arom}$); 128.57 (2 x CH$_{arom}$); 130.21 (d, J_{CP} = 12.7 Hz, =$\underline{C}$HCH); 139.23 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.58. **IR ν (cm⁻¹):** 1246 (P=O); 1058, 1031 (P-O). **MS m/z (%):** 268 (100, [M+H]⁺, 158 (18, [M+H-PO(OMe)₂]⁺). **Yield:** 44%. Colourless oil.

Dimethyl 1-benzyl-3-methyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (31b)

¹H NMR δ (300 MHz, ppm): 1.86 (3H, s (br.), CH₃); 3.19-3.47 (1H, multiplet, NC$\underline{H}_A$H$_B$); 3.63 (d, J_{AB} = 13.2, C$\underline{H}_A$H$_B$Ph); 3.63-3.74 (1H, multiplet, NCH$_A$C$\underline{H}_B$); 3.82 (6H, d, J_{HP} = 10.7 Hz, OCH₃); 3.92 (1H, multiplet, CHP); 4.28 (1H, d, J_{AB} = 13.2 Hz, CH$_A\underline{H}_B$Ph); 5.49-5.52 (1H, multiplet, =CH); 7.21-7.39 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.81 (CH₃); 53.19 (d, J_{CP} = 8.1 Hz, OCH₃); 53.36 (d, J_{CP} = 6.9 Hz, OCH₃); 59.87 (d, J_{CP} = 8.1 Hz, CH₂N); 60.56 (d, J_{CP} = 5.8 Hz, CH₂Ph); 70.84 (d, J_{CP} = 174.2 Hz, CHP);

124.78 (d, J_{CP} = 12.7 Hz, =CH); 126.92, 128.25, 128.60 (CH$_{arom}$); 133.43 (d, J_{CP} = 4.6 Hz, =C$_q$); 139.37 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.69. **IR ν (cm⁻¹):** 1249 (P=O); 1057, 1029 (P-O). **MS m/z (%):** 282 (100, [M+H]⁺). **Yield:** 58%. Colourless oil.

Dimethyl 1,3-dibenzyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (31c)
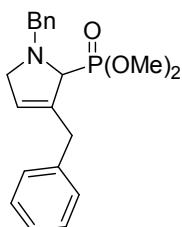
¹H NMR δ (300 MHz, ppm): 3.20-3.34 (1H, multiplet, NCH$_A$H$_B$); 3.43 (1H, d (br.), J_{AB} = 16.2 Hz, CH$_A$H$_B$Ph); 3.60 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$Ph); 3.63-3.76 (2H, multiplet, NCH$_A$CH$_B$, CH$_A$H$_B$Ph); 3.80 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.82 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.89-3.94 (1H, multiplet, CHP); 4.13 (1H, d, J_{AB} = 13.2 Hz, CH$_A$H$_B$Ph); 5.43-5.48 (1H, multiplet, =CH); 7.20-7.34 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 35.33 (CH$_2$Ph); 53.29 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.39 (d, J_{CP} = 8.1 Hz, OCH$_3$); 59.93 (d, J_{CP} = 6.9 Hz, CH$_2$N); 60.65 (d, J_{CP} = 6.9 Hz, CH$_2$Ph); 69.04 (d, J_{CP} = 173.1 Hz, CHP); 125.76 (d, J_{CP} = 11.5 Hz, =CH); 126.37, 127.06, 128.34, 128.49, 128.73, 129,15 (CH$_{arom}$); 137.67 (d, J_{CP} = 4.6 Hz, =C$_q$); 138.89, 139.24 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.69. **IR ν (cm⁻¹):** 1245 (P=O); 1056, 1029 (P-O). **MS m/z (%):** 358 (100, [M+H]⁺) 248 (34, [M+H-PO(OMe)$_2$]⁺). **Yield:** 62%. Colourless oil.

Dimethyl 1-benzyl-3-isopentyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (31d)
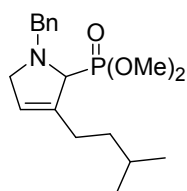
¹H NMR δ (300 MHz, ppm): 0.90 (3H, ~t, J = 6.7 Hz, CH$_3$); 1.25-1.38 (4H, multiplet, CH$_3$, CH); 1.42-1.55 (2H, multiplet, CH$_2$); 2.06-2.31 (2H, multiplet, CH$_2$C$_q$=); 3.20-3.34 (1H, multiplet, NCH$_A$H$_B$); 3.63 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$Ph); 3.65-3.78 (1H, multiplet, NCH$_A$CH$_B$); 3.80 (3H, d, J_{HP} = 10.2 Hz, OCH$_3$); 3.81 (3H, d, J_{HP} = 10.2 Hz, OCH$_3$); 3.93-3.99 (1H, multiplet, CHP); 4.24 (1H, d, J_{AB} = 13.2 Hz, CH$_A$H$_B$Ph); 5.51 (1H, s (br.), =CH); 7.21-7.38 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.15 (CH$_3$); 22.59 (CH$_3$); 27.28 (CH$_2$); 28.76 (CH$_2$C$_q$=); 31.64 (CH); 53.36 (d, J_{CP} = 6.9 Hz, 2xOCH$_3$); 60.02 (d, J_{CP} = 8.1 Hz, CH$_2$N); 60.81 (d, J_{CP} = 6.9 Hz, CH$_2$Ph); 69.87 (d, J_{CP} = 174.2 Hz, CHP); 123.28 (d, J_{CP} = 11.5 Hz, =CH); 127.01, 128.34, 128.67 (CH$_{arom}$); 138.34 (d, J_{CP} = 4.6 Hz, =C$_q$); 139.45 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 24.91. **IR ν (cm⁻¹):** 1249 (P=O); 1058, 1032 (P-O). **MS m/z (%):** 338 (100, [M+H]⁺); 228 (17, [M+H-PO(OMe)$_2$]⁺). **Yield:** 70%. Colourless oil.

Dimethyl 1-benzyl-3-phenyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (31e)
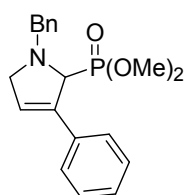
Could only be isolated together with small amounts of pyrrole **30e** because of spontaneous oxidation. Spectral data given below are determined from the mixture and are indicative.

¹H NMR δ (300 MHz, ppm): 3.51 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.52-3.60 (1H, multiplet, NCH$_A$H$_B$); 3.64 (3H, d, J_{HP} = 10.5 Hz, OCH$_3$); 3.82 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$Ph); 3.93-4.05 (1H, multiplet, NCH$_A$CH$_B$); 4.15 (1H, d, J_{AB} = 13.2 Hz, NCH$_A$H$_B$Ph); 4.54-4.59 (1H, multiplet, CHP); 6.17-6.19 (1H, multiplet, =CH); 7.19-7.45 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75**
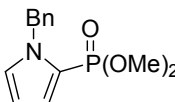
MHz, ppm): 53.20 (d, J_{CP} = 6.9 Hz, OCH$_3$); 60.60 (d, J_{CP} = 4.5 Hz, CH$_2$N); 61.22 (d, J_{CP} = 9.2 Hz, CH$_2$Ph); 68.67 (d, J_{CP} = 173.1 Hz, CHP); 126.98 (d, J_{CP} = 11.5 Hz, =CH); 127.06, 127.24, 127.89, 128.25, 128.43, 128.84 (CH$_{arom}$); 134.05 (C$_{q,arom}$) 137.52 (d, J_{CP} = 3.5 Hz, =C$_q$); 139.12 (C$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 24.64.

5.4 Ring closure – oxidation to 2-phosphono pyrroles
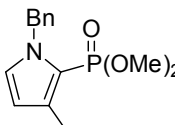
5.4.1 Preparation of *N*-Benzyl pyrroles

To an ovendry roundbottom flask, 0.39 mmol of aminoalkenyl phosphonate **32** is added together with 4 ml of dry dichloromethane. The solution was stirred under a nitrogen atmosphere and 16.4 mg (5 mol%) of Grubbs' second generation catalyst **302** was added. The reaction mixture was then stirred for 2 hours at room temperature, giving approximately 60% conversion to the pyrroline. Then 94.8 mg (0.39 mmol) of TCQ was added and stirring was continued for 3 to 5 hours at room temperature. The course of the reaction was conveniently monitored using ^{31}P NMR spectra of samples directly from the reaction mixture. Only in case of phosphonate **32e**, complete conversion to pyrrole **30e** needed 5 h at reflux followed by 12 h at room temperature. When complete conversion was obtained, the solvent was removed under reduced pressure. The pyrroles **30** were obtained in pure form as brownish oils using column chromatography on silica gel with a hexane, ethyl acetate mixture as a mobile phase.

Dimethyl 1-benzyl-*1H*-pyrrol-2-yl phosphonate (30a)

^{1}H NMR δ (300 MHz, ppm): 3.60 (6H, d, J_{HP} = 11.6 Hz, OCH$_3$); 5.36 (2H, s, NCH$_2$); 6.22-6.26 (1H, multiplet, =CH); 6.86-6.89 (1H, multiplet, =CHC$_q$); 6.90-6.94 (1H, multiplet, =CHN); 7.10–7.34 (5H, multiplet, CH$_{arom}$). **^{13}C NMR d (75 MHz, ppm):** 52.44 (NCH$_2$); 52.75 (d, J_{CP} = 4.6 Hz, OCH$_3$); 109.12 (d, J_{CP} = 13.8 Hz, =CH); 117.63 (d, J_{CP} = 227.3 Hz, =C$_q$P); 122.47 (d, J_{CP} = 17.3 Hz, =CHC$_q$); 127.19, 127.73, 128.67 (CH$_{arom}$); 129.04 (d, J_{CP} = 11.5 Hz, =CHN); 137.9 (C$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 13.63. **IR ν (cm^{-1}):** 1250 (P=O); 1029 (br., P-O). **MS m/z (%):** 266 (100, [M+H]$^+$). **Chromatography:** R$_f$ = 0.26 (Hex/EtOAc 40/60). **Yield:** 75%. Yellow oil.

Dimethyl 1-benzyl-3-methyl-*1H*-pyrrol-2-yl phosphonate (30b)

^{1}H NMR δ (300 MHz, ppm): 2.29 (3H, d, J = 1.4 Hz, CH$_3$); 3.53 (6H, d, J_{HP} = 11.7 Hz, OCH$_3$); 5.38 (2H, s, NCH$_2$); 6.07-6.09 (1H, multiplet, =CH); 6.82 (1H, dd, J_{HP} = 5.0 Hz, J = 2.5 Hz, =CHN); 7.07–7.35 (5H, multiplet, CH$_{arom}$). **^{13}C NMR δ (75 MHz, ppm):** 12.93 (CH$_3$); 52.03 (d, J_{CP} = 4.6 Hz, OCH$_3$); 52.46 (NCH$_2$); 111.25 (d, J_{CP} = 15.0 Hz, =CH); 113.49 (d, J_{CP} = 226.1 Hz, =C$_q$P); 126.91, 127.38 (CH$_{arom}$); 128.54 (d, J_{CP} = 12.7 Hz, =CHN); 128.50 (CH$_{arom}$); 133.47 (d, J_{CP} = 18.5 Hz, =C$_q$); 138.62 (C$_{q,arom}$). **^{31}P NMR δ (121 MHz, ppm):** 14.82. **IR ν (cm^{-1}):** 1249 (P=O); 1025 (br., P-O). **MS m/z (%):** 280 (100, [M+H]$^+$). **Chromatography:** R$_f$ = 0.27 (Hex/EtOAc 40/60). **Yield:** 84%. Yellow oil.

Dimethyl 1,3-dibenzyl-*1H*-pyrrol-2-yl phosphonate (30c)
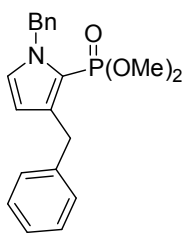
¹H NMR δ (300 MHz, ppm): 3.47 (6H, d, J_{HP} = 11.6 Hz, OCH₃); 4.11 (2H, s, CH₂); 5.38 (2H, s, NCH₂); 6.02 (1H, dd, J_{HP} = 4.2 Hz, J = 2.5 Hz, =CH); 6.84 (1H, dd, J_{HP} = 5.0 Hz, J = 2.5 Hz, =CHN); 7.07–7.35 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 33.06 (CH₂); 52.07 (d, J_{CP} = 5.8 Hz, OCH₃); 52.48 (NCH₂); 110.89 (d, J_{CP} = 16.2 Hz, =CH); 113.47 (d, J_{CP} = 226.0 Hz, =C$_q$P); 125.70, 126.92, 127.43, 128.19, 128.51 (CH$_{arom}$); 128.73 (d, J_{CP} = 11.5 Hz, =CHN); 128.80 (CH$_{arom}$); 137.15 (d, J_{CP} = 18.5 Hz, =C$_q$); 138.44 (C$_{q,arom}$); 141.78 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 14.39. **IR ν (cm⁻¹):** 1240 (P=O); 1023 (br., P-O). **MS m/z (%):** 356 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.29 (Hex/EtOAc 40/60). **Yield:** 72%. Yellow oil.

Dimethyl 1-benzyl-3-isopentyl-*1H*-pyrrol-2-yl phosphonate (30d)
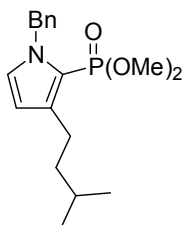
¹H NMR δ (300 MHz, ppm): 0.87-0.92 (3H, multiplet, CH₃); 1.28-1.40 (4H, multiplet, CH, CH₃); 1.54-1.64 (2H, multiplet, CH₂); 2.69 (2H, t, J = 7.8 Hz, CH₂C$_q$=); 3.52 (6H, d, J_{HP} = 11.6 Hz, OCH₃); 5.38 (2H, s, NCH₂); 6.13 (1H, dd, J_{HP} = 4.1 Hz, J = 2.8 Hz, =CH); 6.84 (1H, dd, J_{HP} = 5.1 Hz, J = 2.8 Hz, =CHN); 7.06–7.32 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 14.18 (CH₃); 22.67 (CH₃); 26.96 (CH₂C$_q$=); 31.03 (CH₂); 31.89 (CH); 52.08 (d, J_{CP} = 5.8 Hz, OCH₃); 52.47 (NCH₂); 109.86 (d, J_{CP} = 15.0 Hz, =CH); 112.92 (d, J_{CP} = 226.1 Hz, =C$_q$P); 126.95, 127.42, 128.55 (CH$_{arom}$); 128.71 (d, J_{CP} = 12.7 Hz, =CHN); 138.78 (C$_{q,arom}$); 139.38 (d, J_{CP} = 19.6 Hz, =C$_q$). **³¹P NMR δ (121 MHz, ppm):** 14.87. **IR ν (cm⁻¹):** 1250 (P=O); 1025 (br.) (P-O). **MS m/z (%):** 336 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.46 (Hex/EtOAc 40/60). **Yield:** 70%. Yellow oil.

Dimethyl 1-benzyl-3-phenyl-*1H*-pyrrol-2-yl phosphonate (30e)
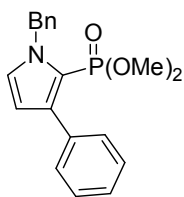
¹H NMR δ (300 MHz, ppm): 3.36 (6H, d, J_{HP} = 11.6 Hz, OCH₃); 5.57 (2H, s, NCH₂); 6.29 (1H, dd, J_{HP} = 4.0 Hz, J = 2.5 Hz, =CH); 6.94 (1H, dd, J_{HP} = 5.0 Hz, J = 2.5 Hz, =CHN); 7.19–7.46 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 52.09 (d, J_{CP} = 5.8 Hz, OCH₃); 52.95 (NCH₂); 110.98 (d, J_{CP} = 13.9 Hz, =CH); 113.79 (d, J_{CP} = 226.1 Hz, =C$_q$P); 126.88, 127.32, 127.58, 128.57 (CH$_{arom}$); 128.66 (d, J_{CP} = 12.7 Hz, =CHN); 129.46 (CH$_{arom}$); 135.99 (C$_{q,arom}$); 137.46 (d, J_{CP} = 18.5 Hz, =C$_q$); 138.28 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 13.77. **IR ν (cm⁻¹):** 1249 (P=O); 1053, 1028 (br., P-O). **MS m/z (%):** 342 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.30 (Hex/EtOAc 40/60). **Yield:** 75%. Brown oil.

Dimethyl 1-benzyl-3-(2-phenylethyl)-*1H*-pyrrol-2-yl phosphonate (30f)
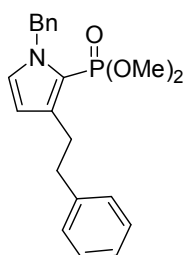
¹H NMR δ (300 MHz, ppm): 2.87-2.92 (2H, multiplet, CH₂Ph); 3.01-3.06 (2H, multiplet, CH₂CH₂Ph); 3.47 (6H, d, J_{HP} = 11.6 Hz, 2 x OCH₃); 5.37 (2H, s, NCH₂); 6.13 (1H, dd, J = 4.1 Hz, J = 2.5 Hz, NCHCH); 6.84 (1H, dd, J = 5.0 Hz, J = 2.5 Hz, NCH); 7.03-7.35 (10H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 29.19 (CH₂CH₂Ph); 37.89 (CCH₂); 52.11 (d, J_{CP} = 5.8 Hz, 2 x OCH₃); 52.52 (NCH₂);
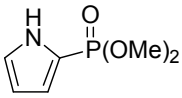
110.12 (d, J_{CP} = 16.2 Hz, NCH$\underline{C}$H); 113.32 (d, J_{CP} = 225.0 Hz, CP); 125.81 (CH$_{arom}$); 126.87 (2 x CH$_{arom}$); 127.47 (CH$_{arom}$); 128.29 (2 x CH$_{arom}$); 128.58 (2 x CH$_{arom}$); 128.62 (d, J_{CP} = 12.7 Hz, NCH); 128.75 (2 x CH$_{arom}$); 138.24 (d, J_{CP} = 19.6 Hz, NC$\underline{C}$); 138.75 (C$_{q,arom}$); 142.32 (C$_{q,arom}$). **³¹P NMR δ (121 MHz, ppm):** 14.52. **IR ν (cm⁻¹):** 1248 (P=O); 1025 (P-O). **MS m/z (%):** 370.2 (100, [M+H]⁺). **Chromatography:** R_f = 0.27 (Hex/EtOAc 60/40). **Yield:** 71%. Brown oil.
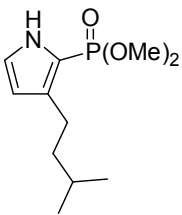
5.4.2 Preparation of NH-pyrroles

To an ovendry roundbottom flask, 0.61 mmol of aminoalkenyl phosphonate **22e,m** was added together with 6 ml of dry dichloromethane and 149 mg (0.61 mmol) of TCQ. The solution was stirred under a nitrogen atmosphere and 25.7 mg (5 mol%) of Grubbs' second generation catalyst **302** was added. The reaction mixture was then stirred during 23 hours at reflux temperature. The course of the reaction was conveniently monitored using ³¹P NMR spectra of samples directly taken from the reaction mixture. When complete conversion was obtained, the solvent was removed under reduced pressure. The pyrroles **312** were obtained in pure form as brownish oils using column chromatography on silica gel with an hexane, ethyl acetate mixture as mobile phase.

Dimethyl *1H*-pyrrol-2-yl phosphonate (312a)

¹H NMR δ (300 MHz, ppm): 3.73 (6H, d, J_{H-P} = 11.6 Hz, OCH$_3$); 6.29-6.33 (1H, multiplet, =CH); 6.73-6.76 (1H, multiplet, =CHC$_q$); 7.07-7.10 (1H, multiplet, =CHN). **¹³C NMR δ (75 MHz, ppm):** 53.00 (d, J_{CP} = 5.8 Hz, OCH$_3$); 109.93 (d, J_{CP} = 15.0 Hz, =CH); 115.16 (d, J_{CP} = 230.8 Hz, =C$_q$P); 118.65 (d, J_{CP} = 17.3 Hz, =CHC$_q$); 124.59 (d, J_{CP} = 12.7 Hz, =CHN). **³¹P NMR δ (121 MHz, ppm):** 15.01. **IR ν (cm⁻¹):** 3199 (NH); 1244 (P=O); 1029 (br.) (P-O). **MS^{EI} m/z (%):** 175 (100, M⁺); 130 (30); 80 (87); 67 (47). **Chromatography:** R_f = 0.20 (EtOAc). **Yield:** 39%. Brown oil.

Dimethyl 3-isopentyl-*1H*-pyrrol-2-ylphosphonate (312b)

¹H NMR δ (300 MHz, ppm): 0.86-0.92 (3H, multiplet, CH$_3$); 1.25-1.41 (4H, multiplet, CH, CH$_3$); 1.52-1.63 (2H, multiplet, CH$_2$); 2.58 (2H, t, J = 7.8 Hz, CH$_2$C$_q$=); 3.71 (6H, d, J_{HP} = 11.6 Hz, OCH$_3$); 6.18-6.21 (1H, multiplet, =CH); 6.93-6.97 (1H, multiplet, =CHN). **¹³C NMR δ (75 MHz, ppm):** 14.04 (CH$_3$); 22.54 (CH$_3$); 26.28 ($\underline{C}$H$_2$C$_q$=); 30.64 (CH$_2$); 31.70 (CH); 52.44 (d, J_{CP} = 5.8 Hz, OCH$_3$); 110.82 (d, J_{CP} = 15.0 Hz, =CH); 111.74 (d, J_{CP} = 229.6 Hz, =C$_q$P); 123.35 (d, J_{CP} = 11.5 Hz, =CHN); 135.21 (d, J_{CP} = 18.5 Hz, =C$_q$). **³¹P NMR δ (121 MHz, ppm):** 16.21. **IR ν (cm⁻¹):** 3215 (NH); 1245 (P=O); 1053, 1030 (P-O). **MS m/z (%):** 246 (100, [M+H]⁺). **Chromatography:** R_f = 0.23 (Hex/EtOAc 2/3). **Yield:** 27%. Brown oil.

5.5 Evaluation of the preparation of bicyclic phosphono β-lactams via RCM

5.5.1 Evaluation of the ring closure of β-lactam 23e

A solution of 0.32 g (1 mmol) of *N*-allyl lactam **23e** in 2 ml of dry dichlormethane was added to a solution of 42.5 mg (5 mol%) of Grubbs' second generation catalyst **302** in 1 ml of dry dichloromethane under a nitrogen atmosphere. The resulting mixture was heated under reflux for one hour, before the solvent was evaporated under reduced pressure. The dimeric azetidinone **314** could be obtained as a mixture of *E* and *Z* isomers using column chromatography. Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible. Major/Minor : 67/33.

Tetramethyl 4-oxo-1-[(*2E*)-4-(4-oxo-2-phosphono-2-(2-phenylethenyl)-azetidin-1-yl)but-2-enyl]-2-(2-phenylethenyl)azetidin-2-yl phosphonate (314)
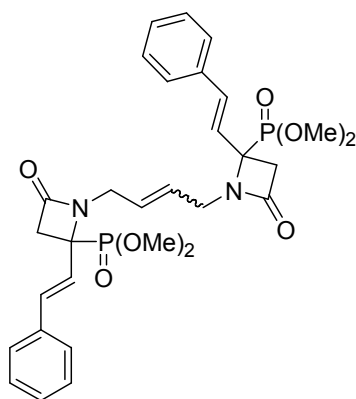
¹H NMR δ (300 MHz, ppm): 2.89-3.07 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 3.33-3.54 (2x 1H, multiplet, CH$_A$H$_B$, m+M); 3.79-3.94 (2x 7H, multiplet, 2x OCH$_3$, CH$_A$H$_B$N, m+M); 4.04-4.18 (2x 1H, multiplet, CH$_A$H$_B$N); 5.82-5.92 (2x 1H, multiplet, =CHCH$_2$, m+M); 6.36-6.51 (2x 1H, multiplet, =CHC$_q$, m+M); 6.66-6.83 (2x 1H, multiplet, =CHPh, m+M); 7.26-7.42 (2x 5H, multiplet, =CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 43.52 (NCH$_2$, m); 43.63 (NCH$_2$, M); 47.57 (CH$_2$, m); 47.89 (CH$_2$, M); 53.82 (d, J$_{CP}$ = 8.1 Hz, OCH$_3$); 54.13 (d, J$_{CP}$ = 6.9 Hz, OCH$_3$); 58.72 (d, J$_{CP}$ = 167.3 Hz, CHP, m); 58.75 (d, J$_{CP}$ = 167.3 Hz, CHP, M); 122.70 (d, J$_{CP}$ = 6.9 Hz, =CHC$_q$, m); 122.84 (d, J$_{CP}$ = 6.9 Hz, =CHC$_q$, m); 126.87 (CH$_{arom}$, m+M); 128.15 (=CHCH$_2$, m); 128.22 (=CHCH$_2$, M); 128.70, 128.83 (CH$_{arom}$, m+M); 134.26 (d, J$_{CP}$ = 9.2 Hz, =CHPh, M); 134.31 (d, J$_{CP}$ = 9.2 Hz, =CHPh, m); 135.50 (br., C$_{q,arom}$); 165.87 (d, J$_{CP}$ = 8.1 Hz, CO, m+M). **³¹P NMR δ (121 MHz, ppm):** 24.21 (m); 24.27 (M). **IR ν (cm⁻¹):** 1757 (C=O); 1251 (P=O); 1032 (br., P-O). **MS m/z (%):** 615 (100, [M+H]⁺). **Chromatography:** R$_f$ = 0.18 (CH$_3$CN/CH$_2$Cl$_2$/MeOH 77/20/3). **Yield:** 43%. Yellow oil.

5.5.2 Preparation of *N*-acetyl 2-phosphono pyrrolines

A 0.05 M solution of 1-(acetylallylamino)alkenyl phosphonate **21e** or **255a** in dry dichloromethane was stirred at room temperature under a nitrogen atmosphere. Then, 5 mol% of Grubbs' second generation catalyst **302** was added and the reaction mixture was refluxed for 2 h, giving complete conversion to the corresponding pyryolines. The solvent was evaporated under reduced pressure and the catalyst was removed over a short silica gel column.

Dimethyl 1-chloroacetyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonate (34)

Obtained as a mixture of two rotamers (ratio 33/67 at 22°C)
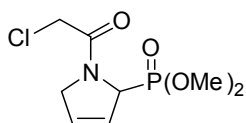
¹H NMR δ (300 MHz, ppm): 3.80 (3H, d, J_{HP} = 10.7 Hz, OCH_3, M); 3.82 (3H, d, J_{HP} = 10.5 Hz, OCH_3, M); 3.77-3.84 (7+1H, multiplet, OCH_3, m, NCH_AH_B, m+M); 4.10 (2H, s, CH_2Cl, M); 4.24 (1H, d, J_{AB} = 12.9 Hz, CH_AH_BCl, m); 4.41-4.48 (2x1H, multiplet, NCH_AH_B, m+M); 4.61 (1H, d, J_{AB} = 12.9 Hz, CH_AH_BCl, m); 5.08-5.14 (1H, multiplet, CHP, m); 5.17-5.23 (1H, multiplet, CHP, M); 5.84-6.12 (2x2H, multiplet, HC=CH, m+M). **¹³C NMR δ (75 MHz, ppm):** 41.66 (CH_2Cl, m); 41.75 (CH_2Cl, M); 53.12 (d, J_{CP} = 5.8 Hz, OCH_3, M); 53.71 (d, J_{CP} = 6.9 Hz, OCH_3, m); 53.89 (d, J_{CP} = 6.9 Hz, OCH_3, M); 54.09 (NCH_2, M); 54.13 (d, J_{CP} = 6.9 Hz, OCH_3, m); 54.62 (NCH_2, m); 61.32 (d, J_{CP} = 158.1 Hz, CHP, M); 61.49 (d, J_{CP} = 160.4 Hz, CHP, m); 123.41 (d, J_{CP} = 8.1 Hz, =CH, m); 124.76 (d, J_{CP} = 6.9 Hz, =CH, M); 127.80 (d, J_{CP} = 10.4 Hz, =CH, M); 129.25 (d, J_{CP} = 10.4 Hz, =CH, m); 165.09 (CO, M); 166.17 (CO, m). **³¹P NMR δ (121 MHz, ppm):** 21.66 (m); 22.91 (M). **IR ν (cm⁻¹):** 1666 (C=O); 1623 (C=C); 1247 (P=O); 1036 (br., P-O). **MS m/z (%):** 254 (100, [M+H]⁺); 256 (28, [M+H+2]⁺). **Chromatography:** R_f = 0.10 (EtOAc). **Yield:** 63%. Brown oil.

Dimethyl 1-acetyl-2,5-dihydro-*1H*-pyrrol-2-yl phosphonates (315)

Obtained as a mixture of two rotamers (ratio 28/72 at 22°C)
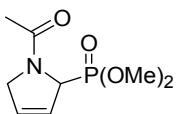
¹H NMR δ (300 MHz, ppm): 2.13 (3H, s, CH_3, M); 2.27 (3H, s, CH_3, m); 3.81 (3H, d, J_{HP} = 10.2 Hz, OCH_3, M); 3.81 (3H, d, J_{HP} = 10.5 Hz, OCH_3, m); 4.00-4.11 (1H, multiplet, NCH_AH_B, m); 4.31-4.39 (2H, multiplet, NCH_2, M); 4.63 (1H, dd, J = 16.9 Hz, J = 16.9 Hz, NCH_AH_B, m); 4.90 (1H, s (br.), CHP, m); 5.15-5.21 (1H, multiplet, CHP, M); 5.83-6.12 (2x2H, multiplet, HC=CH, m+M). **¹³C NMR δ (75 MHz, ppm):** 21.98 (CH_2Cl, m); 22.28 (CH_2Cl, M); 52.78, 52.84, 53.67 (br., OCH_3, m+M, NCH_2, m); 54.81 (NCH_2, M); 60.47 (d, J_{CP} = 158.1 Hz, CHP, M); 62.42 (d, J_{CP} = 160.4 Hz, CHP, m); 123.63 (d, J_{CP} = 8.1 Hz, =CH, m); 124.91 (br., =CH, M); 128.11 (d, J_{CP} = 10.4 Hz, =CH, M); 129.64 (d, J_{CP} = 9.2 Hz, =CH, m); 169.12 (CO, M); 170.29 (CO, m). **³¹P NMR δ (121 MHz, ppm):** 23.86 (m); 22.18 (M). **IR ν (cm⁻¹):** 1651 (C=O); 1620 (C=C); 1245 (P=O); 1033 (br., P-O). **MS m/z (%):** 220 (100, [M+H]⁺). **Chromatography:** R_f = 0.13 (EtOAc). **Yield:** 68%. Brown oil.

6 Synthesis of tricyclic phosphono pyrrolidines

6.1 Preparation of dimethyl (acryloylbenzylamino)furan-2-ylmethyl phosphonate (321)

A solution of 5 mmol of 1-benzylamino-2-furan-2-ylmethyl phosphonate **(22y)** and 10 mmol of pyridine in 12 ml of dry THF was stirred at room temperature under a nitrogen atmosphere. A solution of 7.5 mmol of acryloyl chloride in 3 ml of dry THF was added dropwise to the reaction mixture using a syringe and stirring was

continued for 3 h at room temperature. Then the mixture was poured into 15 ml of a saturated NaHCO$_{3(aq)}$ solution and 15 ml of diethyl ether. The organic phase was collected and the remaining water phase was washed twice with 10 ml of diethyl ether. The combined organic phases were then washed with 10 ml of 1 M HCl$_{(aq)}$ and dried with MgSO$_4$. The product was obtained in high purity after filtration of the solids and evaporation of the solvent under reduced pressure.
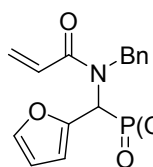
¹H NMR δ (300 MHz, ppm): 3.71 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.80 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$); 4.81 (1H, d, J_{AB} = 18.2 Hz, NCH$_A$H$_B$); 5.10 (1H, d, J_{AB} = 18.2 Hz, NCH$_A$H$_B$); 5.63 (1H, dd, J = 10.1 Hz, J_{AB} = 2.1 Hz, =CH$_A$H$_B$); 6.19 (1H, multiplet, CH=CHO); 6.32 (1H, dd, J = 16.5 Hz, J = 9.9 Hz, HC=CH$_2$); 6.46 (1H, dd, J = 16.5 Hz, J_{AB} = 2.2 Hz, =CH$_A$H$_B$); 6.62 (1H, d, J = 2.7 Hz, CH=C$_q$O); 6.70 (1H, d, J_{HP} = 23.2 Hz, CHP); 6.88 (2H, multiplet, CH$_{arom}$); 7.09-7.20 (3H, multiplet, CH$_{arom}$); 7.25 (1H, d (br.), J = 1.1 Hz, CHO). **¹³C NMR δ (75 MHz, ppm):** 47.19 (d, J_{CP} = 162.7 Hz, CHP); 48.95 (CH$_2$N); 53.44 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.84 (d, J_{CP} = 6.9 Hz, OCH$_3$); 110.75 (CH=CHO); 112.79 (CH=C$_q$); 125.38 (2x CH$_{arom}$); 126.76 (CH$_{arom}$); 127.35 (HC=CH$_2$); 128.31 (2x CH$_{arom}$); 129.90 (=CH$_2$); 137.54 (C$_{q,arom}$); 143.28 (CHO); 146.31 (d, J_{CP} = 10.4 Hz, C$_q$O); 166.91 (d, J_{CP} = 3.5 Hz, C=O). **³¹P NMR δ (121 MHz, ppm):** 21.48. **IR ν (cm⁻¹):** 1029 (P-O); 1053 (P-O); 1229-1252 (P=O); 1647 (C=O). **MS m/z (%):** 350 (100 [M+H]⁺). **Yield:** 99%.

6.2 Preparation of dimethyl (3-*t*-butyl-4-oxo-6-phenyl-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl) phosphonate (323b)

A solution of 5 mmol of *t*-butylaminofuran-2-ylmethyl phosphonate **(22ab)** and 10 mmol of pyridine in 12 ml of dry THF was stirred at room temperature under a nitrogen atmosphere. A solution of 7.5 mmol of cinnamoyl chloride in 3 ml of dry THF was added dropwise to the reaction mixture using a syringe. The mixture was then refluxed for 7 h. Afterwards, the mixture was poured into 15 ml of a saturated NaHCO$_{3(aq)}$ solution and 15 ml of diethyl ether. The organic phase was collected and the remaining water phase was washed twice with 10 ml of diethyl ether. The combined organic phases were then washed with 10 ml of 1 M HCl$_{(aq)}$ and dried with MgSO$_4$. After filtration of the solids and evaporation of the solvent under reduced pressure, a brown oil was found from which the ring closed product could be obtained in pure form using column chromatography.

Dimethyl (3-*t*-butyl-4-oxo-6-phenyl-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl)-phosphonate (323b)
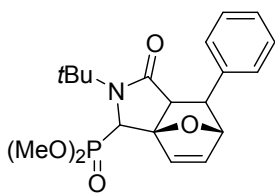
¹H NMR δ (300 MHz, ppm): 1.56 (9H, s, 3x CH$_3$); 2.84 (1H, d, J = 4.4 Hz, CHC$_q$O); 3.75 (1H, dd, J = 4.4 Hz, J = 4.4 Hz, CHPh); 3.87 (3H, d, J_{HP} = 5.8 Hz, OCH$_3$); 3.90 (3H, d, J_{HP} = 5.8 Hz, OCH$_3$); 4.41 (1H, d, J_{HP} = 5.0 Hz, CHP); 5.12 (1H, d, J = 4.4 Hz, CHO); 6.28 (1H, dd, J = 6.0 Hz, J = 1.7 Hz, =CHCHO); 6.75 (1H, d, J = 6.0 Hz, =CHC$_q$); 7.13-7.29 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 27.89 (3x CH$_3$); 49.13 (CHPh); 53.18 (d, J_{CP} = 6.9 Hz, OCH$_3$);

53.93 (d, J_{CP} = 6.9 Hz, OCH$_3$); 55.76 (C̲HC$_q$O); 56.37 (NC$_q$); 57.19 (d, CHP, J_{CP} = 162.7 Hz); 81.67 (CHO); 91.14 (d, J_{CP} = 8.1 Hz, C$_q$O); 126.76 (CH$_{arom}$); 128.04 (2x CH$_{arom}$); 128.34 (2x CH$_{arom}$); 134.21 (=CHC$_q$); 135.50 (=C̲HCHO); 139.20 (C$_{q,arom}$); 175.52 (C=O). **³¹P NMR δ (121 MHz, ppm):** 22.78. **IR ν (cm⁻¹):** 1687 (C=O); 1251 (P=O); 1032, 1046 (P-O). **MS m/z (%):** 392 (100, [M+H]⁺). **Chromatography:** Rf = 0.27 (Hex/EtOAc 50/50). **Yield:** 19%. Yellow oil.

6.3 Intramolecular Diels-Alder with furane (IMDAF)

A solution of 1.25 g of a suitable allylamino-1-furan-2-yl-methyl phosphonate in 13 ml of toluene was refluxed until complete disappearance of the starting material was obtained (monitoring by ³¹P NMR). Then the solvent was removed under reduced pressure and the corresponding adducts were obtained in good purity. Further purification could be performed using column chromatography.

Dimethyl 3-(2-chloroacetyl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates (35a)

The product was obtained as a mixture of two diastereoisomers (ratio: 27/73). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
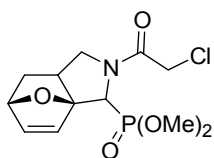
¹H NMR δ (300 MHz, ppm): 1.64 (1H, dd, J_{AB} = 11.6 Hz, J = 7.7 Hz, CH̲$_A$H$_B$, M); 1.86 (1H, ddd, J_{AB} = 11.6 Hz, J = 4.4 Hz, J = 2.8 Hz, CH$_A$H̲$_B$, M); 2.33-2.42 (1H, multiplet, CH, m); 2.56-2.65 (1H, multiplet, CH, M); 3.29 (1H, ~t, J ≈ 8.5 Hz, CH̲$_A$H$_B$N, M); 3.43 (1H, dd, J = 12.1 Hz, J = 7.7 Hz, NCH$_2$, m); 3.82 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$, M); 3.86 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$, m); 3.88 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$, M); 3.90 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$, m); 4.03-4.15 (3+1H, multiplet, CH$_2$Cl, M, CH$_A$H̲$_B$N, m+M); 4.22 (1H, d, J_{AB} = 12.9 Hz, CH̲$_A$H$_B$Cl, m); 4.47 (1H, d, J_{AB} = 12.9 Hz, CH$_A$H̲$_B$Cl, m); 4.68 (1H, d, J_{HP} = 7.2 Hz, CHP, m); 4.97 (1H, d, J_{HP} = 10.7 Hz, CHP, M); 5.04-5.09 (2x1H, multiplet, OCH, m+M); 6.46 (2x 1H, dd, J = 5.9 Hz, J = 1.8 Hz, =CHCHO, m+M); 6.57 (1H, d, J = 5.8 Hz, =CH, m); 6.68 (1H, d, J = 5.8 Hz, =CH, M). **¹³C NMR δ (75 MHz, ppm):** 34.38 (CH$_2$); 36.51 (CH, m); 41.87, 42.04 (CH$_2$Cl, m+M, CH, M); 52.53 (NCH$_2$, m+M); 53.45, 53.52, 53.60, 54.03, 54.12 (OCH$_3$, m+M); 54.91 (d, J_{CP} = 159.2 Hz, CHP, M); 56.40 (d, J_{CP} = 162.7 Hz, CHP, M); 79.22 (CHO, M); 79.31 (CHO, m); 94.01 (d, J_{CP} = 9.2 Hz, OC$_q$, M); 95.47 (d, J_{CP} = 8.1 Hz, OC$_q$, m); 132.75 (=CHC$_q$, m); 133.06 (=CHC$_q$, M); 137.6 (=CH, M); 137.79 (=CH, m); 165.76 (C=O, M); 166.45 (C=O, m). **³¹P NMR δ (121 MHz, ppm):** 21.31 (M); 21.48 (m). **IR ν (cm⁻¹):** 1663 (C=O); 1261 (P=O); 1050 (br., P-O). **MS m/z (%):** 322 (100, [M+H]⁺); 324 (32, [M+H+2]⁺). **Chromatography:** Rf = 0.33 (EtOAc/MeOH 97/3). **Yield:** 75%. Yellow oil.

Dimethyl 3-(4-chlorobutyryl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates (35b)

The product was obtained as a mixture of two diastereoisomers (ratio: 20/80). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
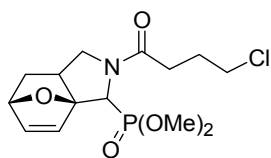
^{1}H NMR δ (300 MHz, ppm): 1.59-1.67 (1H, multiplet, CH$_A$H$_B$, m); 1.63 (2x 1H, dd, J_{AB} = 11.7 Hz, J = 7.7 Hz, C$\underline{H}_A$H$_B$, m+M); 1.85 (1H, ddd, J_{AB} = 11.7 Hz, J = 4.4 Hz, J = 2.8 Hz, CH$_A\underline{H}_B$, M); 2.06-2.24 (2x 2H, multiplet, CH$_2$, m+M); 2.36-2.62 (1+3H, multiplet, CH$_2$CO, M, CH, m+M); 2.76-2.86 (2H, multiplet, CH$_2$CO, m); 3.25 (1H, ~t, J ≈ 9 Hz, NC$\underline{H}_A$H$_B$, M); 3.44 (1H, dd, J = 11.8 Hz, J = 7.7 Hz, NC$\underline{H}_A$H$_B$, m); 3.65 (2x2H, t, J = 6.1 Hz, CH$_2$Cl); 3.79 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$, M); 3.87 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$, M); 3.77-3.88 (7H, multiplet, OCH$_3$, NCH$_A\underline{H}_B$, m); 3.99 (1H, ~t, J ≈ 9 Hz, NCH$_A\underline{H}_B$, M); 4.52 (1H, d, J_{HP} = 8.0 Hz, CHP, m); 4.99 (1H, d, J_{HP} = 10.2 Hz, CHP, M); 5.03-5.07 (2x1H, multiplet, OCH, m+M); 6.45 (2x 1H, dd, J = 5.8 Hz, J = 1.7 Hz, =CHCHO, m+M); 6.60 (1H, d, J = 5.8 Hz, =CH, m); 6.69 (1H, d, J = 5.8 Hz, =CH, M). **^{13}C NMR δ (75 MHz, ppm):** 27.51 (CH$_2$, M); 27.85 (CH$_2$, m); 31.04 (CH$_2$CO, M); 31.16 (CH$_2$CO, m); 34.31 (C$\underline{H}_2$CHO, M); 34.51 (C$\underline{H}_2$CHO, m); 39.71 (CH, m); 41.79 (CH, M); 44.61 (CH$_2$Cl, M); 44.78 (CH$_2$Cl, m); 51.74 (NCH$_2$, m); 52.71(NCH$_2$, M); 53.19, 53.22, 53.30, 53.97 (OCH$_3$, m+M); 54.13 (d, J_{CP} = 159.2 Hz, CHP, M); 56.61 (d, J_{CP} = 162.7 Hz, CHP, M); 79.04 (CHO, m); 79.13 (CHO, M); 94.11 (d, J_{CP} = 9.2 Hz, OC$_q$, M); 95.29 (d, J_{CP} = 9.2 Hz, OC$_q$, m); 132.97 (=CHC$_q$, m); 133.31 (=CHC$_q$, M); 137.32 (=CH, M); 137.49 (=CH, m); 171.14 (C=O, M); 171.89 (C=O, m). **^{31}P NMR δ (121 MHz, ppm):** 21.61 (m); 22.16 (M). **IR ν (cm^{-1}):** 1656 (C=O); 1250 (P=O); 1040 (br., P-O). **MS m/z (%):** 350 (100, [M+H]$^+$); 352 (33, [M+H+2]$^+$). **Chromatography:** Rf = 0.13 (EtOAc). **Mp.:** 91.3°C. **Yield:** 47%. Yellow crystals.

Dimethyl 3-(isobutyryl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates (35c)

The product was obtained as a mixture of two diastereoisomers (ratio: 15/85). Only the signals of the major isomer are reported.
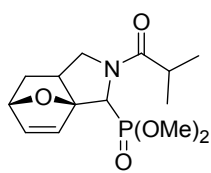
^{1}H NMR δ (300 MHz, ppm): 1.11 (3H, d, J = 6.9 Hz, CH$_3$); 1.17 (3H, d, J = 6.9 Hz, CH$_3$); 1.62 (1H, dd, J_{AB} = 11.6 Hz, J = 7.7 Hz, C$\underline{H}_A$H$_B$); 1.83 (1H, ddd, J_{AB} = 11.6 Hz, J = 4.4 Hz, J = 3.0 Hz, CH$_A\underline{H}_B$); 2.53-2.65 (1H, multiplet, CH); 2.64 (1H, septet, J = 6.9 Hz, C$\underline{H}$(CH$_3$)$_2$); 3.28 (1H, dd, J_{AB} = 9.5 Hz, J = 9.5 Hz, C$\underline{H}_A$H$_B$N); 3.78 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.86 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 4.01 (1H, ddd, J_{AB} = 9.5 Hz, J = 9.5 Hz, J_2 = 0.9 Hz, CH$_A\underline{H}_B$N); 5.03-5.06 (2H, multiplet, CHO, CHP); 6.44 (1H, dd, J = 6.0 Hz, J = 1.9 Hz, =CHC$_q$); 6.70 (1H, d, J = 6.0 Hz, =C$\underline{H}$CHO). **^{13}C NMR δ (75 MHz, ppm):** 18.37 (CH$_3$); 19.68 (CH$_3$); 32.20 (C$\underline{H}$(CH$_3$)$_2$); 34.43 (CH$_2$); 41.87 (CHC$_q$); 52.49 (CH$_2$N); 53.20 (d, J_{CP} = 5.8 Hz, OCH$_3$); 53.28 (d, J_{CP} = 5.8 Hz, OCH$_3$); 54.03 (d, J_{CP} = 159.2 Hz, CHP); 79.10 (CHO); 93.98 (d, J_{CP} = 10.4 Hz, C$_q$O); 133.52 (=$\underline{C}$HC$_q$); 137.49 (=CH); 176.47 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 21.63 (m); 22.44 (major). **IR ν (cm^{-1}):** 1639 (C=O); 1249 (P=O); 1040 (br., P-O). **MS m/z (%):** 316 (100, [M+H]$^+$). **Mp.:** 110-111°C. **Yield:** 53%. Yellow crystals.

Dimethyl 3-(2,2-dichloroacetyl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates (35d)

The product was obtained as a mixture of two diastereoisomers (ratio: 31/69). Signals of the major and minor isomers are indicated as 'm' and 'M' whenever possible.
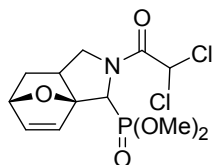
^{1}H NMR δ (300 MHz, ppm): 1.66 (1H, dd, J_{AB} = 11.6 Hz, J = 7.7 Hz, CH$_A$H$_B$, M); 1.87 (1H, ddd, J_{AB} = 11.6 Hz, J = 4.4 Hz, J = 2.9 Hz, CH$_A$H$_B$, M); 2.34-3.44 (1H, multiplet, CH, m) 2.59-2.69 (1H, multiplet, CH, M); 3.46 (1H, dd, J_{AB} = 9.5 Hz, J = 9.5 Hz, NCH$_A$H$_B$); 3.82 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.89 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.72-3.94 (8H, multiplet, OCH$_3$, NCH$_2$, m) 4.17 (1H, ddd, J_{AB} = 9.5 Hz, J = 9.5 Hz, J = 0.9 Hz, NCH$_A$H$_B$, M); 4.60 (1H, d, J_{HP} = 6.6 Hz, CHP, m); 4.98 (1H, d, J_{HP} = 11.0 Hz, CHP, M); 5.07 (2x 1H, multiplet, CHO, m+M); 6.14 (1H, s, CHCl$_2$, M); 6.43-6.50 (2x 1H, multiplet, =CHCHO, m+M); 6.56 (1H, d, J = 6.1 Hz, =CHC$_q$, m); 6.70 (1H, d, J = 5.8 Hz, =CHC$_q$, M). **^{13}C NMR δ (75 MHz, ppm):** 34.29 (CH$_2$, m); 34.40 (CH$_2$, M); 39.32 (CH, m); 42.14 (CH, M); 52.42 (NCH$_2$, M); 53.30, 53.51, 54.31, 54.35 (NCH$_2$, m, OCH$_3$, m+M); 55.61 (d, J_{CP} = 158.1 Hz, CHP, M); 56.46 (d, J_{CP} = 161.5 Hz, CHP, m); 65.19 (CHCl$_2$, M); 65.32 (CHCl$_2$, m); 79.20 (CHO, M); 79.38 (CHO, m); 93.72 (d, J_{CP} = 8.1 Hz, OC$_q$, M); 95.49 (d, J_{CP} = 6.9 Hz, OC$_q$, m); 132.48 (=CHC$_q$, m); 132.91 (=CHC$_q$, M); 137.60 (=CH, M); 137.93 (=CH, m); 162.50 (C=O, M); 163.28 (C=O, m). **^{31}P NMR δ (121 MHz, ppm):** 20.80 (M); 20.91 (m). **IR ν (cm^{-1}):** 1677 (C=O); 1253 (P=O); 1021-1054 (P-O). **MS m/z (%):** 356 (100, [M+H]$^+$); 358.3 (63 [M+H+2]$^+$); 360.0 (9 [M+H+4]$^+$). **Chromatography:** Rf = 0.33 (EtOAc). **Mp.:** 120-121°C. **Yield:** 94%. Yellow crystals.

Dimethyl 3-(2,2,2-trichloroacetyl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates (35e)

The product was obtained in quantitative yield as a mixture of two diastereoisomers (ratio: 21/79). The major isomer could be obtained in pure form by washing the crystals several times with acetone. The remaining filtrate was enriched with the minor isomer, which could be obtained in pure form by subsequent column chromatography.

Major isomer:
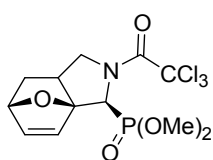
^{1}H NMR δ (300 MHz, ppm): 1.42 (1H, dd, J_{AB} = 11.8 Hz, J = 7.4 Hz, CH$_A$H$_B$); 1.81 (1H, ddd, J_{AB} = 11.8 Hz, J = 3.6 Hz, J = 3.6 Hz); 2.08 (1H, multiplet, CH); 3.40 (1H, dd, J_{AB} = 11.3 Hz, J = 11.3 Hz, CH$_A$H$_B$N); 3.79 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$); 3.83 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$); 4.73 (1H, dd, J_{AB} = 11.3 Hz, J = 6.9 Hz, CH$_A$H$_B$N); 5.07 (1H, d, J_{HP} = 14.0 Hz, CHP); 5.25 (1H, d, J = 4.4 Hz, OCH); 6.46 (2H, multiplet, HC=CH). **^{13}C NMR δ (75 MHz, ppm):** 28.70 (CH$_2$); 44.77 (d, J_{CP} = 2.3 Hz, CH); 53.36 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.61 (d, J_{CP} = 5.8 Hz, OCH$_3$); 55.70 (NCH$_2$); 56.03 (d, J_{CP} = 160.4 Hz, CHP); 81.36 (CHO); 92.97 (CCl$_3$); 94.42 (d, J_{CP} = 4.6 Hz, OC$_q$); 134.39 (=CHC$_q$); 136.86 (=CH); 159.69 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 20.70. **IR ν (cm^{-1}):** 1675 (C=O); 1261 (P=O); 1058, 1039 (P-O). **MS m/z (%):** 390 (86, [M+H]$^+$); 392 (100, [M+H+2]$^+$); 394 (24, [M+H+4]$^+$). **Mp.:** 176-177°C. **Chromatography:** Rf = 0.25 (EtOAc). White crystals.

Minor isomer:
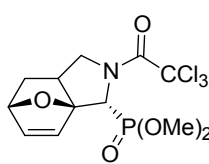
¹H NMR δ (300 MHz, ppm): 1.67 (1H, dd, J_{AB} = 11.6 Hz, J = 7.7 Hz, CH$_A$H$_B$); 1.87 (1H, ddd, J_{AB} = 11.6 Hz, J = 4.1 Hz, J = 3.3 Hz); 2.59-2.68 (1H, multiplet, CH); 3.80-3.89 (1H, multiplet, CH$_A$H$_B$N); 3.83 (3H, d, J_{HP} = 11.0 Hz, OCH$_3$); 3.89 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 4.39 (1H, dd, J = 10.5 Hz, J = 9.6 Hz, CH$_A$H$_B$N); 5.04-5.10 (2H, multiplet, CHP, OCH); 6.47 (1H, dd, J = 5.9 Hz, J = 1.7 Hz, =CHCHO); 6.69 (1H, d, J = 5.9 Hz, =CH). **¹³C NMR δ (75 MHz, ppm):** 34.54 (CH$_2$); 42.96 (CH); 53.54 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.63 (d, J_{CP} = 6.9 Hz, OCH$_3$); 54.64 (NCH$_2$); 57.94 (d, J_{CP} = 158.1 Hz, CHP); 79.10 (CHO); 93.08 (CCl$_3$); 93.18 (d, J_{CP} = 3.5 Hz, OC$_q$); 132.83 (=CHC$_q$); 137.57 (=CHCHO); 159.52 (C=O). **³¹P NMR δ (121 MHz, ppm):** 20.89. **IR ν (cm⁻¹):** 1672 (C=O); 1259 (P=O); 1054, 1037 (P-O). **MS m/z (%):** 390 (90, [M+H]⁺); 392 (100, [M+H+2]⁺); 394 (28, [M+H+4]⁺). **Mp.:** 121-122°C. **Chromatography:** Rf = 0.39 (EtOAc). White crystals.

Dimethyl 3-allyl-10-oxa-3-aza-tricyclo[5.2.1.0¹,⁵]dec-8-en-2-yl phosphonate (320)
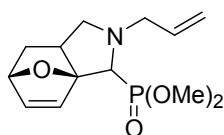
¹H NMR δ (300 MHz, ppm): 1.36 (1H, dd, J_{AB} = 11.4 Hz, J = 7.3 Hz, CH$_A$H$_B$); 1.72 (1H, ddd, J_{AB} = 11.4 Hz, J = 4.5 Hz, J = 2.5 Hz, CH$_A$H$_B$); 2.07-2.22 (2H, multiplet, CH, NCH$_A$H$_B$); 3.16 (dd, 1H, J_{AB} = 13.6 Hz, J = 8.2 Hz, NCH$_A$H$_B$CH=); 3.29 (1H, d, J_{HP} = 6.6 Hz, CHP); 3.37 (1H, ddd, J = 6.4 Hz, J = 6.4 Hz, J = 1.7 Hz, NCH$_A$H$_B$); 3.77 (1H, ddt, J_{AB} = 13.7 Hz, J = 4.8 Hz, J = 1.7 Hz, NCH$_A$H$_B$CH=); 3.86 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.88 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 4.99 (1H, dt, J = 4.4 Hz, J = 1.4 Hz, CHO); 5.13 (1H, d, J = 10.1 Hz, =CH$_A$H$_B$); 5,21 (1H, dd, J = 17.2 Hz, J$_2$ = 1.1 Hz, =CH$_A$H$_B$); 5.91 (1H, dddd, J = 17.2 Hz, J = 10.1 Hz, J = 8.2 Hz, J = 4.8 Hz, =CH); 6.33 (1H, ddd, J = 6.1 Hz, J = 1.7 Hz, J = 0.6 Hz, =CHCHO); 6.62 (1H, d, J = 6.1 Hz, =CHC$_q$O). **¹³C NMR δ (75 MHz, ppm):** 30.32 (CH$_2$); 42.57 (CH); 53.26 (d, J_{CP} = 7.0 Hz, OCH$_3$); 53.63 (d, J_{CP} = 8.1 Hz, OCH$_3$); 58.45, 58.60 (NCH$_2$, NCH$_2$CH=); 61.02 (d, J_{CP} = 178.8 Hz, CHP); 79.47 (CHO); 96.67 (d, J_{CP} = 5.8 Hz, C$_q$O); 117.38 (=CH$_2$); 134.83 (=CHC$_q$O); 134.91 (=CH); 135.63 (=CHCHO). **³¹P NMR δ (121 MHz, ppm):** 24.64. **IR ν (cm⁻¹):** 1644 (C=C); 1235-1256 (P=O); 1035, 1061 (P-O). **MS m/z (%):** 286 (100, [M+H]⁺). **Chromatography:** Rf = 0.25 (EtOAc). **Yield:** 23%. Yellow oil.

Dimethyl 3-benzyl-4-oxo-10-oxa-3-aza-tricyclo[5.2.1.0¹,⁵]dec-8-en-2-yl phosphonate (323a)
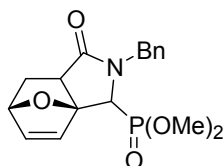
¹H NMR δ (300 MHz, ppm): 1.65 (1H, dd, J_{AB} = 12.4 Hz, J = 8.8 Hz, CH$_A$H$_B$); 2.25 (1H, ddd, J_{AB} = 11.8 Hz, J = 4.6 Hz, J = 3.6 Hz, CH$_A$H$_B$); 2.67 (1H, dd, J = 8.8 Hz, J = 3.6 Hz, CHC$_q$); 3.82 (3H, d, J_{HP} = 10.6 Hz, OCH$_3$); 3.83 (3H, d, J_{HP} = 10.7 Hz, OCH$_3$); 3.93 (1H, d, J_{HP} = 5.5 Hz, CHP); 4.26 (1H, d, J_{AB} = 15.1 Hz, NCH$_A$H$_B$); 5.03 (1H, d, J = 4.6 Hz, CHO); 5.33 (1H, d, J_{AB} = 15.1 Hz, CH$_A$H$_B$N); 6.38 (1H, dd, J = 6.1 Hz, J = 1.7 Hz, =CHCHO); 6.58 (1H, d, J = 6.1 Hz, =CHC$_q$) 7.20-7.36 (5H, multiplet, CH$_{arom}$). **¹³C NMR δ (75 MHz, ppm):** 28.87 (CH$_2$); 45.30 (NCH$_2$); 46.60 (CHC$_q$); 53.13 (d, J_{CP} = 6.9 Hz, OCH$_3$); 53.47 (d, J_{CP} = 6.9 Hz, OCH$_3$); 54.84 (d, J_{CP} = 162.7 Hz, CHP); 78.31 (CHO); 89.61 (d, J_{CP} = 6.9 Hz, C$_q$O); 127.60 (CH$_{arom}$);

128.01 (2x CH$_{arom}$); 128.66 (2x CH$_{arom}$); 132.71 (=$\underline{C}$HC$_q$); 135.18 (C$_{q,arom}$); 136.91 (=$\underline{C}$HCHO); 174.84 (C=O). **^{31}P NMR δ (121 MHz, ppm):** 21.95. **IR ν (cm^{-1}):** 1648 (C=O); 1252 (P=O); 1029, 1052 (P-O). **MS m/z (%):** 350 (100, [M+H]$^+$). **Yield:** 96%. Colourless oil.

*G*eneral *D*iscussion, *C*onclusions

and *P*erspectives

❧❧❧❧❧❧

During the last five decades, the biological potential of the aminoalkyl phosphonates has been widely acknowledged with their use as amino acid bioisosteres, calcium complexing agents, tetrahedral transition state analogues, etc... This success has also brought azaheterocyclic phosphonates under the attention of many researchers, for example as conformationally restricted derivatives. However, this class of compounds is far less known and additional synthetic methods are required to obtain a wider variety of compounds belonging to this class. Mainly two strategies can be applied covering this challenge: (a) phosphonylation of a preformed azaheterocyclic ring, or (b) cyclization of a phosphonylated precursor. The latter can be considered to be the most versatile pathway and was evaluated for different substrates and ring closure reaction types in this research.

Mainly α-aminoalkyl phosphonates have been used in this research as starting materials for further functionalization and ring closure. Next to the widely applied Kabachnik-Fields type three component condensation, α-aminoalkyl phosphonates can also be obtained via phosphonylation of a suitable imine. To overcome the poor nucleophilicity of dialkyl phosphites **(i)**, they can be silylated first using TMSCl and a base. However, nucleophilic addition of **(iii)** to imines proceeded slowly, generating side products because of prolonged reaction times.
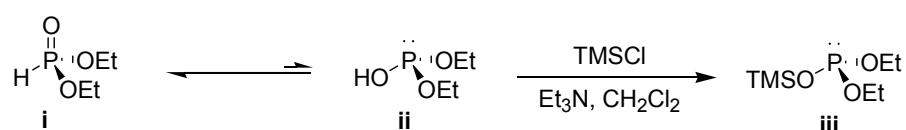
Furthermore, when α,β-unsaturated imines **(iv)** were used, an unprecedented 1,4-1,2-tandem addition was observed using dialkyl trimethylsilyl phosphites **(iii)**. The reaction course was complicated by the occurrence of a kinetically favoured, reversible 1,2-addition. However, the more slowly proceeding 1,4-addition yields enamine **(viii)** which readily tautomerizes to the corresponding imine **(ix)** under acidic conditions. A fast second phosphite addition then yields the thermodynamically favoured 3-phosphonyl 1-aminoalkyl phosphonates (PAP) **(xii)**. Imines carrying a less steric phenyl group on the nitrogen atom failed to react in the 1,4-addition because the 1,2-addition is too much favoured causing the initial equilibrium to shift completely away from the imine **(iv)**. From the atom balance of the reaction, it was clear that protons were consumed during the reaction. Therefore, the reaction was greatly enhanced by adding sulphuric acid to the medium. The intermediate enamine **(viii)** and imine **(x)** could only be detected by depleting the reaction mixture of protons causing the reaction to stop at the enamine stage. The second role of the acid appeared to be the activation of the imine by protonation. The reaction with tris(trimethylsilyl) phosphite proceeds via similar reaction kinetics, however yielding the corresponding free phosphonic acids after a final methanolysis.
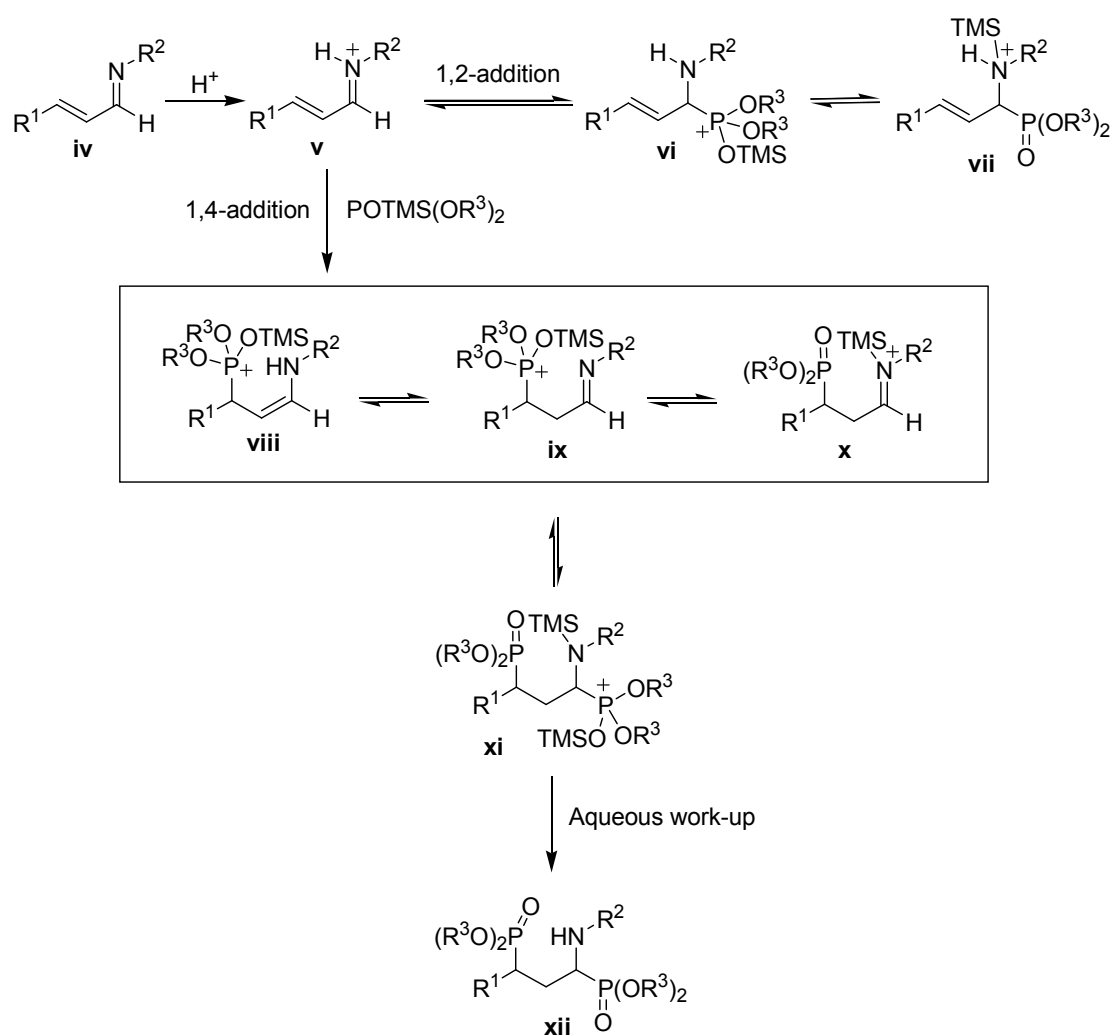
Trialkyl phosphites (TAP) were found to perform the same 1,4-1,2-tandem addition. Modified reaction conditions were required to ensure dealkylation of the intermediate phosphonium salts. Nevertheless, a similar effect of protons to the reaction was observed. In the case of trialkyl phosphites, 1,2-addition is kinetically disfavoured. Therefore, no initial equilibrium with the 1,2-adduct was found. The 1,4-adduct **(xv)** is the main reaction intermediate and the final 1,2-addition is the rate limiting step.
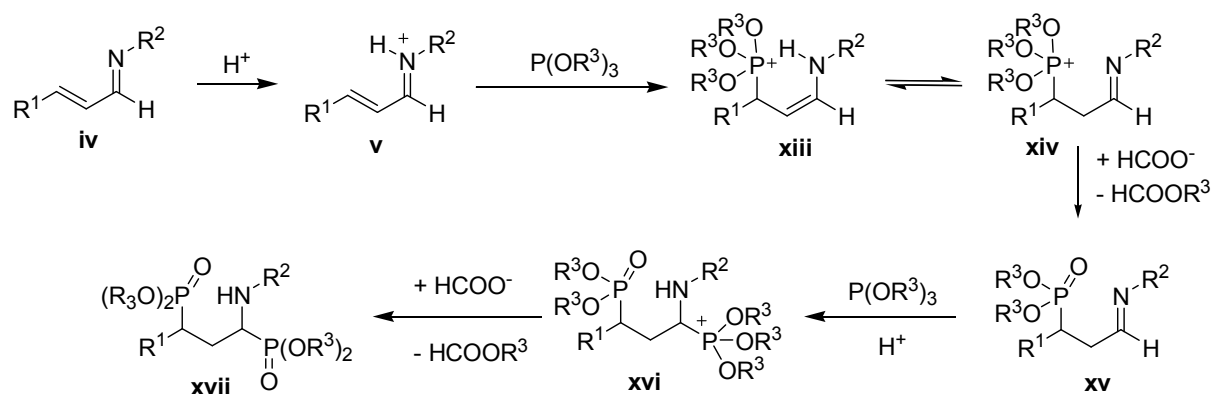
For this reason, only the 1,4-adducts could be obtained when the highly steric *t*Bu group was used on nitrogen and optimal conversion to PAP was obtained with a phenyl substituent. This reactivity order is opposite to that of the DAPTMS addition, making both methods perfectly complementary. The difference in affinity towards 1,2- or 1,4-addition between TAP and DAPTMS can not be explained based on steric or hard/soft dissimilarities. Coordination of the electrophilic silicon atom with the imine nitrogen atom brings the nucleophile and electrophile into close vicinity to each other, favouring nucleophilic attack in the 1,2-position. TAP on the other hand lacks any coordination and prefers 1,4-attack, probably because of steric reasons.
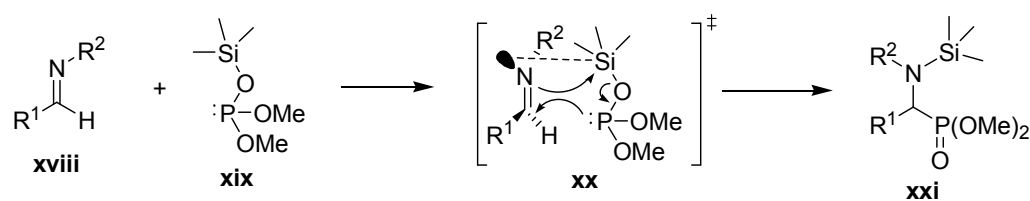
An excellent method to prepare the desired α-aminoalkyl phosphonates **(xxiii)** was developed then by refluxing aldimines in the presence of two equivalents of dialkyl phosphite (DAP) in methanol. No other additives were required. The excess of phosphite was easily removed via an acid/base extraction and the α-aminoalkyl phosphonates were obtained in high yield and purity. Furthermore, complete regioselectivity was observed when α,β-unsaturated imines are used. This observation supported the reaction mechanism proceeding through a four-membered ring transition state **(xxii)**.
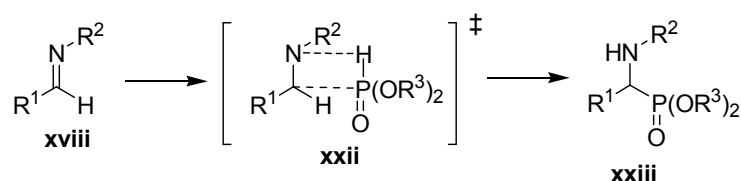
The resulting α-aminoalkyl phosphonates **(xxiii)** could then be acylated using chloroacetyl chloride and triethyl amine, pyridine or pyridine/DMAP, depending on the R^1 substituent. Furyl derivatives were converted most easily, while poor results were obtained with phenyl or alkyl derivatives. The same *N*-chloroacetyl aminoalkyl phosphonates **(xxvi)** could be obtained from the corresponding imines **(xviii)** via a one-pot acylation/phosphonylation in THF. Using these conditions, a very reactive acyliminium intermediate **(xxiv)** was formed, that could easily hydrolyse or eliminate hydrochloric acid. Therefore, this method was only useful when aromatic imines are used. Addition of a trialkyl phosphite then yielded phosphonium salt **(xxv)** which was subsequently dealkylated by the chloride anions present in the reaction medium. Also in this case, bad results were obtained with imines derived from benzaldehyde. When α,β-unsaturated imines were used, 1,4-addition of the phosphite was observed as a side reaction (up to 25%).
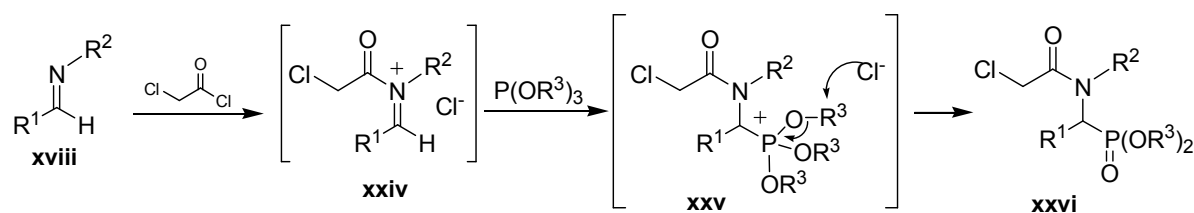
Treatment of the obtained *N*-chloroacetyl aminoalkyl phosphonates **(xxvi)** with a strong base, such as sodium hydride or LiHMDS, resulted in a phosphorus stabilized carbanion which is subsequently alkylated intramolecularly. The corresponding 4-phosphono β-lactams **(xxviii)** were obtained in high yield and purity, opposite to similar substrates reported before, carrying a carboxylate group instead of a phosphonate. This clearly illustrates the remarkable efficiency of a phosphonate group in stabilizing a carbanion. Nitrogen or phosphonate deprotection of the 4-phosphono β-lactams failed using several generally applied methods.
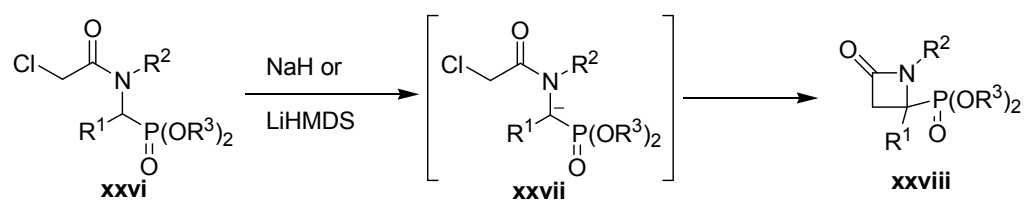
When *N*-chloroacetyl aminoalkenyl phosphonates **(xxix)** were used, an ambident anion was formed that could ring close to a four- or a six-membered ring.

Surprisingly, only the highly strained four-membered ring **(xxxii)** was formed. Replacing the phenyl group in **(xxix)** with a methyl resulted in problematic preparation of the corresponding *N*-chloroacetyl aminoalkenyl phosphonate and a complex mixture during the ring closure. When phosphonate **(xxxiv)** containing a bicyclic cyclohexenyl substituent was evaluated, no trace of the six-membered ring was found.
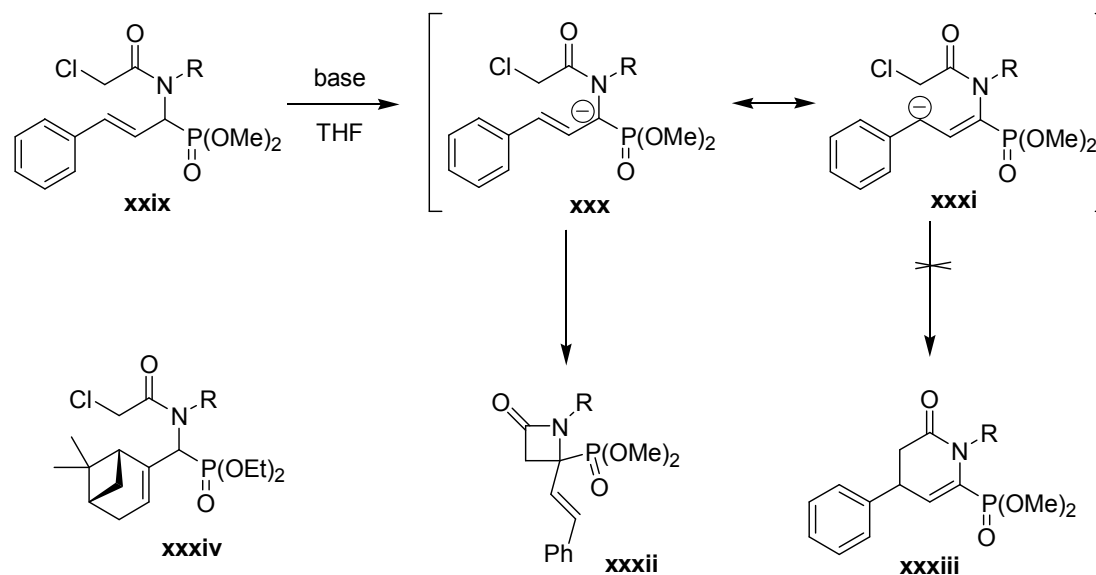
Intermolecular reactions with the anion generated from *N*-acetyl aminoalkenyl phosphonate **(xxxv)** which is not prone to intramolecular reactions, demonstrated its ambient nature. Reaction with hard (H^+, D^+) or soft electrophiles mainly proceeded at the γ-position. Therefore, HSAB considerations were not satisfactory to explain the particular regioselectivity of the intramolecular alkylation, which proceeded exclusively at the α-position. This was also confirmed by theoretical calculations displaying only small differences in hardness of both anionic positions.

X = H, D; ratio **xxxvii:xxxviii** = 13:87
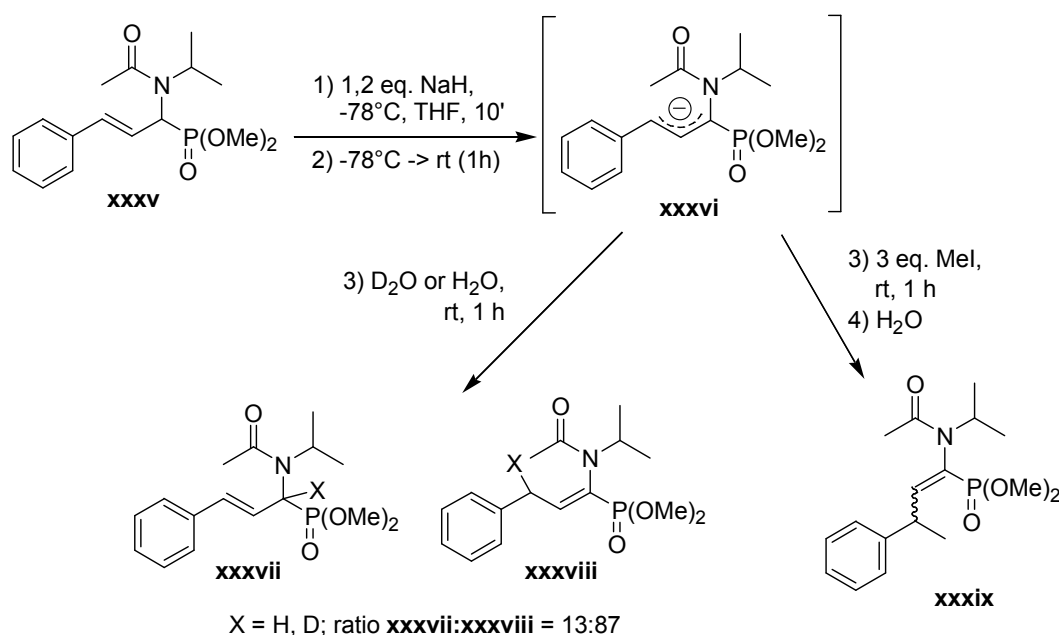
Finally, the key factor determining the regioselectivity was found to be a hindered rotation around the N-C_α bond, causing the amide group to be pointing away from the γ-anionic position. This was confirmed by optimized conformation calculations of the anions and the transition states for four- en six-membered ring formation. Solvent and counterion effects needed to be taken properly into account in order to be able to correctly predict the actual conformations.

From these results, it was clear that the alkenyl substituent and the nitrogen alkyl substituent are very proximate in this type of molecules. This property appeared to be advantageous for the synthesis of pyrrolines and pyrroles using RCM. For this reason, substituted acroleines **(l)** were converted to the corresponding α-aminoalkenyl phosphonates **(lii)**. Benzylation using benzyl bromide in the presence of K_2CO_3 then yielded phosphonates **(liii)** that were treated with 2nd generation Grubbs' ruthenium catalyst to yield the corresponding 2-phosphono 3-pyrrolines **(liv)**. Although ring-closing metathesis (RCM) has been developed to a powerful technique for the preparation of medium-sized rings, it has not been evaluated for the synthesis of azaheterocyclic phosphonates, until now. Furthermore, the RCM reaction proceeded smoothly in the presence of a nucleophilic nitrogen atom without the need to convert it to the hydrochloric acid salt. Also very high substitution patterns were well tolerated by the RCM catalyst on condition that initiation could occur on one of both olefins.
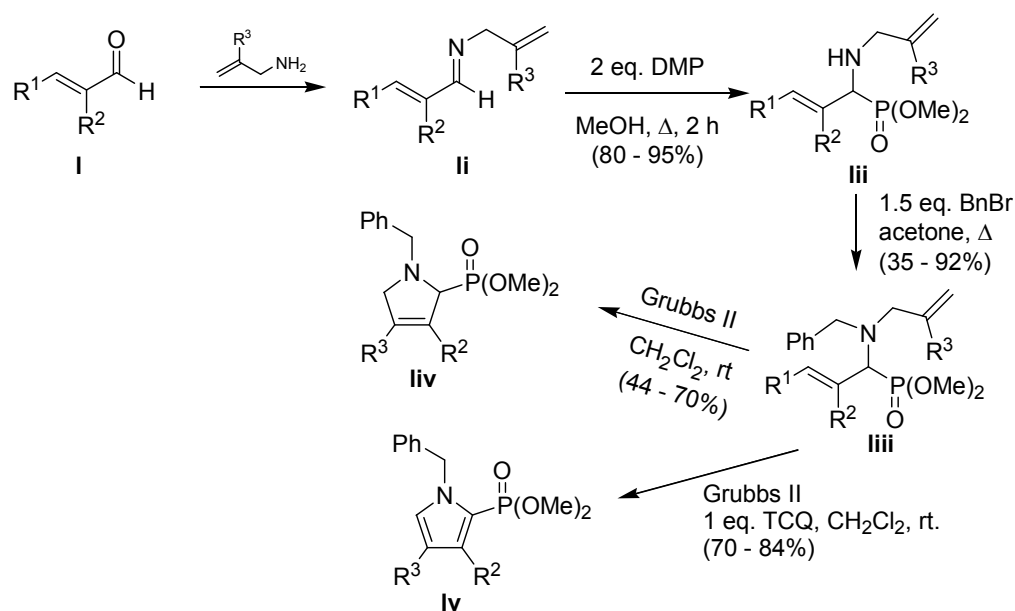
Furthermore, a one-pot protocol using Grubbs' 2nd generation catalyst together with tetrachloroquinone (TCQ) was developed at the SynBioC research group to obtain the corresponding pyrroles. Applying this methodology to substrates **(liii)** then yields the corresponding 2-phosphono pyrroles **(lv)**. A synergism was observed between the RCM catalyst and TCQ enhancing the oxidation rate and allowing substrates to the reaction that otherwise fail to react because of catalyst inhibition. Although phosphono pyrroles may possess interesting biological properties, they have been studied only very scarcely in the past.
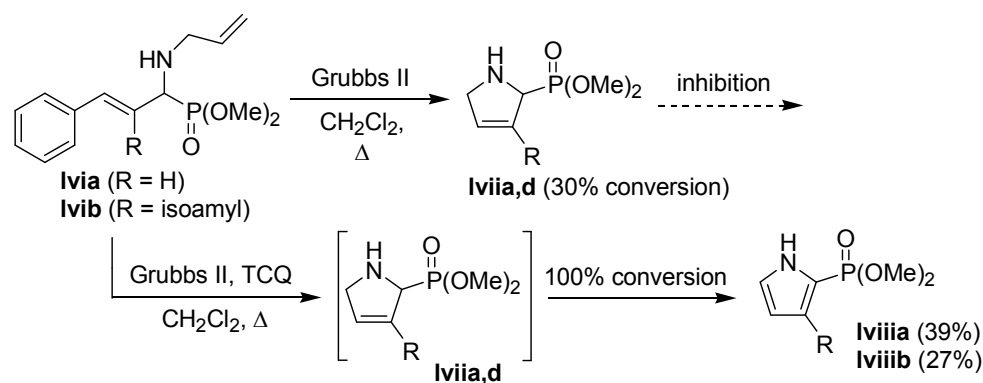
In an attempt to synthesize carbapenem type structure **(lxiii)**, β-lactam **(lx)** was submitted to the RCM catalyst. However, only dimerization occurred, probably because the lactam **(lx)** is missing the favourable conformation observed with *N*-acyl aminoalkenyl phosphonates **(lix)**. When the five membered ring was constructed first using an RCM reaction, the subsequent ring closure to lactams **(lxiii)** failed.
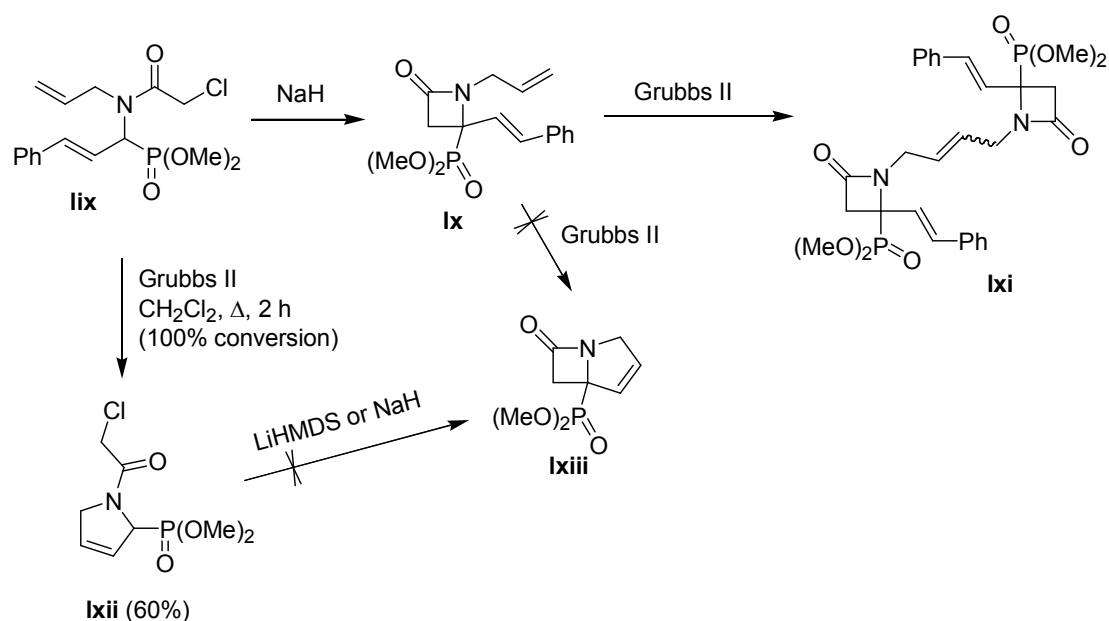
Finally, the observed conformational properties of *N*-acyl aminoalkyl phosphonates have also been exploited to obtain complex azaheterocyclic phosphonates using an IMDAF reaction. For this purpose, (acylamino)-furan-2-yl-methyl phosphonates **lxvi** have been prepared using the reaction conditions described above. The cycloaddition was performed under thermal conditions in toluene giving the tricyclic phosphonates **lxviii** in high yield. The reaction rate was strongly dependent on the steric bulk of the amide side chain. Furthermore, a high degree of stereocontrol was observed during the cycloaddition reaction. The most stable stereoisomers were formed under thermodynamic control.
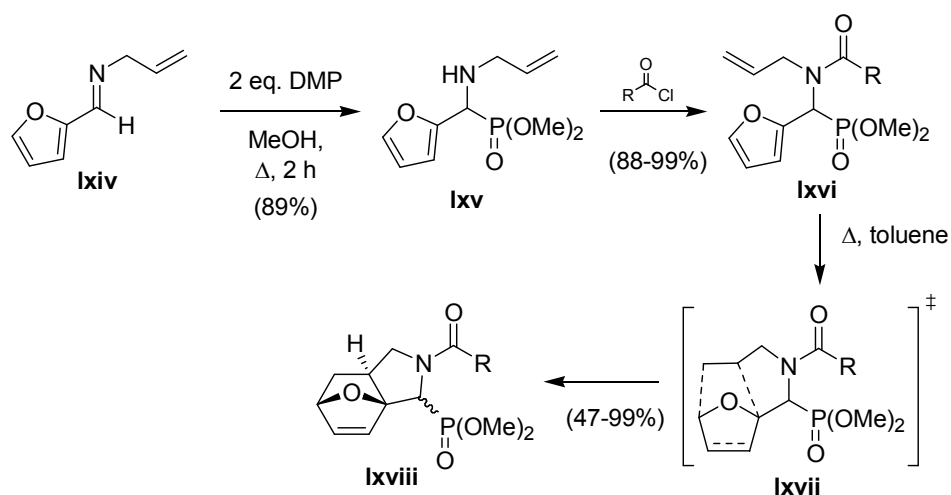
From the results in this research, some perspectives to future work have to be formulated regarding the preparation of azaheterocyclic phosphonates. Firstly, the structural characterization of the diphosphonylation products of α,β-unsaturated imines (PAP's) should help other researchers to more easily detect these products in

their reaction mixtures when trying to make aminoalkyl phosphonates. In the past, many research groups have overlooked these products as minor constituents of their reaction mixtures because of their low visibility in NMR and their high retention on polar stationary phases during chromatographic purifications.

Furthermore, the mechanistical considerations of the double addition reactions have led to a better understanding of the use of dialkyl, trialkyl and silylated phosphites as nucleophiles in phosphonylation reactions of imines. This should enable researchers to select the right nucleophile and reaction conditions depending on the type of aminoalkyl phosphonates desired.

Secondly, using α-aminoalkyl phosphonates as substrates, a variety of azaheterocyclic phosphonates have been synthesized. A thorough screening of these derivatives is required in order to establish their biological potential, which may also be enhanced by further modification, e.g. dealkylation or hydrolysis of the phosphonate esters, nitrogen deprotection, ring opening of the oxa-bridge in the IMDAF products,... Also the PAP's, being derivatives of glutamic acid, deserve a profound investigation of their biological activity.

Finally, the structural insights that have been gained by studying the four-membered ring formation starting from *N*-chloroacetyl aminoalkenyl phosphonates can be elaborated to a more diverse strategy to obtained azaheterocyclic phosphonates.

Summary

In this thesis, new synthetic pathways to azaheterocyclic phosphonates were studied. Starting from imines, different types of aminoalkyl phosphonates can be obtained depending on the nucleophile and the reaction conditions used. With dialkyl phosphites, the desired α-aminoalkyl phosphonates are obtained in high yield and purity after a simple acid, base extraction. When dialkyl trimethylsilyl phosphites are reacted with α,β-unsaturated imines, 3-phosphono 1-aminoalkyl phosphonates (PAP's) are obtained when the reaction is performed in a sufficiently strong acidic medium. The mechanism involves an initial 1,4-addition of the phosphite, followed by tautomerization of the intermediate enamine and a second phosphite addition. Similar products are obtained when trialkyl phosphites are used together with formic acid. However, the different impact of steric bulk of the substrate to the reaction end-product reveals mechanistic differences between both nucleophilic reagents.

The obtained α-aminoalkyl phosphonates can be smoothly acylated to obtain *N*-chloroacetyl aminoalkyl phosphonates. The same products can also be obtained starting from the imines in a one-pot acylation, phosphonylation through an intermediate acyliminium ion. However, several side reactions can be observed when using the second method. When treated with a strong base, a phosphorus stabilized carbanion is generated in the *N*-chloroacetyl aminoalkyl phosphonate, which then smoothly undergoes intramolecular alkylation yielding 4-phosphono β-lactams.

Also in the case of *N*-chloroacetyl aminoalkenyl phosphonates, that are giving rise to an ambident allyl anion, four-membered rings are formed exclusively. This unexpected phenomenon was studied in more detail on experimental and theoretical grounds. The transition state for the more stable six-membered ring is disfavoured with about 25 kJ/mol because of a restricted rotation about the N-C(P)

σ-bond. For this reason, the *N*-alkyl chain is proximate to the *P*-alkenyl chain. This conformational property of the *N*-acyl aminoalkyl phosphonates can also be exploited in other ring clsoure reactions.

The aminoalkyl phosphonates under investigation therefore are excellent substrates for an RCM reaction between an *N*-allyl and the *P*-alkenyl chain. In this way, 2-phosphono 3-pyrrolines can be formed. Also substrates containing basic nitrogen atoms are converted smoothly by the RCM catalyst. Basic 2-phosphono 3-pyrrolines can be oxidized to the corresponding 2-phosphono pyrroles using tetrachloroquinone. Both reactions, RCM and oxidation, can be performed in the same pot at the same time. Even more, a synergism between both reactions can be observed when secondary amines are used in the reaction.

Finally, *N*-allyl furan-2-ylmethyl phosphonates are excellent substrates in IMDAF reactions because of their aforementioned conformational properties. In this way, tricyclic phosphono pyrrolidines can be formed with controlled stereochemistry. The reaction rate of the IMDAF reaction is enhanced due to the presence of a bulky phosphonate group. The stereochemistry of the products can be examined through careful investigation of the NMR spectral data.

*S*amenvatting

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In dit onderzoek werden nieuwe synthesewegen naar azaheterocyclische fosfonaten onderzocht. Verschillende types aminoalkylfosfonaten kunnen bekomen worden uitgaande van iminen, afhankelijk van het nucleofiel en de reactiecondities die worden gebruikt. Met dialkylfosfieten kunnen de gewenste α-aminoalkyl fosfonaten met hoog rendement en zuiverheid bekomen worden na een eenvoudige zuur, base extractie. Wanneer dialkyl trimethylsilylfosfieten gereageerd worden met α,β-onverzadigde iminen, worden 3-fosfono-1-aminoalkylfosfonaten bekomen als de reactie uitgevoerd wordt onder voldoende zure condities. Het mechanisme van deze reactie omvat een 1,4-additie gevolgd door een tautomerisatie van het intermediaire enamine en een tweede fosfietadditie. Wanneer trialkylfosfieten gebruikt worden in combinatie met mierenzuur, worden dezelfde producten bekomen. De verschillende impact van de stericiteit van het substraat op het uiteindelijke eindproduct onthult mechanistische verschillen tussen beide fosforreagentia.

De bekomen α-aminoalkylfosfonaten kunnen gemakkelijk geacyleerd worden tot *N*-chlooracetyl aminoalkylfosfonaten. Dezelfde producten kunnen ook bekomen worden uitgaande van de iminen via acylering en fosfonylering van het intermediaire acylfosfonaat in één pot. Bij deze tweede methode kunnen echter verschillende zijreacties optreden. Wanneer de *N*-chlooracetyl aminoalkylfosfonaten behandeld worden met een sterke base, ontstaat een anion dat door de fosfonaatgroep gestabilseerd wordt en vervolgens verder reageert met de vorming van een 4-fosfono-β-lactam via intramoleculaire alkylatie.

Ook wanneer *N*-chlooracetyl aminoalkenylfosfonaten gebruikt worden, die aanleiding geven tot een ambident allylanion, worden enkel de vierringen gevormd. Deze onverwachte regioselectiviteit werd in meer detail bestudeerd op experimentele en theoretische basis. De transitietoestand voor de meer stabiele zesring ligt 25 kJ/mol hoger dan deze voor de vierring, omwille van een gehinderde rotatie rond

de N-C(P) σ–binding. Hierdoor is de *N*-alkyl keten dichtbij de *P*-alkenyl keten gepositioneerd. Deze bijzondere conformatie van *N*-chlooracetyl aminoalkyl-fosfonaten kan ook uitgespeeld worden voor andere types ringsluitingen.

Zo zijn de aminoalkylfosfonaten uit dit onderzoek uitermate geschikt voor een RCM reactie tussen een *N*-allyl en de *P*-alkenyl groep. Op deze manier worden 2-fosfono-3-pyrrolines gevormd. Ook deze substraten met een basisch stikstofatoom worden gemakkelijk omgezet door de RCM katalysator. Basische 2-fosfono-3-pyrrolines kunnen geoxideerd worden tot de overeenkomstige 2-fosfonopyrrolen met tetrachloorquinon. Beide reacties, RCM en oxidatie, kunnen tegelijkertijd in hetzelfde medium uitgevoerd worden. Bovendien kan een synergie worden waargenomen tussen beide reacties wanneer secundaire amines als substraat worden gebruikt.

Tenslotte zijn ook *N*-allyl furan-2-ylmethyl fosfonaten ideale substraten in IMDAF-reacties omwille van hun bijzondere conformatie zoals die hierboven werd beschreven. Op deze manier kunnen tricyclische fosfonopyrrolidines bereid worden met een vaste stereochemie. De reactiesnelheid van de IMDAF-reactie wordt verhoogd door de aanwezigheid van de omvangrijke fosfonaatgroep. De stereochemie van de producten kan bestudeerd worden aan de hand van de NMR spectrale gegeven.

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Appendices

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Appendix A:

Phosphorus reagents and intermediates: properties

	Abbreviation	δ(^{31}P)	Solvent	Properties
(structure: H-P(=O)(OMe)OMe)	DMP	11.1	CDCl$_3$	Colourless liquid; bp. 170°C
(structure: H-P(=O)(OEt)OEt)	DEP	7.9	CDCl$_3$	Colourless liquid; bp. 50°C/2 mmHg
(structure: H-P(=O)(OH)OH)		5.5	D$_2$O	White, sticky solid
(structure: P(OMe)(OMe)OMe)	TMP	142.0	CDCl$_3$	Colourless liquid; bp. 111°C, very bad smell
(structure: P(OEt)(OEt)OEt)	TEP	139.6	CDCl$_3$	Colourless liquid; bp. 156°C, very bad smell
(structure: P(OMe)(OMe)OTMS)	DMPTMS	126.2	CDCl$_3$	Colourless liquid; bp. 38°C/10 mmHg
(structure: P(OEt)(OEt)OTMS)	DEPTMS	128.0	CDCl$_3$	Colourless liquid; bp. 66°C/15 mmHg
(structure: P(OTMS)(OTMS)OTMS)		113.2	CDCl$_3$	Colourless liquid; bp. 129-130°C/25 mmHg
(structure: H-P(=O)(OTMS)OTMS)		-13.8	CDCl$_3$	Colourless liquid; bp. 92-93°C/20 mmHg

Appendix B: Selected ^{31}P and ^{13}C NMR data of PAP's 196

^{31}P NMR data[‡]

Nr	R^1	R^2	R^3	R^4	R^5	Isomer M δ (ppm)	δ (ppm)	^{4}J (Hz)	Isomer m δ (ppm)	δ (ppm)	^{4}J (Hz)
196a	Ph	Ph	H	H	Me	28.74	31.30	9.7	28.47	30.76	¤
196b	Ph	Ph	H	H	Et	26.29	29.05	9.7	26.20	28.60	¤
196c	Bn	Ph	H	H	Me	31.27	32.08	9.7	30.41	31.23	¤
196d	Bn	Ph	H	H	Et	28.91	29.86	9.7	28.16	28.99	¤
196e	Allyl	Ph	H	H	Me	31.37	32.14	9.7	30.41	31.20	¤
196f	Allyl	Ph	H	H	Et	29.02	29.89	9.7	28.25	28.98	¤
196g	CH$_2$CH$_2$indole	Ph	H	H	Et	29.04	39.99	9.7	28.22	29.04	¤
196h	iPr	Ph	H	H	Me	31.62	32.10	9.7	30.66	31.28	¤
196i	iPr	Ph	H	H	Et	29.09	29.70	9.7	28.41	28.94	¤
196j	tBu	Ph	H	H	Me	31.00	31.88	5.8	30.60	31.14	¤
196k	tBu	Ph	H	H	Et	28.84	29.64	6.0	28.74	28.91	¤
196l	tBu	Me	H	H	Me	31.75	37.99	5.2	30.61	37.11	2.2
196m	tBu	Me	H	Me	Me	31.36	38.85	3.0	§	§	§
196n	iPr	Myrt.		H	Me	31.59	39.02	3.0	32.87	37.83	2.2
196o	tBu	Myrt.		H	Me	31.59	38.95	3.7	34.07	37.79	¤

^{13}C NMR data[‡]

Nr	1 Major isomer δ (ppm)	^{1}J (Hz)	^{3}J (Hz)	1 Minor isomer δ (ppm)	^{1}J (Hz)	^{3}J (Hz)	2 Major isomer δ (ppm)	^{2}J (Hz)	2 Minor isomer δ (ppm)	^{2}J (Hz)	3 Major isomer δ (ppm)	^{1}J (Hz)	^{3}J (Hz)	3 Minor isomer δ (ppm)	^{1}J (Hz)	^{3}J (Hz)
a	48.09	154.6	16.2	48.63	155.9	11.5	31.05	8.1	32.01	¤	39.88	139.6	13.8	40.12	137.3	8.1
b	48.41	154.6	16.2	48.99	166.1	11.5	31.01	8.1	32.00	¤	40.45	139.6	13.8	40.74	145.4	8.1
c	49.94	148.8	16.1	50.57	145.4	12.7	30.18	8.1	30.58	¤	39.18	139.6	13.8	39.73	137.3	¤
d	51.17	141.9	16.2	51.74	150.0	13.3	30.68	8.1	31.15	¤	40.32	139.6	14.4	40.89	137.3	5.8
e	50.36	141.9	16.2	51.12	152.3	13.9	30.28	8.1	30.90	¤	39.66	139.6	15.0	40.37	137.3	5.8
f	50.97	152.3	16.2	51.70	151.1	13.8	30.56	8.1	31.06	¤	40.29	138.5	13.8	41.00	137.3	5.8
g	51.70	144.2	16.2	52.75	150.0	12.7	30.15	6.9	30.94	¤	39.89	138.5	13.9	40.67	136.2	6.9
h	48.55	145.4	12.7	49.27	153.5	13.9	30.53	8.1	31.33	¤	39.63	141.9	10.4	40.47	137.3	¤
i	49.03	140.8	17.3	49.64	152.9	14.4	30.58	6.9	31.51	¤	41.19	136.2	15.0	40.98	136.7	4.0
j	46.66	160.4	17.3	47.48	152.9	13.8	32.68	6.9	34.86	3.5	39.65	136.2	9.2	40.41	137.3	¤
k	46.88	159.2	17.9	47.84	152.3	13.9	32.87	6.9	35.10	¤	40.28	136.1	9.2	41.04	136.1	¤
l	46.94	145.4	¤	47.00	163.8	¤	35.02	¤	34.72	¤	26.34	141.9	6.9	27.03	139.6	¤
m	45.11	150.0	12.1	§	§	§	38.43	6.9	§	§	34.98	139.6	8.1	§	§	§
n	55.30	148.8	¤	53.18	132.7	¤	40.59	¤	40.67	¤	25.06	139.6	11.5	26.44	139.6	16.2
o	54.22	148.8	¤	#	#	#	41.68	¤	#	#	25.93	139.6	13.9	#	#	#

‡ All data were collected at 22°C with deuterated chloroform as a solvent

¤ No coupling could be detected. In some cases, line broadening was observed. The resolution of the obtained ^{13}C spectra was 1.15 Hz

Signals could not be attributed due to the low abundance of the isomer in the mixture

§ Compound exists of two enantiomers (not visible in NMR)

Appendix C:

Selected NMR data of a-amino phosphonates 22

Structure (left)	δ(^{31}P)	δ(^{1}H)	^{2}J (Hz)	δ(^{13}C)	^{1}J (Hz)	Structure (right)
cinnamyl, HN–Ph, P(OEt)$_2$	22.95	4.48	25.9	54.06	154.6	cinnamyl, HN–Bn, P(OMe)$_2$
	26.70	~3.70	#	57.41	156.9	
cinnamyl, HN–Bn, P(OEt)$_2$	24.42	3.67	19.3	57.72	154.6	cinnamyl, HN–PMB, P(OMe)$_2$
	26.79	~3.69	#	57.30	155.8	
cinnamyl, HN–allyl, P(OMe)$_2$	26.77	~3.78	#	57.72	156.9	cinnamyl, HN–methallyl, P(OMe)$_2$
	26.90	3.71	19.5	57.45	156.9	
cinnamyl, HN–tryptaminyl, P(OEt)$_2$	24.44	3.70	19.1	59.11	155.8	cinnamyl, HN–iPr, P(OMe)$_2$
	27.04	3.82	20.0	56.26	156.9	
cinnamyl, HN–iPr, P(OEt)$_2$	24.85	3.77	21.2	56.71	155.8	cinnamyl, HN–tBu, P(OMe)$_2$
	27.02	3.90	24.2	53.89	158.1	
cinnamyl, HN–C(CH$_3$)$_2$, P(OEt)$_2$	26.42	3.86	24.8	54.16	155.8	cinnamyl (methyl), HN–allyl, P(OMe)$_2$
	26.98	3.70	21.5	62.97	153.5	
allyl–NH, isobutyl, P(OMe)$_2$	26.94	3.66	20.6	59.74	152.3	allyl–HN, Cl, P(OMe)$_2$
	27.64	4.25	22.6	54.78	156.9	
	23.84	3.93	24.2	62.69	162.7	
allyl–NH, ethylidene, P(OMe)$_2$	26.87	3.80	22.6	60.82	156.9	allyl–HN, P(OMe)$_2$
	27.40	4.29	26.4	54.52	160.4	
allyl–NH, benzyl, P(OMe)$_2$	27.40	3.41	21.7	58.90	154.6	allyl–NH, Ph, P(OMe)$_2$
	27.56	3.50	21.5	60.17	154.6	

The CHP columns span δ(^{1}H), ^{2}J (Hz), δ(^{13}C), and ^{1}J (Hz).

	δ(^{31}P)	δ(^{1}H)	^{2}J (Hz)	δ(^{13}C)	^{1}J (Hz)	
			CHP			
(structure: ClH$_2$N-Bn, styryl-2-NO$_2$, P(OMe)$_2$=O)	18.28	3.95	#	54.09	154.6	(structure: HN-propargyl, styryl-2-NO$_2$, P(OMe)$_2$=O)
	25.70	4.12	18.1	56.50	155.8	
(structure: pinene, HN-Bn, P(OMe)$_2$=O)	26.87	3.49	20.9	60.00	156.9	(structure: pinene, HN-Bn, P(OEt)$_2$=O)
	26.60	3.46	21.2	59.56	156.9	
	24.37	3.45	20.9	50.29	156.9	
	24.57	3.43	21.2	59.90	156.9	
(structure: pinene, HN-allyl, P(OMe)$_2$=O)	27.04	3.50	21.2	59.55	156.9	(structure: pinene, HN-iPr, P(OMe)$_2$=O)
	26.76	3.54	20.9	59.96	156.9	
	26.96	3.55	23.1	58.07	159.2	
	26.82	3.58	23.1	58.39	156.9	
(structure: pinene, HN-tBu, P(OMe)$_2$=O)	27.02	3.57	25.3	55.22	161.5	(structure: furan, HN-Bn, P(OMe)$_2$=O)
	26.49	3.47	24.7	55.68	161.5	
	24.01	4.12	22.3	52.71	161.5	
(structure: furan, HN-allyl, P(OMe)$_2$=O)	24.16	4.06	22.3	52.80	162.7	(structure: furan, HN-allyl, P(OEt)$_2$=O)
	21.82	~3.98	#	53.29	161.5	
(structure: furan, HN-tBu, P(OMe)$_2$=O)	24.27	4.26	25.6	49.27	167.3	(structure: phenyl, HN-Bn, P(OMe)$_2$=O)
	26.44	4.05	20.1	59.29	154.6	
(structure: phenyl, HN-iPr, P(OMe)$_2$=O)	27.00	4.17	22.3	57.98	154.6	(structure: phenyl, HN-iPr, P(OEt)$_2$=O)
	24.74	~4.14	#	58.30	153.5	
(structure: cyclohexyl, HN-iPr, P(OMe)$_2$=O)	31.77	2.78	16.8	57.59	144.2	(structure: HN-Bn, iPr, P(OMe)$_2$=O)
	31.75	2.78	14.5	59.25	142.0	
(structure: iPr, HN-iPr, P(OMe)$_2$=O)	31.84	2.81	16.5	57.39	144.2	

Coupling constant could not be measured due to overlapping signals.

Appendix D:

Selected ^{31}P and ^{13}C NMR data[‡] of 4-phosphono β-lactams

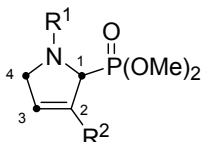| Nr	R^1	R^2	R^3	^{31}P δ (ppm)	^{13}C (2) δ (ppm)	^3J (Hz)	^{13}C (3) δ (ppm)	^2J (Hz)	^{13}C (4) δ (ppm)	^1J (Hz)
23a	Ph	PhCH=CH	Me	24.19	163.41	8.1	49.42	0	59.82	168.5
23b	Bn	PhCH=CH	Me	24.01	166.06	6.9	47.87	0	59.34	167.3
23c	Bn	PhCH=CH	Et	21.70	166.21	7.5	47.81	0	59.47	166.7
273	Bn	PhCH$_2$CH$_2$	Et	24.46	166.13	6.9	43.12	0	58.42	163.8
23d	PMB	PhCH=CH	Me	24.06	166.00	8.1	47.87	0	59.28	167.3
23e	Allyl	PhCH=CH	Me	24.23	165.97	7.5	47.85	0	58.88	167.3
23f	iPr	PhCH=CH	Me	24.75	165.39	8.1	47.13	0	58.06	167.9
23g	Ph	Furyl	Me	21.80	163.77	7.4	47.56	2.4	55.91	172.1
23h	Bn	Furyl	Me	21.36	166.21	8.6	46.07	0	54.75	173.4
23i	Allyl	Furyl	Me	22.06	166.03	8.1	46.14	2.3	54.64	174.2
23j	Bn	Ph	Me	23.84	167.19	7.3	48.52	0	61.28	163.5
23l[#]	Bn		Et	21.86	167.41	6.9	44.81	0	60.95	165.0
23l[¤]				22.00	Not observed		44.91	0	60.33	166.1

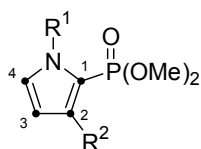‡ All data were collected at 22°C with deuterated chloroform as a solvent
Major isomer
¤ Minor isomer

Appendix E:

*Selected ^{31}P and ^{13}C NMR data[‡] of pyrrolines **31** and pyrroles **30**, **312***

Nr	R[1]	R[2]	^{31}P δ (ppm)	^{13}C (1) δ (ppm)	^{1}J (Hz)	^{13}C (2) δ (ppm)	^{2}J (Hz)	^{13}C (3) δ (ppm)	^{3}J (Hz)	^{13}C (4) δ (ppm)	^{3}J (Hz)
31a	Bn	H	24.58	68.36	176.5	130.21	12.7	124.00	5.8	60.10	5.8
31b	Bn	Me	24.69	70.84	174.2	133.43	4.6	124.78	12.7	59.87	8.1
31c	Bn	Bn	24.69	69.04	173.1	137.67	4.6	125.76	11.5	59.93	6.9
31d	Bn	isoamyl	24.91	69.87	174.2	138.24	4.6	123.28	11.5	60.02	8.2
31e	Bn	Ph	24.64	68.67	173.1	137.52	3.5	126.98	11.5	60.60	4.5

Nr	R[1]	R[2]	^{31}P δ (ppm)	^{13}C (1) δ (ppm)	^{1}J (Hz)	^{13}C (2) δ (ppm)	^{2}J (Hz)	^{13}C (3) δ (ppm)	^{3}J (Hz)	^{13}C (4) δ (ppm)	^{3}J (Hz)
312a	H	H	15.01	115.16	230.8	118.65	17.3	109.93	15.0	124.59	12.7
312b	H	isoamyl	16.21	111.74	229.6	135.21	18.5	110.82	15.0	123.35	11.5
30a	Bn	H	13.63	117.63	227.3	122.47	17.3	109.12	13.8	129.04	11.5
30b	Bn	Me	14.82	113.49	226.1	133.47	18.5	111.25	15.0	128.54	12.7
30c	Bn	Bn	14.39	113.47	226.0	137.15	18.5	110.89	16.2	128.73	11.5
30d	Bn	isoamyl	14.87	112.92	226.1	139.38	19.6	109.86	15.0	128.71	12.7
30e	Bn	Ph	13.77	113.79	226.1	137.46	18.5	110.98	13.9	128.66	12.7
30f	Bn	Phenethyl	14.52	113.32	225.0	138.24	19.6	110.12	16.2	128.62	12.7

‡ All data were collected at 22°C with deuterated chloroform as a solvent; the resolution of the ^{13}C experiment used, was 1.2 Hz.

Appendix F:

Selected NMR data‡ of 3-(acyl)-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl phosphonates 35

^{13}C and ^{31}P NMR data

		35a CH$_2$Cl		35b (CH$_2$)$_3$Cl		35c CH(CH$_3$)$_2$		35d CHCl$_2$		35e CCl$_3$	
	R :	M	m	M	m	M	m	M	m	M	m
C1	δ	94.01	95.47	94.11	95.29	93.98	#	93.72	95.49	94.42	93.18
C1	J$_{CP}$	9.2	8.1	9.2	9.2	10.4	#	8.1	6.9	4.6	3.5
C2	δ	54.91	56.40	54.13	56.61	54.03	#	55.61	56.46	56.03	57.94
C2	J$_{CP}$	159.2	162.7	159.2	162.7	159.2	#	158.1	161.5	160.4	158.1
C4	δ	52.53	52.53	52.71	51.74	52.49	#	52.42	#	55.70	54.64
C5	δ	41.87	36.51	41.79	39.71	41.87	#	42.14	39.32	44.77	42.96
C5	J$_{CP}$	0	0	0	0	0	#	0	0	2.3	0
C6	δ	34.38	#	34.31	34.51	34.43	#	34.40	34.29	28.70	34.54
C7	δ	79.22	79.31	79.13	79.04	79.10	#	79.20	79.38	81.36	79.10
C8	δ	137.6	137.79	137.32	137.49	137.49	#	137.60	137.93	136.86	137.57
C9	δ	133.06	132.75	133.31	132.97	133.52	#	132.91	132.48	134.39	132.83
C=O	δ	165.76	166.45	171.14	171.89	176.47	#	162.50	163.28	159.69	159.52
^{31}P	δ	21.31	21.48	22.16	21.61	22.44	21.63	20.80	20.91	20.70	20.89

^{1}H NMR coupling constants:

		35a CH$_2$Cl		35b (CH$_2$)$_3$Cl		35c CH(CH$_3$)$_2$		35d CHCl$_2$		35e CCl$_3$	
	R :	M	m	M	m	M	m	M	m	M	m
H6α-H5		7.7	#	7.7	#	7.7	#	7.7	#	7.4	7.7
H5-H6β		2.8	#	2.8	#	3.0	#	2.9	#	3.6	3.3
H6α-H6β		11.6	#	11.7	#	11.6	#	11.6	#	11.8	11.6
H7-H6β		4.4	#	4.4	#	4.4	#	4.4	#	4.4	4.1

‡ All data were collected at 22°C with deuterated chloroform as a solvent

Could not be measured adequately

❧✦❦

*C*urriculum *V*itae

❧❧❦❦♆✦

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Carreer

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01/05/2006 - Research Technologist at Taminco nv. (Ghent).

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Peer reviewed

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N. Dieltiens, K. Moonen, C. V. Stevens. "*Enyne metathesis-oxidation sequence for the synthesis of 2-phosphono pyrroles, proof of the 'yne-then-ene' pathway.*" Accepted in *Chem. Eur. J.* **2006.**

V. Van Speybroeck, K. Moonen, K. Hemelsoet, C. V. Stevens, M. Waroquier. "*Non-expected four-membered over six-membered ring formation during the synthesis of azaheterocyclic phosphonates: experimental and theoretical evaluation.*" *J. Am. Chem. Soc.* **2006**, *128*, 8468-8478.

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9th Sigma-Alldrich Organic Synthesis Meeting, 1-2/12/2005, Spa.
K. Moonen, E. Van Meenen, A. Verwée, C. V. Stevens. "*Tandem 1,4-1,2-addition of phosphites to a,ß-unsaturated imines.*" (Poster).

Video conference "Chemie voor meer toekomst", KVIV, 05/10/2005, Beerse.

Renewable Resources and Biorefineries Conference, 19-21/09/2005, Ghent, Belgium (member of the organizing committee).

2èmes Journées Nord-Européennes des Jeunes Chercheurs, 24-25/03/2005, Villeneuve d'Ascq, France.
K. Moonen, C. V. Stevens. "*Synthesis of 4-phosphono-β-lactams.*" (Lecture).

8th Sigma-Alldrich Organic Synthesis Meeting, 2-3/12/2004, Spa.
D. Acke, K. Moonen, E. Van Meenen, C. V. Stevens. "*Straightforward Continuous Synthesis of α-Aminophosphonates under Microreactor Conditions.*" (Poster).

2004 Lilly European Distinguished Lectureship, Prof. J. E. Baldwin, Synthesis and Biosynthesis of Antibiotics, 17/11/2004, Namur.

16th International Conference on Phosphorus Chemistry, 05/07 – 09/07/2004, Birmingham, UK.
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7de Vlaams jongerencongres van de chemie (KVCV), 16/04/2004, Gent (poster).
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Award

Belgochlor Award, 7[de] Vlaams jongerencongres van de chemie (KVCV), Gent, 2004.

Miscellaneous

Member of the organizing committee of the 1st International Renewable Resources and Biorefineries Conference (RRBConference) – Ghent, 09/2005.

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