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Enantioselective synthesis of α-aminophosphonic acid derivatives

Aitor Maestro Burzaco

2019

“No one can pass through life, any more than he can pass through a bit of country, without leaving tracks behind, and those tracks may often be helpful to those coming after him in finding their way”

Robert Baden-Powell

Me gustaría expresar mi más sincero agradecimiento a los Drs. Francisco Palacios y Javier Vicario, directores de este trabajo, por haberme dado la oportunidad de realizar mi tesis doctoral bajo su supervisión, por su apoyo, su dedicación y por lo mucho que he podido aprender de ellos durante estos años.

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A mi familia y amigos, por su apoyo.

Summary

α-Aminophosphonic acids and their derivatives are widely present in biologically attractive products like drugs and agrochemicals.

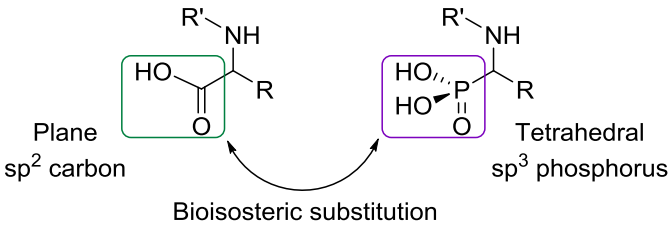


Figure 1. α-Aminophosphonic acids are bioisosters of α-amino acids.

The high interest of α-aminophosphonic acid derivatives in industry has led to a development of multiple synthetic routes for their preparation. In addition, due to the importance of using enantiomerically pure compounds for biological applications, during the last decades, an increasing number of asymmetric synthesis of α-aminophosphonates have been reported. The main strategies in this field consit in the formation of C-P bonds, through hydrophosphonilation of imines and asymmetric hydrogenations of phosphorated enamines, but the asymmetric strategies that imply C-C bond formation are almost unexplored.

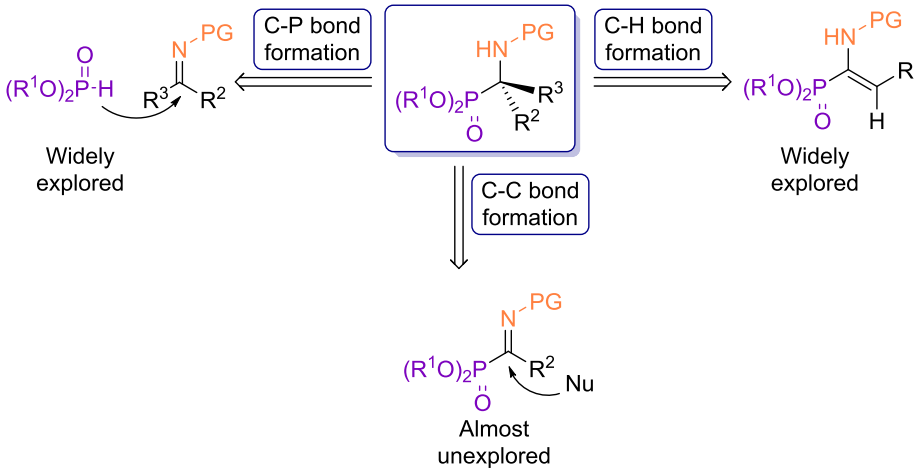


Figure 2. Main strategies for the asymmetric synthesis of α-aminophosphonates.

In this context, the main objective of this Ph.D. thesis has been the synthesis of α-iminophosphonates and the enantioselective addition of nucleophiles to these phosphorylated imines.

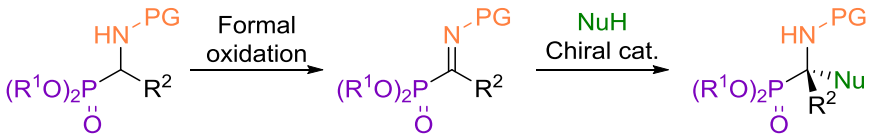


Figure 3. Main objective of this thesis.

First, the synthetic applications of phosphorylated aldimines have been studied in the Friedel-Crafts reaction of indoles. The reaction successfully yields the desired indolyl phosphoglycines when amides (PG = Bz) and carbamates (PG = Troc) are used as protecting groups of the imine. In addition, the organocatalytic asymmetric

version of the reaction has also been explored, obtaining enantiomeric excesses rangin from 68 to 82 %.

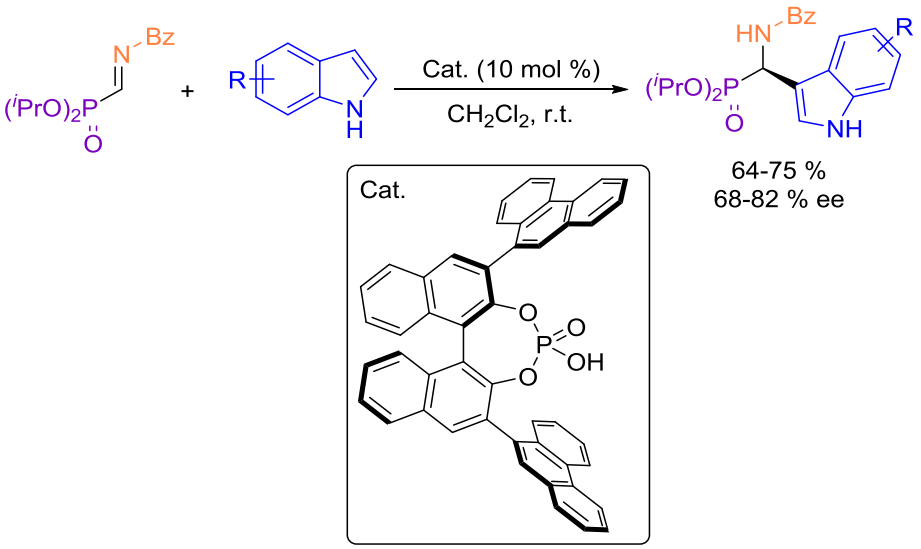


Figure 4. Asymmetric Friedel-Crafts reaction of indoles with α-aldiminophosphonates (*J. Org. Chem.* **2019**, *84*, 1094−1102).

On the other hand, when bulky amines (PG = Trt) or sulfonamides (PG = Ts) are used as protecting groups in the Friedel-Crafts reaction, bisindole phosphonates are selectively obtained. In view of the anticancer activity of some bis indole products reported on the literature, the antiproliferative effect of our products against lung and ovarian cancer cell lines was additionally tested. More than 20 bis(3-indolyl)methane phosphonate derivatives were synthesized and these compounds were found to have high activity and selectivity against cancer cells with respect to non malignant cell line, with the best IC_{50} values of 0.06 µM.

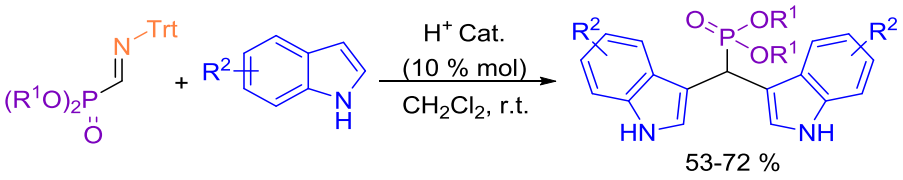


Figure 5. Synthesis of bis-(3-indolyl)methane phosphonates (*Eur. J. Med. Chem.* **2018**, *158*, 874-883).

Next, during a short stay in the Stratingh Institute for Chemistry of the University of Groningen, the asymmetric addition of organometallic aliphatic nucleophiles to α-phosphorylated ketimines has been also explored. Unfortunately, even though the conversion of the imine to the addition product has been successfully achieved using organozinc bromides as nucleophiles, the obtained enantioselectivities were found to be very low.

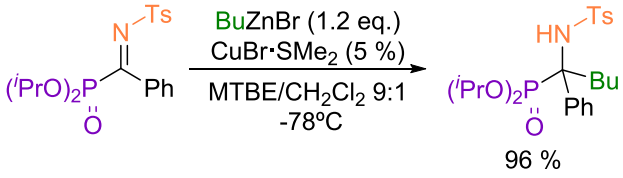


Figure 6. Alkylation of ketiminophosphonates using BuZnBr.

Finally, aza-Reformatksy reaction of acyclic ketimines for the preparation of phosphorated analogs of aspartic acid has been studied. The use of dimethylzinc as catalyst and dry air instead of inert atmosphere are found to be crucial for the synthesis of the desired products. In addition, the enantioselective version of this reaction has been achieved using substituted BINOL derivatives as chiral ligand, thus allowing to obtain enantioselectivities up to 99 %. In addition,

promising preliminary results of some of these compounds as selective antiproliferative agents for cancer cell lines are also reported.

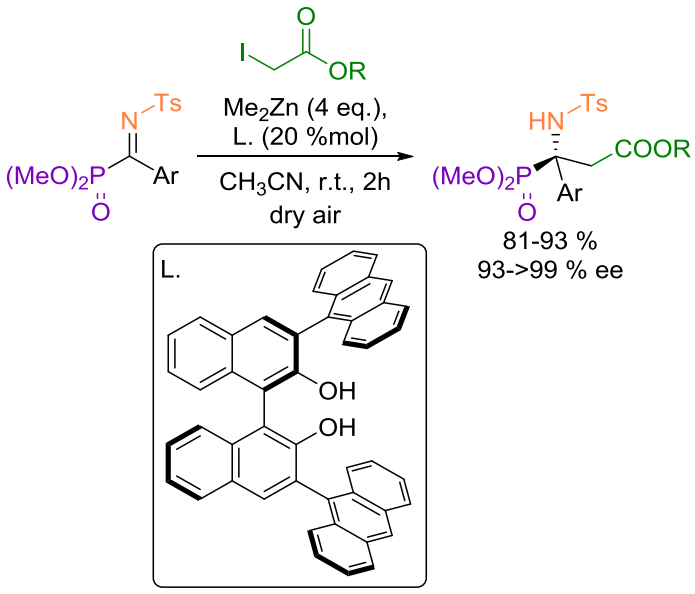


Figure 7. Aza-Reformatksy reaction using α-phosphorylated ketimines.

Resumen

Los ácidos α-aminofosfónicos y sus derivados son estructuras muy frecuentes en productos con alto interés biológico como fármacos y agroquímicos.

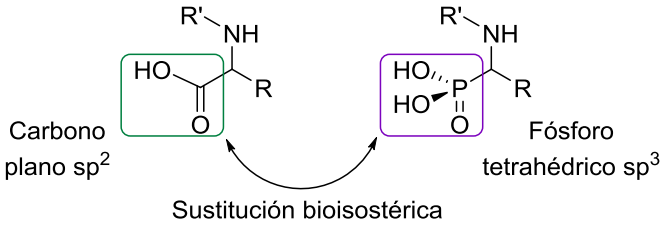


Figura 1. Los ácidos α-aminofosfónicos son bioisósteros de α-aminoácidos.

El elevado interes de la industria en derivados de ácidos α-aminofosfónicos ha dado lugar al desarrollo de múltiples rutas sintéticas para su preparación. Además, dada la importancia de utilizar compuestos enantioméricamente puros en aplicaciones biológicas, el número de ejemplos de síntesis asimétricas de α-aminofosfonatos descritos ha ido en aumento durante las últimas décadas. Las principales estratégias en este campo consisten en la formación de enlaces C-P mediante hidrofosfonilación de iminas e hidrogenaciones asimétricas de enaminas fosforadas, pero no existen muchos ejemplos de formación asimétrica de enlaces C-C.

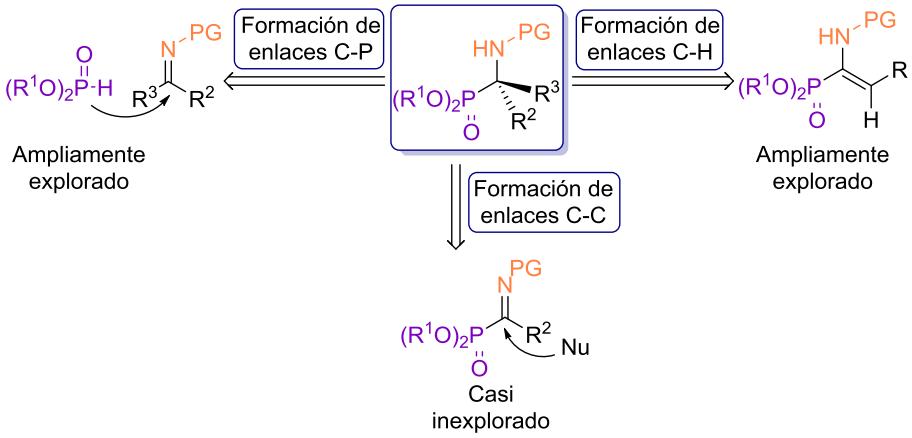


Figura 2. Principales estratégias para la sintesis asimétrica de α-aminophosphonates.

En este contexto, el principal objetivo de esta tesis doctoral ha sido la sintesis de α-iminofosfonatos y la posterior adición enantioselectiva de nucleófilos a las mismas.

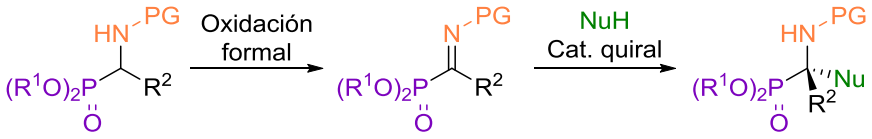


Figura 3. Objetivo principal de esta tesis.

En primer lugar, se estudiaron las aplicaciones sintéticas de aldiminas fosforadas en la reacción de Friedel-Crafts con indoles. La reacción permite obtener las indolil fosfoglicinas deseados cuando los grupos protectores utilizados son amidas (PG = Bz) y carbamatos (PG = Troc). Además, también se estudió la versión organocatalítica de esta reacción, obteniendo excesos enantioméricos de 68 a 82 %.

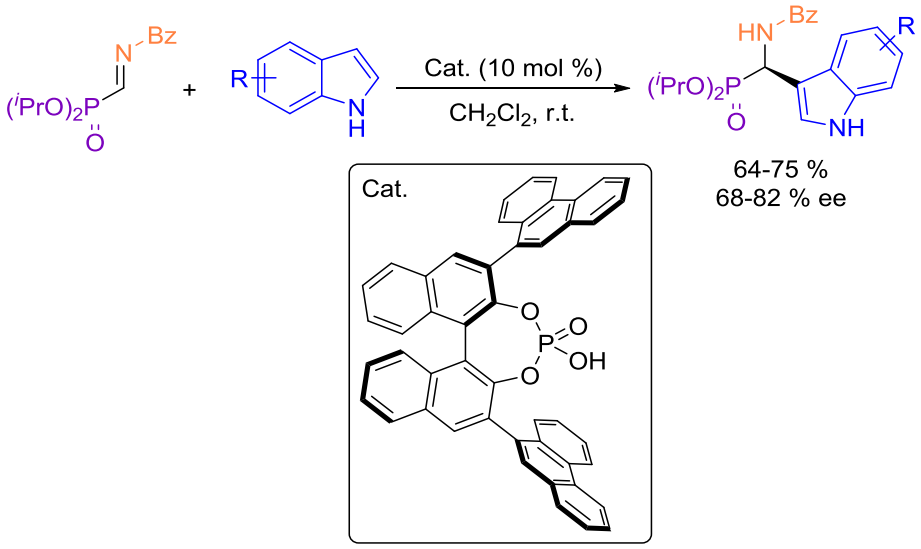


Figura 4. Reacción asimétrica de Friedel-Crafts de indoles con α-aldiminofosfonatos (*J. Org. Chem.* **2019**, *84*, 1094−1102).

Por otro lado, cuando se utilizan aminas voluminosas (PG = Trt) o sulfonamidas (PG = Ts) como grupos protectores en la reacción de Friedel-Crafts, se obtienen selectivamente bisindoles fosforados. Debido a que algunos compuestos que contienen bisindoles en su estructura han sido descritos como agentes anticancerosos, también se ha estudiado el efecto antiproliferativo de estos bisindoles fosforados frente a células cancerosas de pulmón y ovario. Se han sintetizado más de 20 derivados de bisindol fosforados y estas nuevas moléculas han demostrado tener alta actividad y selectividad frente a células cancerosas en comparación con células no cancerosas, con valores de IC_{50} de hasta 0.06 μM.

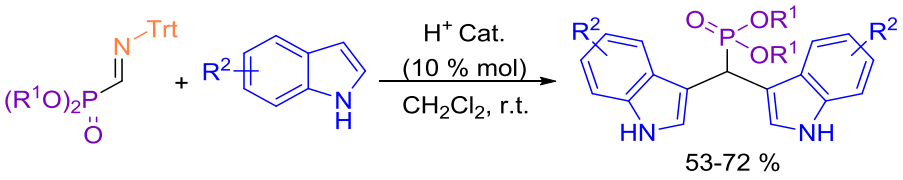


Figura 5. Síntesis de bis indoles fosforados (*Eur. J. Med. Chem.* **2018**, *158*, 874-883).

A continuación, durante una breve estancia en el Stratingh Institute for Chemistry de la Universidad de Groningen, se ha estudiado la adición asimétrica de cadenas alquílicas sobre cetiminas fosforadas utilizando reactivos organometálicos. Desafortunadamente, a pesar de que se ha logrado obtener conversiones elevadas de la imina al producto deseado utilizando bromuros de alquílzinc como nucleófilos, las enantioselectividades obtenidas en el proceso fueron limitadas.

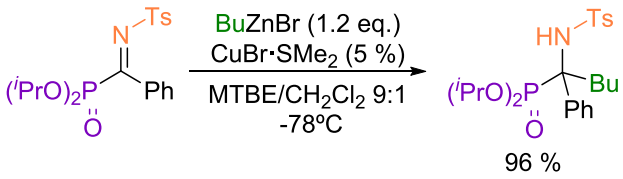


Figura 6. Alquilación de cetiminas fosforadas mediante adición de BuZnBr.

Finalmente, se ha estudiado la reacción aza-Reformatsky sobre cetiminas acíclicas para dar derivados fosforados de ácido aspártico. El uso de dimetilzinc como catalizador y una atmósfera de aire seco en lugar de atmósfera inerte son cruciales para obtener los productos deseados. Además, la versión enantioselectiva de esta reacción ha sido

llevada a cabo utilizando ligandos quirales derivados de BINOL, permitiendo la obtención de los productos finales con excesos enantioméricos superiores al 99 %. Así mismo, también se han realizado ensayos preliminaries de algunos de estos compuestos para valorar su actividad como agentes antiproliferativos de células cancerosas, obteniendo hasta la fecha resultados prometedores.

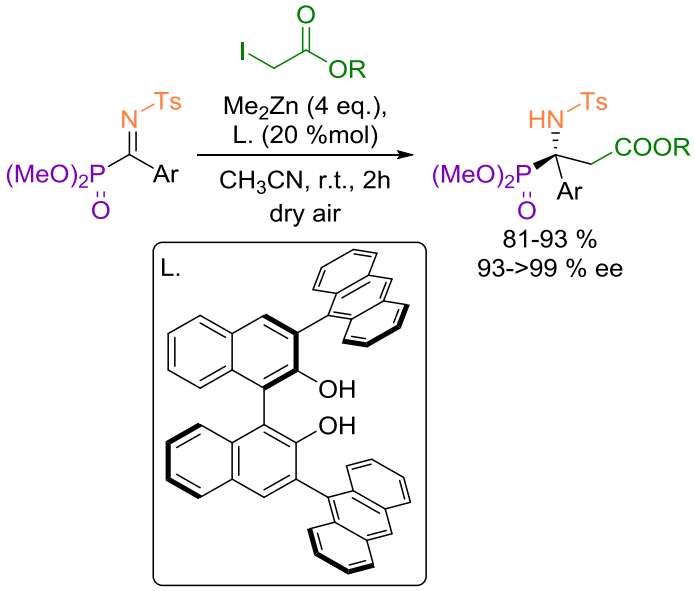


Figura 7. Reacción aza-Reformatksy sobre cetiminas acíclicas fosforadas.

Abbreviations and acronyms

Alk	Alkyl
BIM	Bis-(3-indolyl)methane
BIMP	Bis-(3-indolyl)methane phosphonate
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOX	bis(oxazoline)
BPE	1,2-Bis(2,5-diphenylphospholan-1-yl)ethane
Bz	Benzoyl
calcd..	calculated
Cat.	Catalyst
Conv.	Conversion
COSY	Corelated spectroscopy
DCC	*N*,*N*-dicyclohexylcarbodiimide
DEPT	Distortionless Enhanced Polarization Transfer
DMAP	4-Dimethyaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
de	Diastereomeric excess
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
eq.	equivalents
ESI	Electrospray ionization
HOE	Heteronuclear Overhauser effect
HOESY	Heteronuclear Overhauser enhancement spectroscopy
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy
IR	Infrared spectroscopy
JosiPHOS	Chiral diphosphine ferrocenyl ligand family

L	Ligand
LC	Liquid chromatography
MeOBIPHEP	2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
Mp	Melting point
MTBE	Methyl *tert*-butyl ether
n.d.	Not determined
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
Np	Neopentyl
Nu	Nucleophile
ox.	oxidation
OTf	Triflate
PG	Protecting group
PheBOX	Bis(oxazolin)phenyl
Py	Pyridine
PyBOX	Bis(oxazolin)pyridine
Q-TOF	Quadrupole Time Of Flight
r.t.	Room temperature
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TCCA	Trichloroisocyanuric acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsily
Troc	2,2,2-trichloroethoxycarbonyl
Trt	Trityl
Ts	Tosyl
UV	Ultraviolet light
VAPOL	2,2′-Diphenyl-(4-biphenanthrol)
WalPHOS	Chiral diphosphine ferrocenyl ligand family

Table of contents

Introduction 23

Objectives 61

Chapter 1. Synthesis of α-iminophosphonates 67

Chapter 2. Friedel-Crafts reactions of α-aldiminophosphonates with indole derivatives 89

Chapter 3. Synthesis and antiproliferative evaluation of bis-(3-indolyl)methane phosphonates 115

Chapter 4. Nucleophilic addition of organometalic reagents to α-ketiminophosphonates. 137

Chapter 5. Enantioselective aza-Reformatksy reaction of α-ketiminophosphonates 157

Conclusions 177

Experimental section 183

General methods and materials 185

Chapter 1. Synthesis of α-iminophosphonates 188

Synthesis of aldimines **71** 188

Synthesis of ketimines **49** 212

Chapter 2. Friedel-Crafts reactions of α-aldiminophosphonates with indole derivatives 261

General procedure for the asymmetric Friedel-Crafts reaction of α-aldiminophosphonates **71** and indole derivatives **99** 261

Determination of the absolute configuration of **102c** 277

Chapter 3. Synthesis and antiproliferative evaluation of bis-(3-indolyl)methane phosphonates 281

General procedure for the synthesis of BIMPs **103** 281

Hydrolysis of phosphonate 302

General procedure for the synthesis *N*-methylated substrates 304

Chapter 4. Nucleophilic addition of organometalic reagents to α-ketiminophosphonates 307

General procedure for the addition of methylmagnesium bromide to ketimines **49** 307

Chapter 5. Enantioselective aza-Reformatksy reaction of α-ketiminophosphonates 313

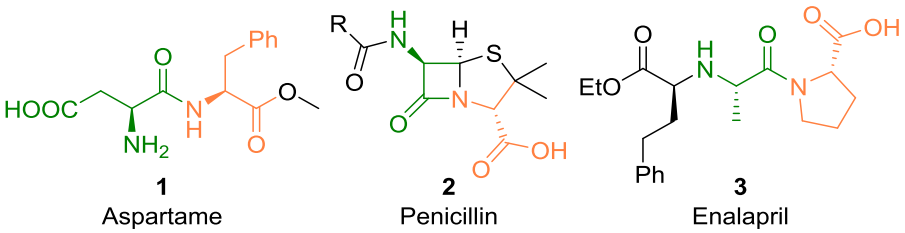
General procedure for the asymmetric synthesis of aza-Reformatsky products **145** 313

Selective hydrolysis of phosphonate 340

Synthesis of β-lactam derivative **148** 342

Introduction

α-Amino acids are a key structure in living organisms as the essential part of proteins and peptides. Many amino acid derivatives are daily used in diverse biological applications like sweetener aspartame **1**, antibiotic penicillin **2** or antihypertensive enalapril **3** (Figure 8). Due to the relevance of α-amino acids in nature, a vast number of methods for the synthesis of natural and non-natural α-amino acids and their mimetics have been developed.[1]



1 Aspartame **2** Penicillin **3** Enalapril

Figure 8. Biologically active peptides.

In medicinal chemistry is typical to find a lead compound, which has a desired pharmacological activity along with some undesirable side effects or other associated drawbacks. In order to overcome these limitations and further develop our toolbox in

medicinal sciences, bioisosterism represents one useful approach, which is widely used for the rational modification of lead compounds into safer and more clinically effective agents.[2]

In particular, α-aminophosphonic acids **5** are the result of a bioisosteric substitution of a planar carboxylic acid by a phosphonic acid group in α-amino acid structures **4** (Figure 9).

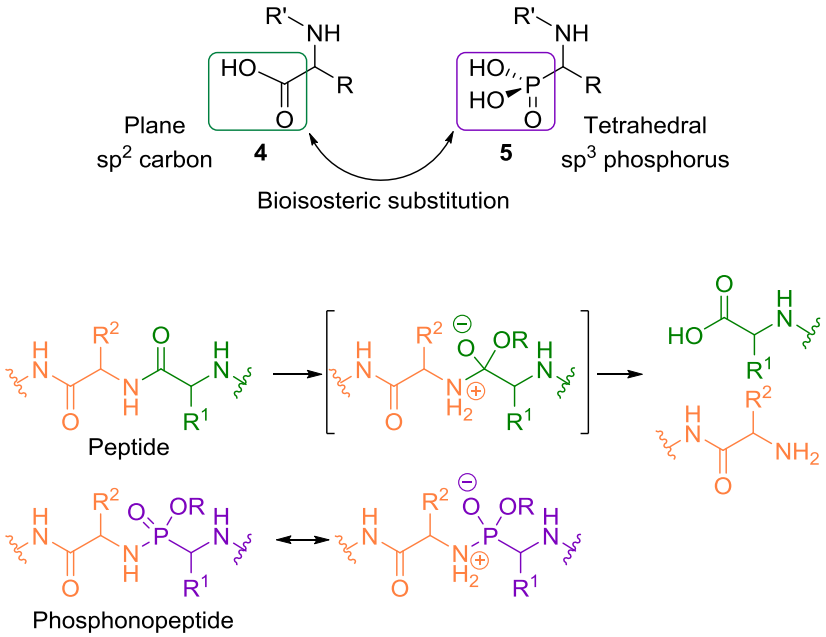


Figure 9. α-Aminophosphonic acids can mimic the transition state of peptide cleavage.

This isosteric replacement is of great interest since, due to the tetrahedral configuration of the phosphorus atom, α-aminophosphonate derivatives can behave as stable analogs of the transition state of peptide cleavage, thus inhibiting enzymes engaged in proteolysis processes and, consequently, they show an assorted biological activity.[3]

In fact, numerous α-aminophosphonic acid derivatives display activity as agrochemicals[4] as well as antimicrobial,[5] antioxidant[6] or anticancer agents[7] and show promising biological properties for the treatment of infectious diseases [8] (Figure 10).

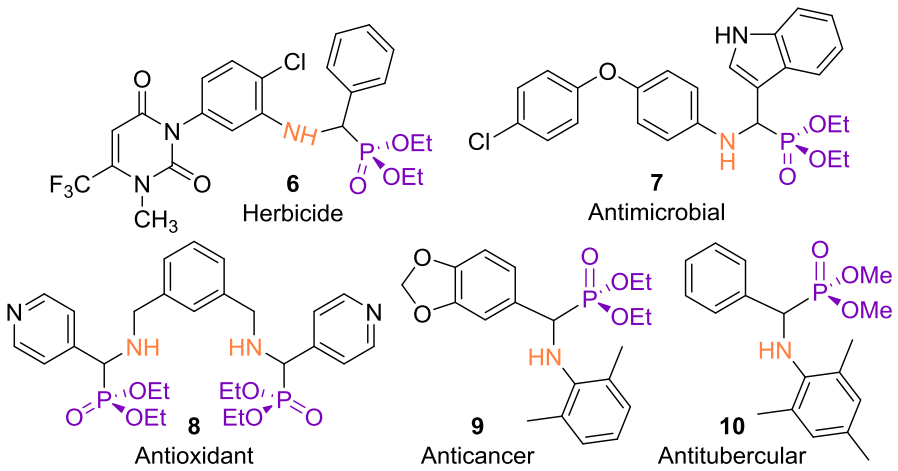
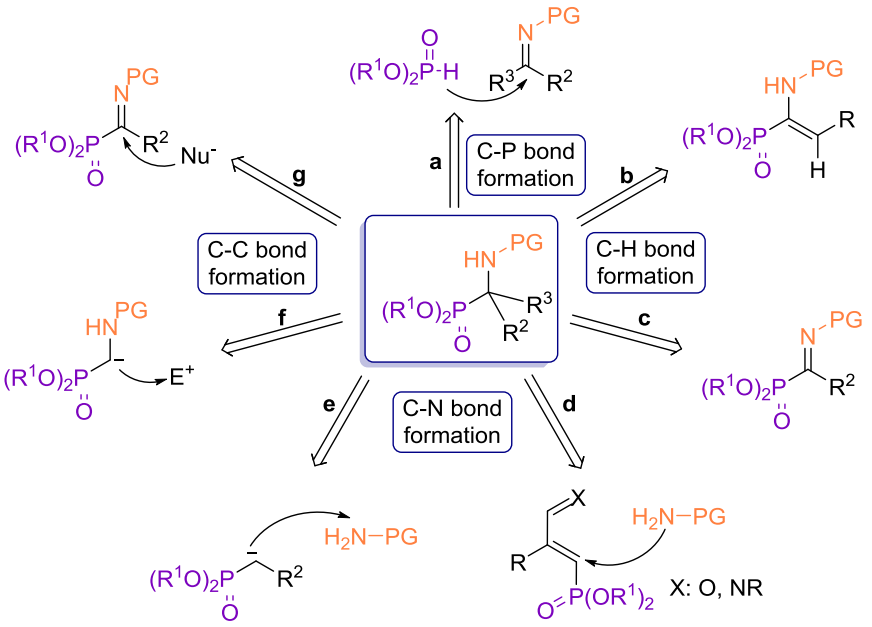


Figure 10. Some biologicaly active α-aminophosphonic acid derivatives.

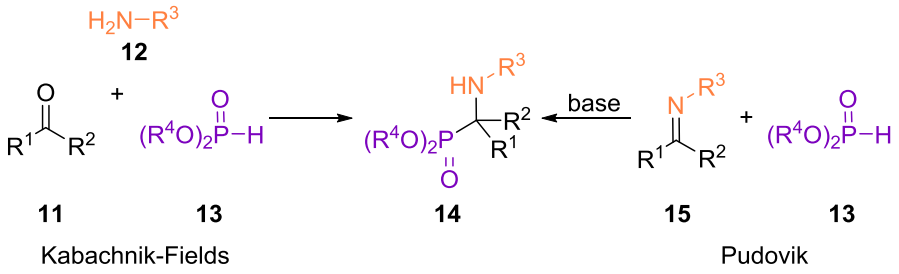
α-Aminophosphonic acids are often obtained by hydrolysis from their phosphonate esters and, depending on the type of bond created in the key reaction leading to the formation of α-aminophosphonates, it is possible to classify the existing methods for their synthesis in four main groups (Scheme 1):[9]

1. C-P bond formation, by addition of phosphorus nucleophiles to imines (Scheme 1, **a**).
2. C-H bond formation, by catalytic hydrogenation of α-phosphorated enamines or imines (Scheme 1, **b**, **c**).
3. C-N bond formation, by addition of amines to conjugate imino- and keto-phosphonates (Scheme 1, **d**) or electrophilic amination of alkyl phosphonates (Scheme 1, **e**).
4. C-C bond formation, by either electrophilic substitution of other α-aminophosphonates (Scheme 1, **f**) or addition of carbon nucleophiles to α-iminophosphonates (Scheme 1, **g**).



Scheme 1. Strategies for the synthesis of α-aminophosphonates.

The first synthesis of α-aminophosphonates **14**, and one of the most widely used method for their preparation nowadays, is the Kabachnik-Fields reaction, independently discovered by Martin Izrailevich Kabachnik and Ellis K. Fields in 1952.[10] Although the mechanism of this reaction is not fully understood, this methodology is based on a multicomponent process, where a carbonyl compound **11**, an amine **12** and dialkylphosphite **13** are involved (Scheme 2). Other typical way to obtain α-aminophosphonates, related to the above method is the Pudovik reaction,[11] consisting in a nucleophilic addition of dialkyl or diarylphosphites **13** to imines **15** under basic conditions (Scheme 2).



Scheme 2. Kabachnik-Fields and Pudovik reactions.

When talking about biologically active compounds it is necessary to keep in mind the tridimensional model for the atom of carbon, introduced by Le Bel[12] and Van'tHoff[13] in 1874, as well as the concept of chirality, widely used after de definition by the physicist Sir William Thomson:[14] *"I call my geometrical figure, or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."* (Figure 11).

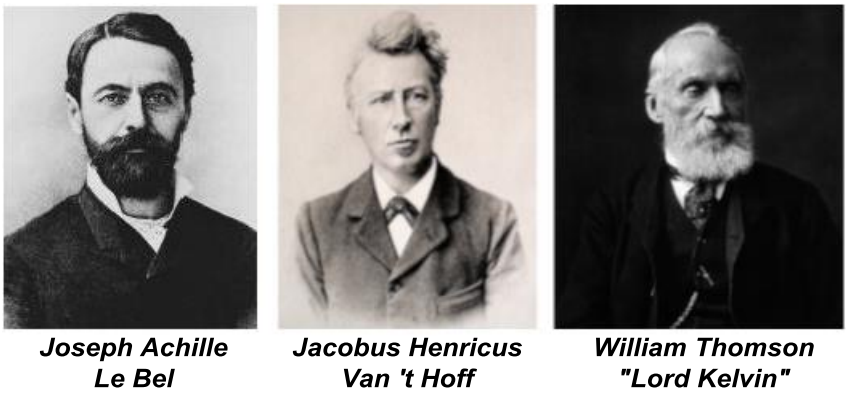
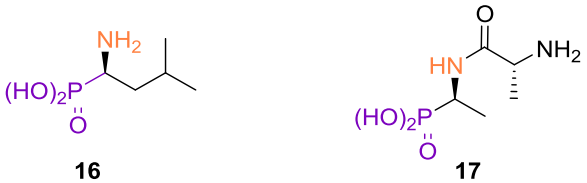


Figure 11. Le Bel, Van´t Hoff and Thompson.

Following this proposals, a carbon atom linked to four different substituents can generate two molecules with identical chemical composition but with a different spatial distribution that we nowadays know as enantiomers. Most of the amino acids are chiral molecules and it is possible to find them in the nature as a single enantiomer.

In general, the two enantiomers of a molecule show almost identical chemical and physical properties. However, in the presence of a chiral environment, such as the active site of an enzyme, the enantiomers may have different properties and it is easy to find examples in which both enantiomers of a molecule generate a different response in the same biochemical process. For instance, Darvon (dextropropoxyphene) is used as analgesic drug while on the other hand its enantiomer Novrad (levopropoxiphene) has antitussive activity. As a curiosity, it is interesting to note that their names, Darvon and Novrad, are also mirror images. In a similar way, limonene can be also used as example, where *R* isomer smells like orange while the *S* isomer has lemon smell.

As in the case of α-amino acids, we can also find some examples of biologically active α-aminophosphonic acids with clear differences depending on the absolute configuration of the stereogenic carbons. That is the case of *R* isomer of phospholeucine **16**, which has higher activity as a leucine-peptidase inhibitor than the *S* isomer,[15] and (*S*),(*R*)-alaphosphalin **17**, which is stronger as antibiotic than the other three possible isomers (Figure 12).[16]



16 (*R*)-Phospholeucine

17 (*S*),(*R*)-Alaphosphalin

Figure 12. Most active enantiomers of phospholeucine and alaphosphalin.

In order to avoid tragedies, such as the thalidomide case,[17] pharmaceutical industries as well as drug regulatory agencies have set among their synthetic objectives the preparation of enantiomerically pure molecules. Taking into account the applications of α-aminophosphonates as bioactive molecules, the development of synthetic methodologies to obtain them with high optical purity is a goal of great interest in organic chemistry.

It is important to note that the conventional chemical reactions for the formation of new carbon-carbon and carbon-heteroatom bonds lead normally to racemic mixtures. During the last decades, the demand of optically pure compounds has increased not only at a laboratory scale, but also at industrial scale.[18] For this reason, three basic strategies have been developed for the preparation of enantiomerically pure molecules (Figure 13).

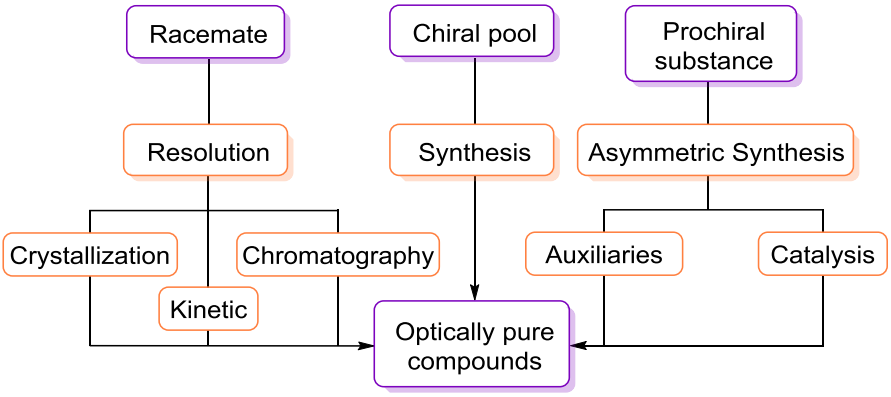


Figure 13. Several methods for the synthesis of optically pure compounds.

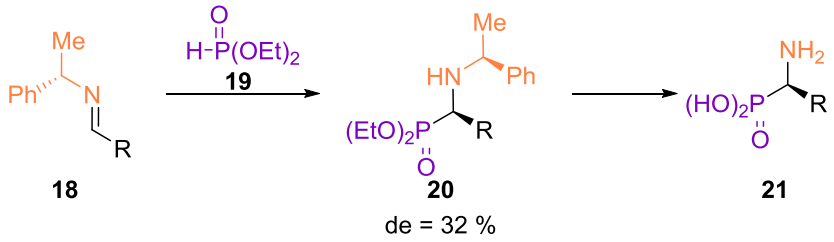
The resolution of racemates is the most classic method for the separation of two enantiomers from a racemic mixture and is one of the most used methods at industrial scale. The main resolution methods are resolution by crystallization, chromatographic resolution, kinetic resolution and dynamic kinetic resolution.[19] Except for the last one, the maximum yield of the global process is 50 % but using dynamic kinetic resolution,[20] which combines dynamic resolution and *in situ* racemization, is it possible to obtain a single enantiomer in quantitative yield.

The chiral pool strategy implies the use of cheap and optically pure compounds (typically amino acids, terpenes, sugars or alkaloids) as starting materials in order to synthesize the desired product. Although it is an effective technique at an industrial level for the high scale synthesis of simple bioactive compounds, it requires the design

a specific route for each compound. Other handicaps of this method include the dependence on the availability of the required starting reagents and the risk of racemization of the stereogenic carbon under certain reaction conditions. Despite these disadvantages, it is still a very useful strategy for the synthesis of compounds with biological interest like Taxol® or ingenol,[21] as well as for the preparation of widely used chiral auxiliaries, ligands for metal complexes and organocatalysts.[22]

The third strategy for the synthesis of enantiomerically pure compounds is the asymmetric synthesis.[23] In this case, a stereocontroled reaction allows to directly obtain enantioenriched products. Chiral auxiliaries can control the stereoselectivity of the reaction, but this adds two more steps to the synthetic route; one for the introduction of the chiral auxiliary in the starting material and another one for its removal, and it still requires a stoichiometric amount of the auxiliary. In addition, the ideal chiral auxiliary must be able to be recovered and recycled. For those reasons, asymmetric catalytic methods like bio catalysis,[24] metal catalysis[25] and organocatalysis,[26] in which substoichiometric amounts of the chiral inductor are used, are more attractive and have been widely developed during the last years, for the asymmetric synthesis of organic compounds in general[23] and for α-aminophosphonates in particular.[27]

The first report of an enantiomerically pure α-amino-phosphonate was achieved thanks to the Pudovik reaction in 1972, when Gilmore and McBride described the diastereoselective addition of diethyl phosphite **19** to an imine **18**, which was previously synthesized from the condensation of a chiral amine with aldehydes (Scheme 3).[28]

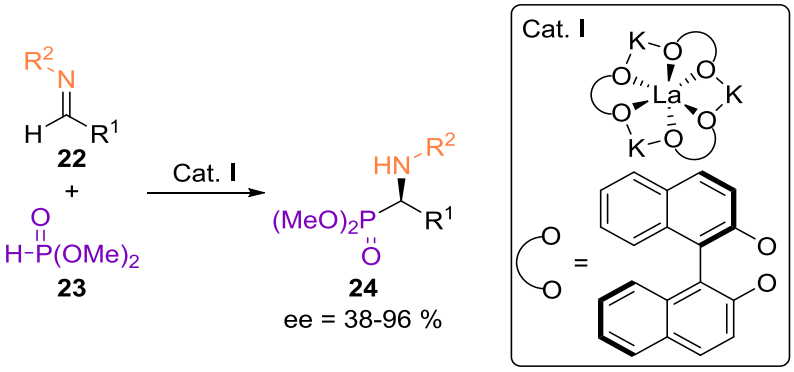


Scheme 3. First synthesis of enantiomerically pure α-aminophosphonates.

In the next decade, some enantiomerically pure α-aminophosphonates were reported by resolution of racemates, using commercially available and cheap dibenzoyl tartaric acid as resolution agent.[29] After that, numerous articles have been published not only for the synthesis of enantioenriched α-aminophosphonates,[30] which allow to obtain the corresponding α-aminophosphonic acids, but also for the synthesis of α-aminophosphonate derived oligopeptides[31] using chiral auxiliaries.

In this regard, our research group reported in 2010 a diastereoselective addition of TADDOL phosphite to imines with diastereomeric ratios up to 95:5 which provides an efficient method for the preparation of enantiopure α-aminophosphonic acids.[32] Despite the fact that the use of chiral auxiliaries is a useful method to obtain enantiopure compounds, the additional synthetic steps of this strategy and the required stoichiometric amount of the chiral auxiliary make it less attractive than asymmetric catalytic methods.

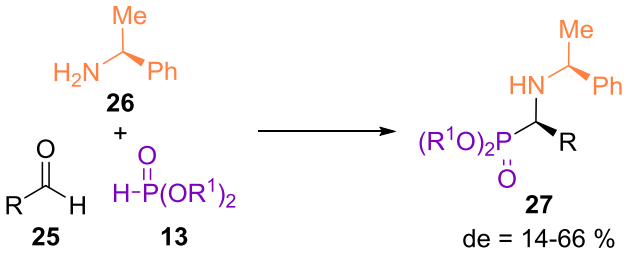
Based on Pudovik´s methodology, Shibasaki´s group achieved the first enantioselective hydrophosphonylation of imines **22** in 1995 using lanthanum-potassium-BINOL complex **I** as catalyst, and obtaining enantiomeric excesses ranging from moderate to good (Scheme 4).[33]



Scheme 4. First enantioselective hydrophosphonylation of imines.

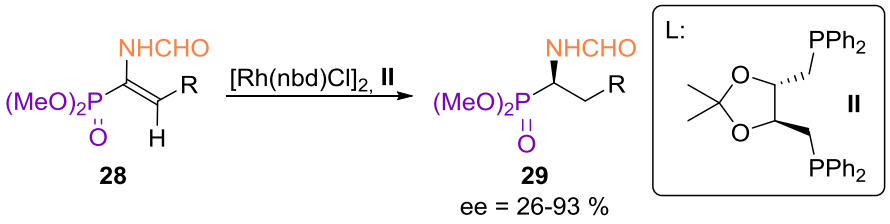
After that, several examples of asymmetric catalytic methods for the hydrophosphonylation of aldimines to afford enantioenriched α-aminophosphonates have been reported.[34]

Even though the first asymmetric synthesis of optically active α-aminophosphonates using Pudovik´s methodology was reported in the 1970s decade, it was not until 1998 when Heydari et al.[35] successfully carried out the first example of an asymmetric synthesis of α-aminophosphonates *via* Kabachnik-Fields reaction, the other main approach to α-aminophosphonic acids (Scheme 2). As in the case of Pudovik method, they used α-methylbenzylamine **26** as chiral auxiliary. Despite of the high yield of the reaction, the diastereomeric excesses of the α-aminophosphonates **27** were moderate (Scheme 5).



Scheme 5. First example of a diastereoselective Kabachnik-Fields reaction.

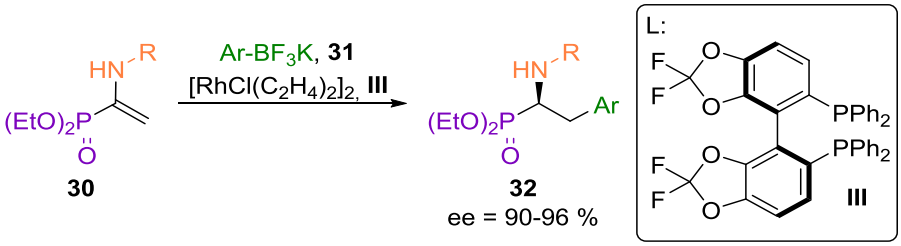
Another approach for the synthesis of optically pure α-aminophosphonates is the catalytic hydrogenation of α-dehydroaminophosphonates (Scheme 6).



Scheme 6. First catalytic hydrogenation of phosphorylated enamines.

In this field it should be mentioned the work of Schöllkopf´s group in 1985[36] which implies not only the first catalytic hydrogenation of phosphorylated enamines **28**, but also the first catalytic enantioselective synthesis of α-aminophosphonates **29**. Using Rhodium catalyst and phosphine containing chiral ligand **II** they were able to obtain enantioselectivities up to 93 %. Based on Schöllkopf´s work, during the following decades, some authors were able to successfully hydrogenate α-dehydro-aminophosphonates in an asymmetric fashion.[37]

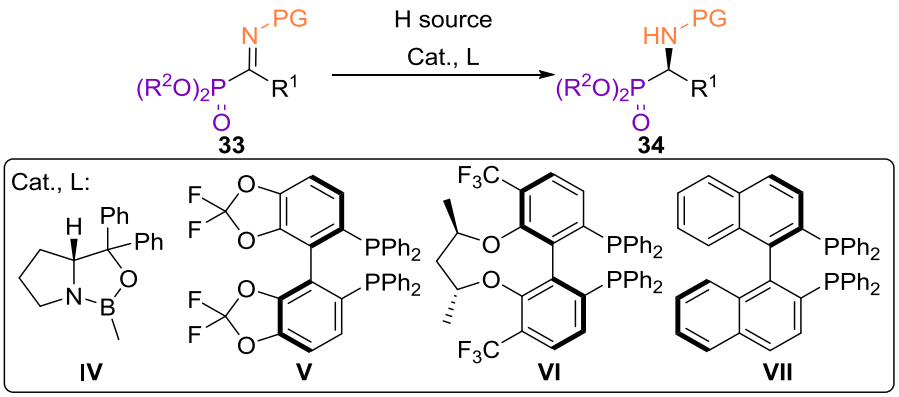
Moreover, in 2013 a single case of asymmetric hydroarylation of phosphorylated enamines **30** was described by Darses's group, using potassium organotrifluoroborates **31** as reagents and a Rhodium complex, bearing difluorophos ligand **III**, as catalyst (Scheme 7).[38]



Scheme 7. Hydroarylation of α-enaminophosphonates.

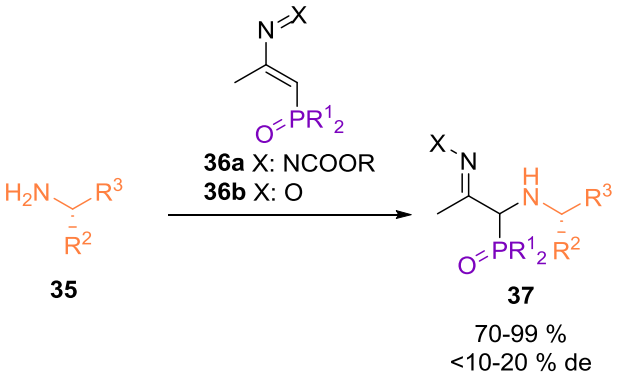
More recently, several authors have described some examples for the asymmetric hydrogenations of α-ketiminophosphonates **33** using oxazaborolidines **IV**, palladium or rhodium complexes and chiral ligands **V**-**VII** as catalysts (Table 1).[39]

Table 1. Catalytic hydrogenation of α-phosphorylated imines.



Entry	H source	Cat, L	ee (%)
1	Catecholborane	**IV**	30-72
2	H_2	$Pd(OCOCF_3)_2$, **V**	85-99
3	H_2	$Pd(OCOCF_3)_2$, **VI**	93-98
5	H_2	$[Rh(COD)_2]^+SbF_6^-$, **VII**	51-94

Regarding C-N bond formation strategies, a particular case of diastereoselective synthesis of α-aminophosphonates was described in our research group through a nucleophilic addition of amines **35** to phosphorated 1, 2-diaza-1, 3-butadienes **36a** (X = NCOOR)[40] and nitrosoalkenes **36b** (X = O) (Scheme 8).[41] The reaction worked with good yields but moderate diastereomeric ratios. Unfortunately, the enantioselective version of this reaction is still unexplored.



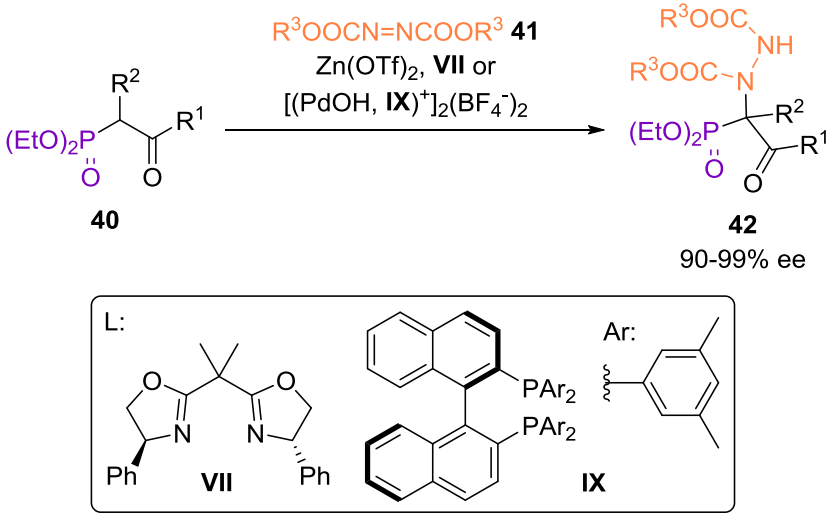
Scheme 8. Diastereoselective addition of amines to phosphorated diazabutadienes and nitrosoalkenes.

Even though it has not been widely explored, some cases of stereoselective electrophilic amination have been described. For instance, in 1992, Denmark´s group reported the synthesis of enantiomerically pure (*S*)-1-amino-1-phenylmethylphosphonic acid **39** starting from phosphonate derivative **38** and using oxazaphosphorinane as chiral auxiliary (Scheme 9).[42]

Scheme 9. Diastereoselective examples of electrophilic amination.

During the next years other authors reported the use of chiral 1, 3, 2-oxazaphospholanes[43] and α-alkyl phosphonamides[44] as chiral auxiliaries in similar asymmetric electrophilic amination processes.

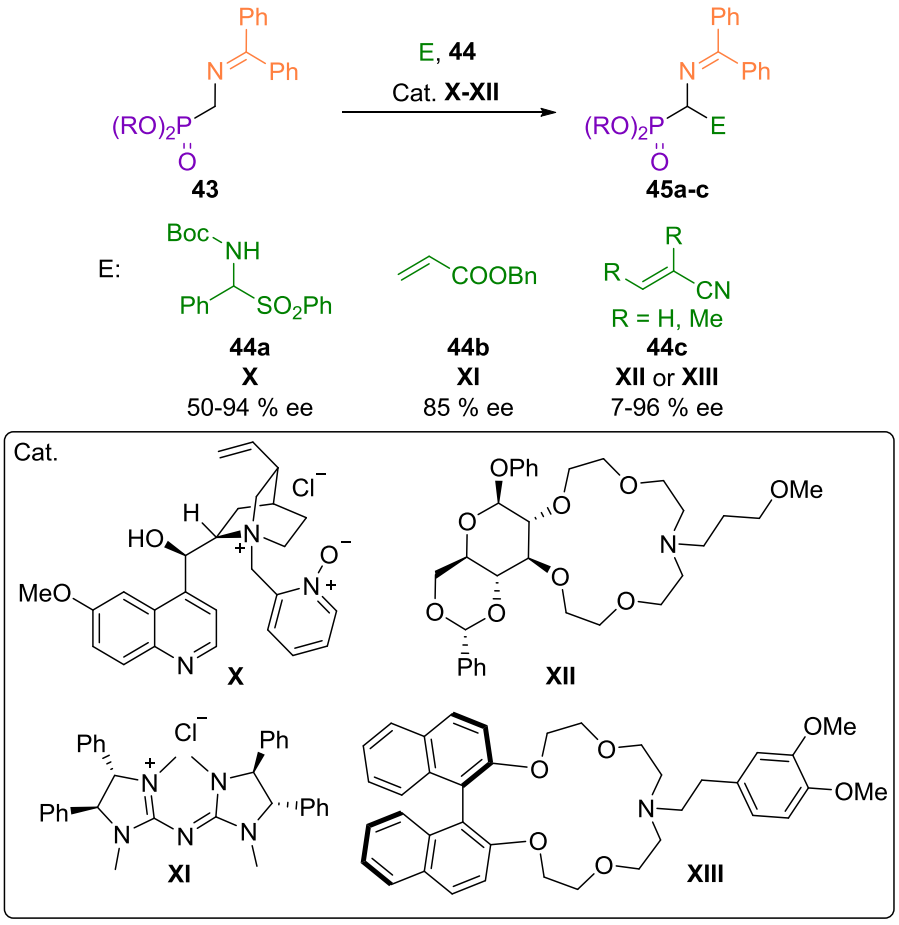
Up to the date, there are only two examples of catalytic asymmetric electrophilic amination reactions for the synthesis of optically pure α-aminophosphonates (Scheme 10). Jørgensen reported the first one in 2005, where they were able to obtain enantiomeric excesses above 90 % in the addition of racemic α-aminophosphonates **40** to azodicarboxylates **41** catalyzed by a combination of chiral BOX ligand **VII** and $Zn(OTf)_2$.[45] The same year, Kim´s group published a highly enantioselective electrophilic α-amination of similar β-keto phosphonates **40** using palladium catalyst and BINAP derivative **IX** as chiral ligand, to obtain enantiomeric excesses up to 99 %. [46]



Scheme 10. Enantioselective electrophilic amination for the synthesis of α-aminophosphonates.

Other of the approaches for the synthesis of optically active α-aminophosphonates consists in the electrophilic substitution of phosphoglycines **44**. Despite there are many examples of racemic syntheses, a few enantioseletive cases have been described by using chiral phase transfer catalysts **X**-**XIII** to provide good yields and moderate to good enantioselectivities (Scheme 11).[47]

In addition, Che's group reported the only example to date for the synthesis of quaternary α-aminophosphonates using α-aryl diazophosphonates, aromatic amines and aldehydes as starting materials.[48]

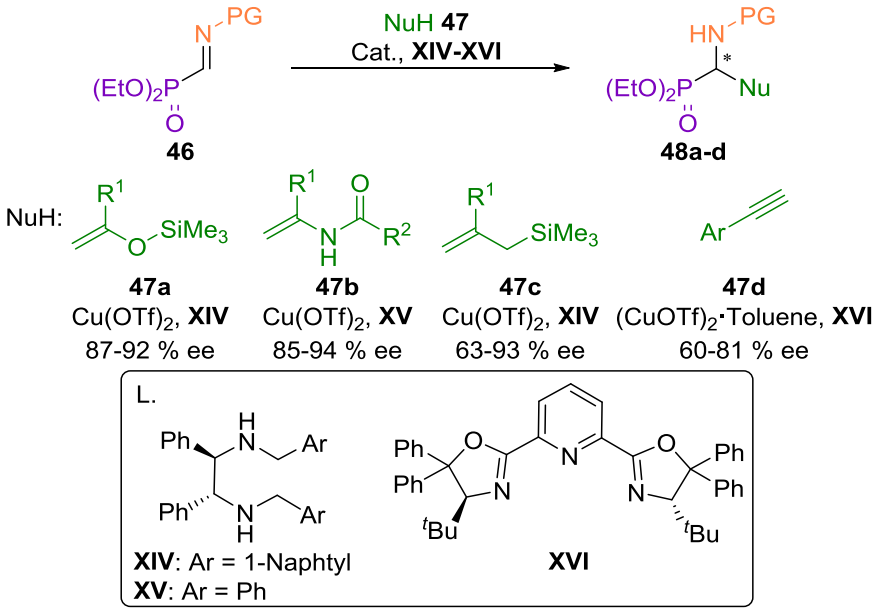


Scheme 11. Electrophilic substitution of α-aminophosphonates.

Finally, one of the less studied methods for the synthesis of α-aminophosphonates is the addition of nucleophilic reagents to α-iminophosphonates. It should be noted that, due to the extreme moisture sensitivity and to the high reactivity of starting α-iminophosphonate substrates, there are not too many references in

this field and most of the asymmetric examples have been described during the last decade.[9]

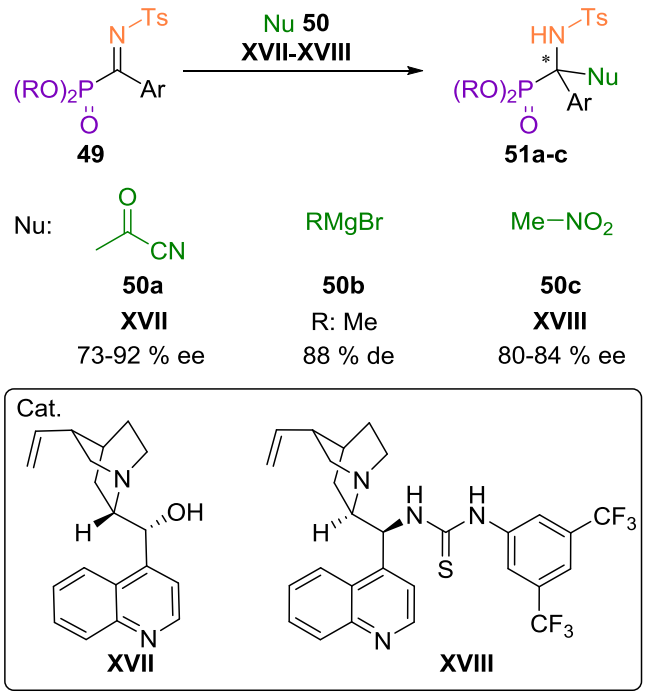
While the synthesis of α-aldiminophosphonates **46** was described by Steglich in 1986,[49] it was not until 2004 when Kobayashi, using his methodology, reported the nucleophilic addition of silyl enol ethers **47a**,[50] enamides **47b**[51] or alylsilanes **47c**[52] with excellent enantiomeric excesses, using chiral Cu(II)-diamine complexes **XIV**-**XV** as catalysts (Scheme 12).



Scheme 12. Enantioselective nucleophilic addition to α-aldiminophosphonates.

On the other hand, Zhao´s group described the enantioselective alkynylation of these aldiminophosphonates using in this case a Cu(I)-PYBOX complex **XVI**.[53]

In order to improve the diversity of substituents in α-aminophosphonate products, during the last years, our research group has been working on the synthesis and applications of α-iminophosphonates (Scheme 13).

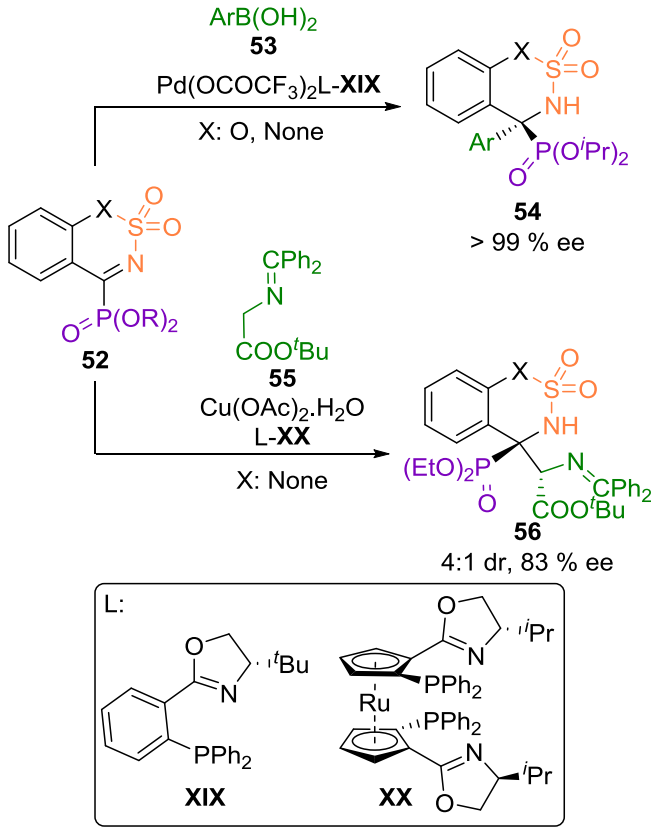


Scheme 13. Enantioselective nucleophilic addition to α-ketiminophosphonates.

In this context, the synthesis of new aromatic α-ketiminophosphonates **49** and their nucleophilic cyanation reaction to afford enantioenriched quaternary aminophosphonates **51a** was reported in 2012.[54] After that, the diastereoselective addition of organometallic reagents **50b** to TADDOL derived iminophosphonates[55] and the enantioselective addition of nitromethane **50c**[56] were performed with excellent results.

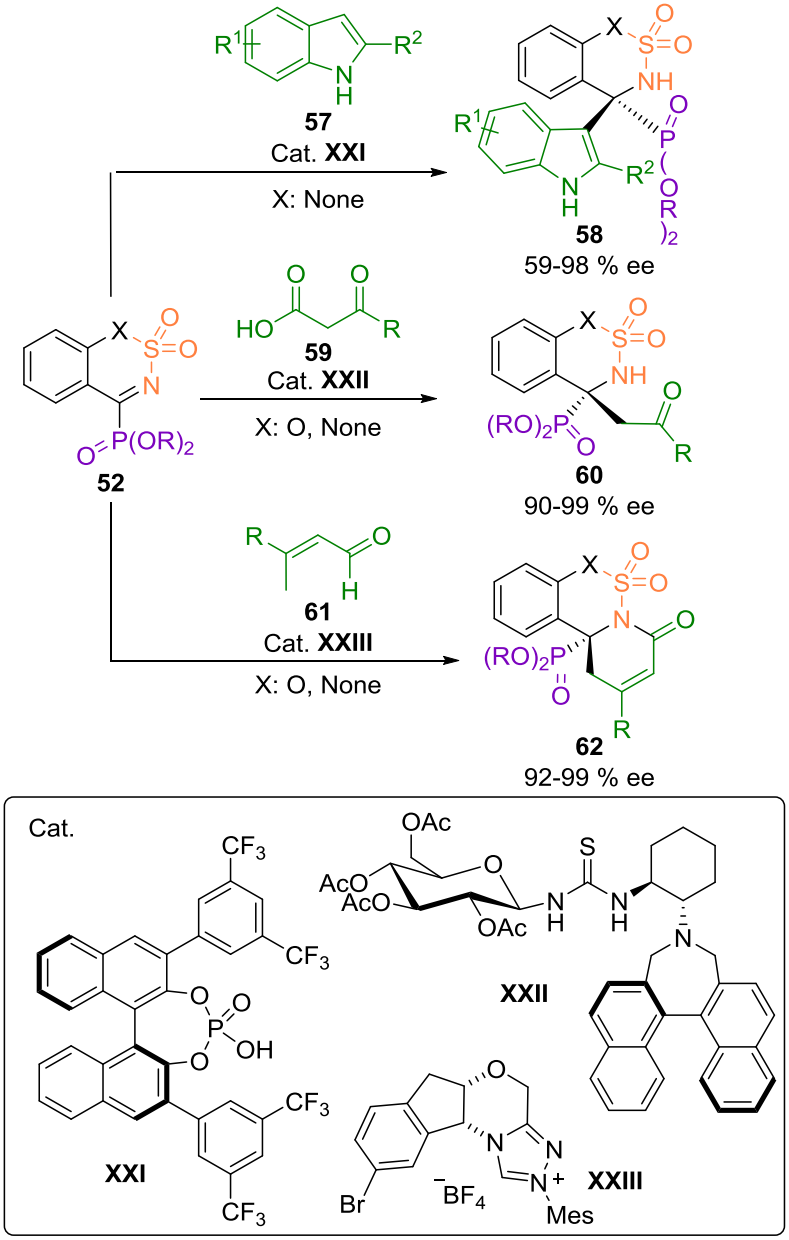
In addition, Onys'ko's group reported a proline catalyzed reaction of acetone to α-fluoroalkyl ketiminophosphonates[57] and Ohshima described a few examples of (PheBOX)Rhodium(III) catalyzed asymmetric alkynylation of α-trifluoromethyl iminophosphonates.[58]

More recently, less moisture sensitive cyclic ketimines **52** have been described in 2016 by Zhou´s group[39a] and they have reported a palladium catalyzed enantioselective arylation with boronic acids **53** to this substrates leading to the formation of quaternary α-aminophosphonates **54**.[59] Based on this work, Zhang's group reported a single example of Cu(II) catalyzed enantioselective Mannich-type addition of glycine schiff bases **55** to 5-membered cyclic α-ketiminophosphonate **52** (Scheme 14) to yield also quaternary α-aminophosphonate **56**.[60]



Scheme 14. Metal catalyzed enantioselective addition to cyclic α-ketiminophosphonates.

In addition to this work, some organocatalyzed additions on these cyclic ketimines have been reported during the last years. In 2017, Zhou published a Brønsted acid **XXI** catalyzed Friedel-Crafts reaction of indoles **57** to 5-membered cyclic imines **52** to afford cyclic α-aminophosphonates **58** with good to excellent enantioselectivities (Scheme 15).[61]



Scheme 15. Organocatalyzed asymmetric additions to cyclic ketiminophosphonates.

One-year later Ma´s group reported a highly efficient organocatalyzed decarboxylative Mannich addition of β-keto acids **59**[62] to cyclic ketimines **52**, where they are able to drop the loading of catalyst **XXII** to 1% without losing any enantioselectivity in the obtained cyclic α-aminophosphonate **60**. Some of the most recent reactions using these imines were simultaneously reported by Chi and Ye, who achieved asymmetric [4+2] cyclizations catalyzed by *N*-heterocyclic carbine **XXIII** (Scheme 15).[63]

All these research works illustrate the importance of *α*-aminophosphonic acids and their derivatives for biological purposes, in particular their phosphonate esters. Even though the synthesis of these α-aminophosphonates has been achieved over the years, in racemic and enantioselective fashions, the development of new synthetic routes for the preparation of new optically active α-aminophosphonates and their biological evaluation is still a subject of interest.

During the last decade, an increasing activity on the synthesis and applications of α-iminophosphonates as starting materials to obtain those enantioenriched α-aminophosphonates has been noticed, making this methodology an attractive tool for this purpose.

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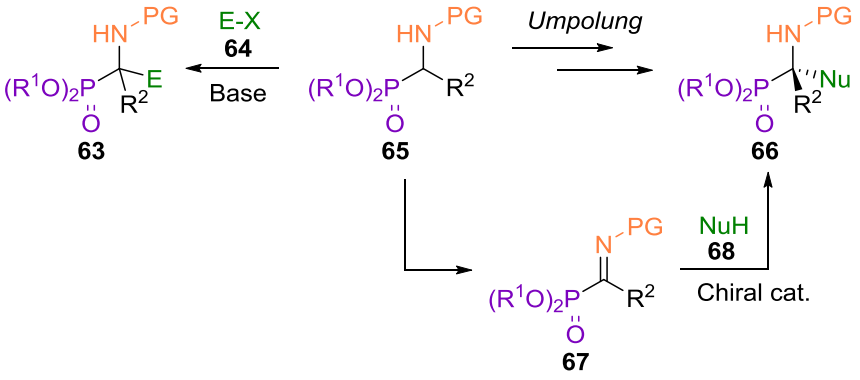
Objectives

Due to their biological interest, during the last decades, our research group has been working in the synthesis and reactivity of organophosphorus compounds. Particularly, the development of new strategies for the asymmetric preparation of α-aminophosphonic acid derivatives has been one of the main focuses of interest. In this regard, it should be noted that, while the most widely used methodology for the preparation of enantioenriched α-aminophosphonates is the asymmetric hydrophosphonylation of aldimines, the Pudovik reaction has often failed when applied to ketimines with just a few examples up to date.[64] For this reason, during the last years, the development of new methodologies for the preparation of quaternary aminophosphonates has grown interest in organic chemistry. In this field, α-iminophosphonates have demonstrated to be useful synthetic intermediates for the preparation of both, trisubstituted and tetrasubstituted α-aminophosphonates.[50-63]

Having all this in mind, our first purpose in this thesis is the synthesis of α-iminophosphonates **67** starting from α-aminophosphonates **65** and, then, look at their reaction with

different nucleophilic reagents **68,** in order to obtain new substituted α-aminophosphonates **66**. In this way, the over-all reaction of α-aminophosphonates **65** with nucleophiles **68** can be considered as an *umpolung* process[65] where the polarity of the α-position to the phosphorus atom is inverted with respect to the typical functionalization of α-aminophosphonates with electrophiles **64** (Scheme 16).



Scheme 16. Strategies for the functionalyzation of α-aminophosphonates.

Once the synthesis of imines **67** and α-aminophosphonates **66** is accomplished, our next goal will be to explore the enantioselective processes by means of the addition of different nucleophiles in the presence of chiral catalysts, in order to obtain optically active α-aminophosphonates.

Finally, due to the biological importance of α-aminophosphonic acid derivatives and, considering the experience in our research group with *in vitro* essays, the evaluation of the cytotoxicity of some of the synthesized compounds in different cancer cell lines is also intended in order to elaborate structure-activity profiles of selected families of compounds.

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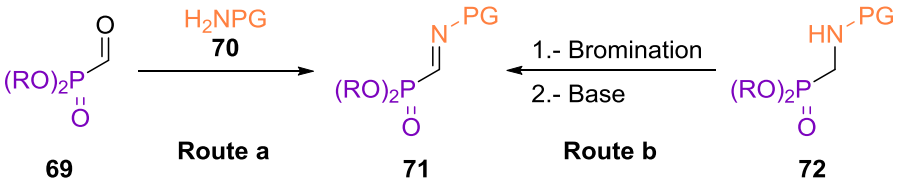
Chapter 1

Synthesis of α-iminophosphonates

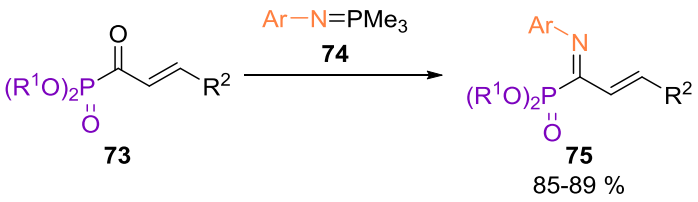
As proposed in the objectives, in the first part of this Ph.D. thesis, the synthesis of α-phosphorylated imines will be discussed. In this regard, the simplest method for the synthesis of imines consists in the direct condensation of amines with the corresponding carbonyl compounds. Even though this method has been successfully used for the synthesis of imines over the years, there are not too many examples of the synthesis of α-iminophosphonates starting from carbonyl compounds. One of the main reasons seems to be the high moisture sensitivity of α-iminophosphonates if compared to other imine substrates, which makes crucial to remove all the water generated during the condensation. Up to the date, the only examples of direct condensation products with α-phosphorylated carbonylic compounds are the stable α-ketophosphonate derived oximes[66] and hydrazones.[67] The use of alkyl amines has already shown to afford amides through an initial nucleophilic attack to the acyl phosphonate followed by elimination of the phosphonate group,[68] making this substrates ideal for acylation reactions in the absence of acid species but not for the preparation of α-iminophosphonates.

For the particular case of α-aldiminophosphonates **71**, even the synthesis of the starting material it is not trivial. Formyl phosphonates **69** are extremely moisture sensitive, readily affording the corresponding hydrates, and therefore they have to be prepared using unstable Murray reagent,[69] making the synthesis of their imines a challenging goal (Scheme 17, **route a**). In fact, most of the references using α-aldiminophosphonates as starting materials are based on Steglich's methodology,[49] which consists in a formal oxidation of stable phosphoglycine derivatives **72** as starting materials without water generation in the process (Scheme 17, **route b**).



Scheme 17. Synthetic routes to aldiminophosphonates.

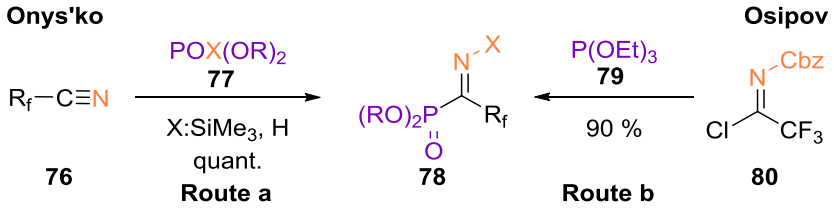
In the past, our research group has been working on the synthesis and reactivity of organophosphorus compounds and, in particular, the synthesis of α-iminophosphonate derivatives and their synthetic applications has been one of the main research focuses during the last few years. In 2011, based in the previous experience with highly reactive phosphazene species **74**,[70] the synthesis of α,β-unsaturated ketiminophosphonates **75** through an aza-Wittig reaction was achieved (Scheme 18).[71]



Scheme 18. Synthesis of ketiminophosphonates through aza-Wittig reaction.

Since *N*-acyl, *N*-phosphoryl or *N*-sulfonyl phosphazenes were proved to be non-reactive towards α-acylphosphonates, this methodology only provides the possibility to access to *N*-aryl protected α-iminophosphonates **75**.

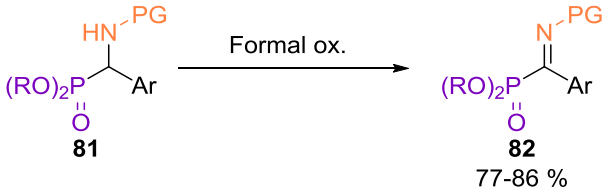
Due to the low stability of the α-aryl and α-alkyl α-iminophosphonates synthesized with this method[72] the only α-alkyl substituted ketiminophosphonates described are α-fluoroalkylated imines **78**. The first method for the synthesis of these imines was described by Onys'ko´s group through the phosphonylation of the corresponding nitriles **76** (Scheme 19, **route a**). In addition, they reported some nucleophilic additions to these imines to afford racemic α-aminophosphonates.[73] In 2010, Osipov reported a different pathway for the synthesis of α-trifluoromethyl α-iminophosphonates by an Arbuzov reaction between chlorinated imines **80** and triethyl phosphite (**79**) (Scheme 19, **route b**).[74]



Scheme 19. Synthesis of fluorinated α-iminophosphonates **78**.

Even these methodologies have been tested in previous works in our group, they have proved to be uneffective for non fluorinated substrates.

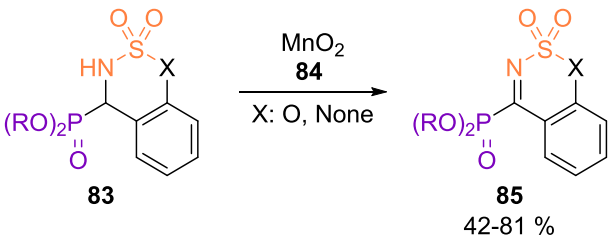
Based on Steglich's methodology for the synthesis of phosphorylated aldimines **71**, a new synthesis of α-aryl ketiminophosphonates **82** through a formal oxidation of α-aminophosphonates was reported in 2012.[54] In this case, the synthesis was performed using the corresponding α-aryl α-aminophosphonates **81** as starting materials (Scheme 20).



Scheme 20. Synthesis of α-aryl α-iminophosphonates.

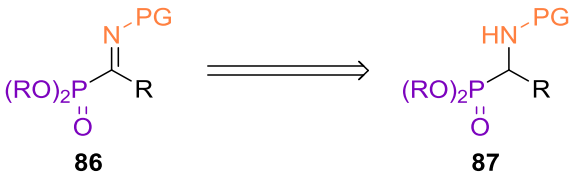
Unfortunately, this new methodology is not useful for the preparation of α-alkyl α-ketiminophosphonates as a result of the low acidity of the α-hydrogen during the β-elimination step.

Following this approach, in 2016, Zhou´s group reported the synthesis of 5- and 6- membered cyclic sulfonyl ketimines **85** from the corresponding cyclic amines **83**. In this case, they allow to obtain the desired α-iminophosphonates **85** in a single step by a direct oxidation of α-aminophosphonates **83** with freshly prepared manganese (IV) oxide **84** (Scheme 21).[39a]



Scheme 21. Zhou´s cyclic ketiminophosphonates.

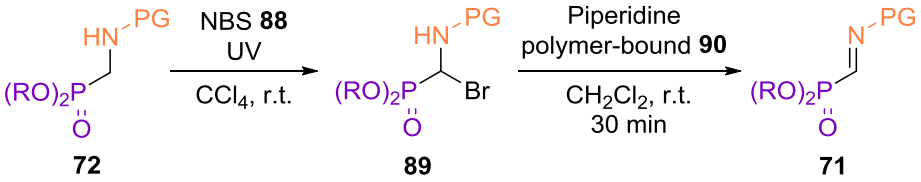
Having in mind all the considerations mentioned above, first we faced the synthesis of both, α-phosphorylated aldimines and ketimines, by a formal oxidation of the corresponding α-aminophosphonates (Scheme 22).



Scheme 22. Retrosynthesis of α-iminophosphonates.

Considering the proposed approach, the methodology comprises several steps and a few differences for the synthesis of aldimines and ketimines.

For the synthesis of α-aldiminophosphonates **71**, phosphoglycines **72**, previously prepared using procedures based on Kabachnik-Fields[75] and Pudovik[76] methodologies, were dissolved in carbon tetrachloride and stirred with NBS under ultraviolet light (Scheme 23).



Scheme 23. Synthesis of α-aldiminophosphonates **71** by a formal oxidation.

α-Bromo, α-aminophophonates **89** were found to be susceptible to spontaneously loose bromine in most of the cases and

were used directly *in situ* after a quick filtration. The β-elimination of hydrogen bromide was promoted by using an excess of polymer supported organic base, which allowed to change the typical aqueous work up by a simple filtration step, affording a clear solution of α-iminophosphonates **71**.

Both reactions can be easily monitored by ^{31}P-NMR until the starting material is completely consumed (Figure 14).

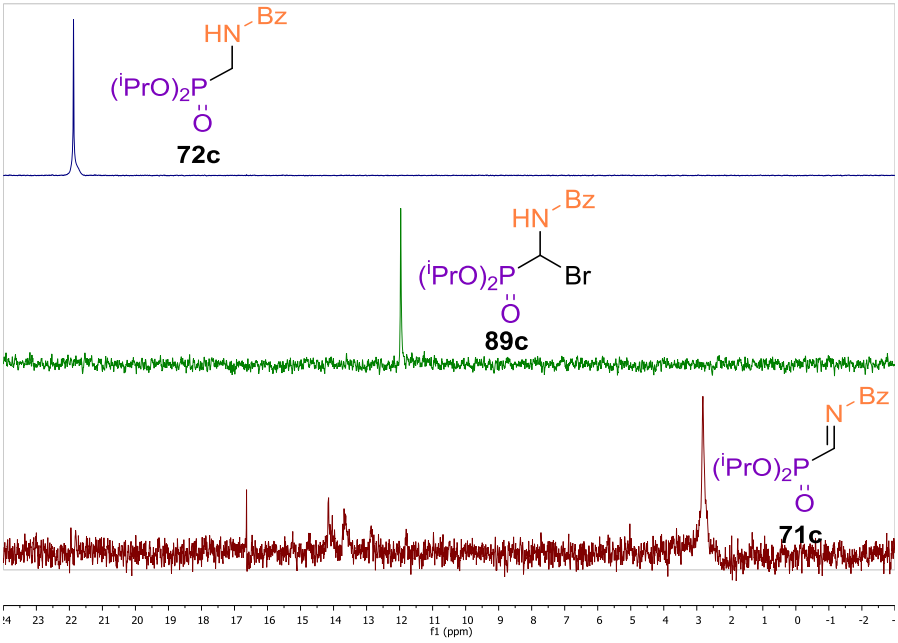


Figure 14. ^{31}P-NMR (crude) monitoring of the synthesis of α-aldiminophosphonates **71**.

When the free-radical bromination of α-aminophosphonates **72** ends, a drop of above 10 ppm on the ^{31}P-NMR spectra is observed, and this is followed by a second drop of 10 ppm when the imine substrate **71** is formed.

Remarkably, when trityl protecting group (PG = Trt = CPh_3) was used on α-aminophosphonate **72** and the mixture derived from the bromination step was analyzed, we were pleased to find that the β-elimination of hydrogen bromide in these α-bromo, α-aminophophonates **89** was spontaneous and aldimines **71** were directly obtained (Figure 15).

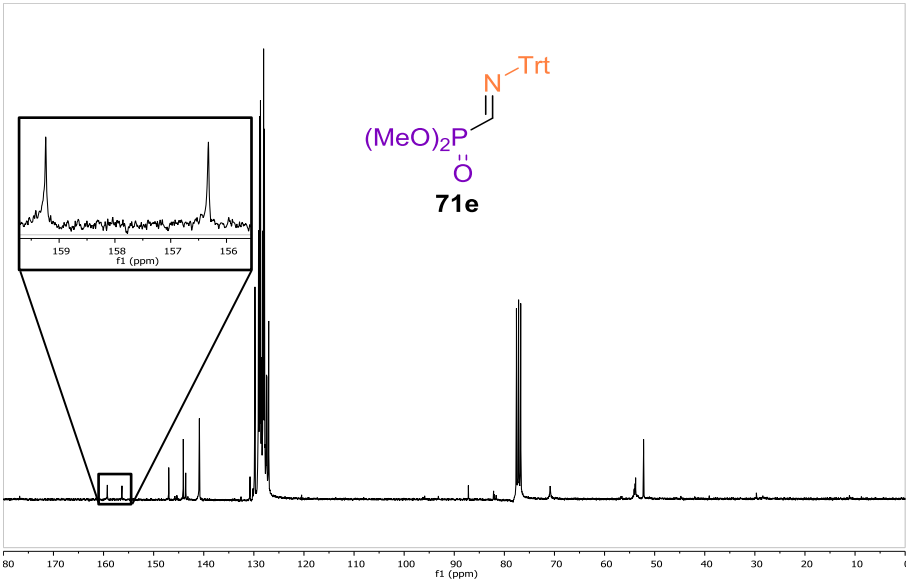


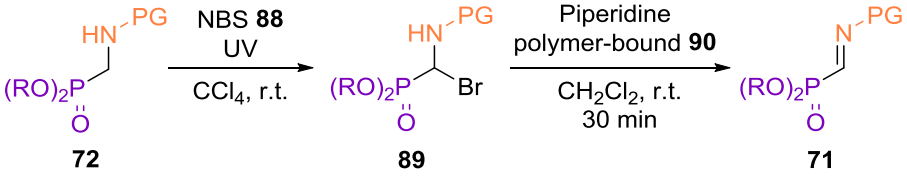
Figure 15. ^{13}C-NMR of *N*-trityl protected aldimine **71e**.

This was evidenced not only from a drop of 20 ppm in the ^{31}P-NMR shift but also for the characteristic doublet signal of the iminic carbon on the ^{13}C-NMR spectra at δ = 157.8 ppm, with a coupling constant of $^{1}J_{PC}$ = 219.7 Hz, which can be easily differentiated from the carbon shift of brominated α-aminophosphonates **89**, at δ = 58.3 ppm with a coupling constant of $^{1}J_{PC}$ = 194.8 Hz.

Using this methodology we were able to synthesize several aldimines holding different protecting groups at the nitrogen, such as 2,2,2-trichloroethoxycarbonyl (Table 2, entries 1, 2), benzoyl (Table 2, entry 3), tosyl (Table 2, entry 4) and trityl (Table 2, entries 5-10), as well as diferent alkyl and aryl phosphonates such as Me (Table 2, entry 5), Et (Table 2, entries 1, 6), ^{i}Pr (Table 2, entries 2-4, 7), Bn (Table 2, entry 9) and Ph (Table 2, entry 10).

Nevertheles, it should be noted that, in most cases, the synthesis of *tert*-butyl α-iminophosphonates could not be achieved, probably due to steric hindrance at the halogenated carbon that may block the polymer supported base to promote the β-elimination of the hydrobromic acid. Di-*tert*-butyl phosphonate substrates are however successfully obtained directly from α-aminophosphonates **72** if *N*-tritylamines are used as starting materials (Table 2, entry 8). Due to their high moisture sensitivity and reactivity, all the imine substrates were readly used as pure solutions after filtration as soon as the full conversion in their synthesis was confirmed by ^{31}P-NMR.

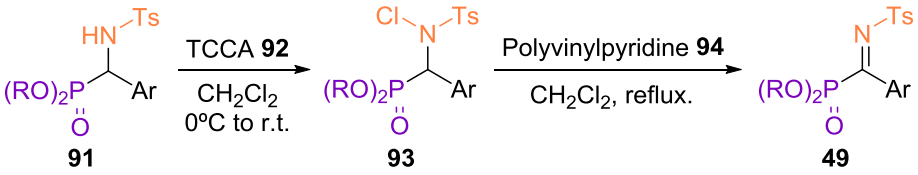
Table 2. Synthesized α-aldiminophosphonates **71**.



Entry	Comp.	R	PG	Conv.
1	**71a**	Et	Troc	100
2	**71b**	^{i}Pr	Troc	100
3	**71c**	^{i}Pr	Bz	100
4	**71d**	^{i}Pr	Ts	100
5	**71e**	Me	Trt	100
6	**71f**	Et	Trt	100
7	**71g**	^{i}Pr	Trt	100
8	**71h**	^{t}Bu	Trt	100
9	**71i**	Bn	Trt	100
10	**71j**	Ph	Trt	100

Unfortunately, the synthesis of α-ketiminophosphonates using this methodology was unfeasible. In this case the radical bromination does not work, probably because of the steric crowding present in α-aminophosphonates **91**. For this reason, an excess of cheap TCCA **92** was used as halogen source in order to chlorinate the nitrogen of substrates **91**. As in the previous case, the next step consists in a β-elimination of hydrogen chloride using in this case insoluble polyvinyl pyridine **94**, to obtain in most cases the desired pure α-aminophosphonates **49** in good yields as stable crystalline solids (Scheme 24).

In this case, tosyl was selected as the protecting group for a double reason. First, it increases the reactivity of the imine groups towards nucleophiles and, moreover, it helps the purification of the substrates by simple crystallization.



Scheme 24. Synthesis of *N*-Tosyl α-ketiminophosphonates.

Regarding the monitoring of the process, here again we find the characteristic drop on the ^{31}P-NMR shift when α-aminophosphonates **89** are completely halogenated, lower than in the case of the aldimines, due to the higher distance in this case from the halogenated position to the phosphorus atom, the completion of the β-elimination step can also be clearly detected (Figure 16).

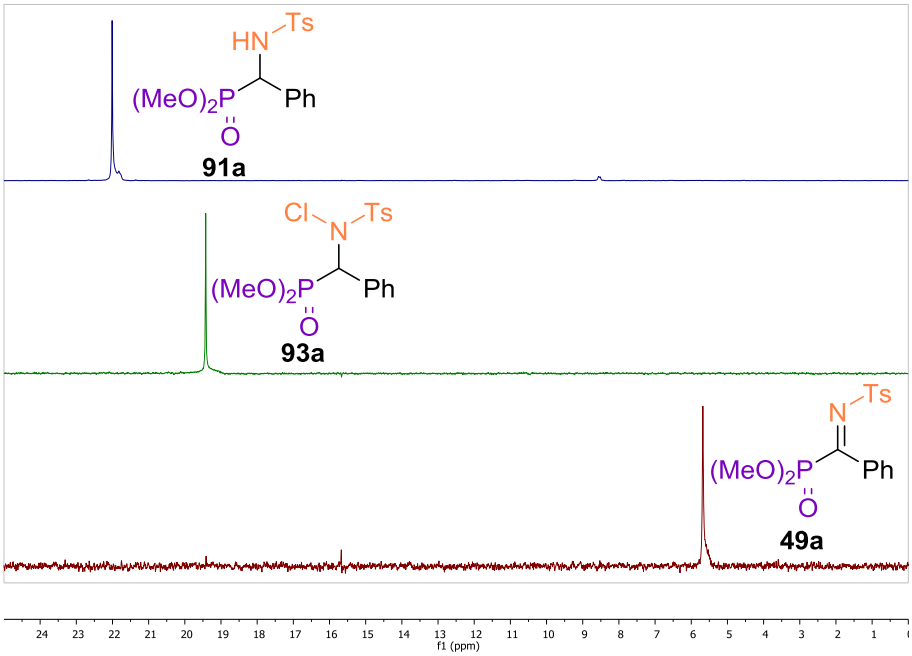
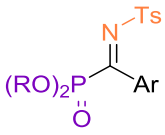


Figure 16. ^{31}P-NMR monitoring of the synthesis of α-ketiminophosphonates **49**.

The reaction tolerates the presence of different alkyl and aryl groups at the phosphonate moiety such as Me (Table 3, entry 1), Et (Table 3, entry 2), ^{i}Pr (Table 3, entry 3), Bn (Table 3, entry 4) or Ph (Table 3, entry 5). The reaction can be generalized to the synthesis of α-iminophosphonates with aromatic substituents bearing electron donating groups like Me (Table 3, entries 6-7).

Table 3. Synthesized α-ketiminophosphonates **49**.



93

Entry	Comp.	R	Ar	Yield (%)
1	**49a**	Me	Ph	86
2	**49b**	Et	Ph	79
3	**49c**	^{i}Pr	Ph	77
4	**49d**	Bn	Ph	79
5	**49e**	Ph	Ph	84
6	**49f**	Me	4-Me-C_6H_4	91
7	**49g**	Me	3-Me-C_6H_4	88
8	**49h**	Me	4-$SCCl_3$-C_6H_4	91
9	**49i**	Me	4-F-C_6H_4	92
10	**49j**	Me	4-Cl-C_6H_4	92
11	**49k**	Me	4-Br-C_6H_4	86
12	**49l**	Me	3-F-C_6H_4	89
13	**49m**	Me	3-Cl-C_6H_4	90
14	**49n**	Me	2-F-C_6H_4	89
15	**49o**	Me	3,4-Cl_2-C_6H_3	49
16	**49p**	Me	3,4-F_2-C_6H_3	90
17	**49q**	Me	2,4-F_2-C_6H_3	94
18	**49r**	Me	C_6F_5	95
19	**49s**	Me	3-Cl-4-MeO-C_6H_3	86
20	**49t**	Me	4-NO_2-C_6H_4	85
21	**49u**	Me	4-CF_3-C_6H_4	87
22	**49v**	Me	4-biphenyl	89
23	**49w**	Me	5-Cl-2-thienyl	79

In addition, aromatic imines bearing some weak electron withdrawing groups such as F (Table 3, entries 9, 12, 14), Cl (Table 3, entries 10, 13) or Br (Table 3, entry 11), as well as strong electron withdrawing ones like NO_2 (Table 3, entry 20) and CF_3 (Table 3, entry 21) are effectively obtained using this methodology. Moreover, some polysubstituted aryl groups, including polychlorinated (Table 3, entry 15), polyfluorinated (Table 3, entries 16, 17), perfluorophenyl group (Table 3, entry 18) and also a combination of activating and deactivating groups in the aromatic ring (Table 3, entry 19) can be equally used. To complete the scope of aromatic groups in these imines, biphenyl (Table 3, entry 22) and heteroaromatic thienyl moiety (Table 3, entry 23) were also found as tolerated groups. Unfortunately, due to the high bulkiness of the system during the β-elimination step, this methodology cannot be used for the synthesis of most of *ortho* substituted α-aryl α-iminophosphonates and the only ones that can be obtained by this method are o-fluorinated imines **49** (Table 3, entries 14, 17, 18).

However, one of the drawbacks of this methodology is that α-alkyl imines cannot be obtained due to the low acidity of the α-proton in *N*-chloro α-aminophosphonates **93** that does not make possible the β-elimination step as a result of the weak basicity of the polymeric base.

As expected, α-iminophosphonates **49** were found to be slightly less reactive than aldimines **71** and they could be fully characterized by NMR, IR and HRMS and stored for several months under anhydrous conditions. For examples, the most typical chemical shift of α-phosphorated imine **49a** in ^{1}H-NMR is the doublet at δ = 3.72 ppm corresponding to the six protons of the methoxy groups of the phosphonate, which are coupled with the phosphorus atom with a characteristic coupling constant of $^{3}J_{PH}$ = 10.9 Hz (Figure 17).

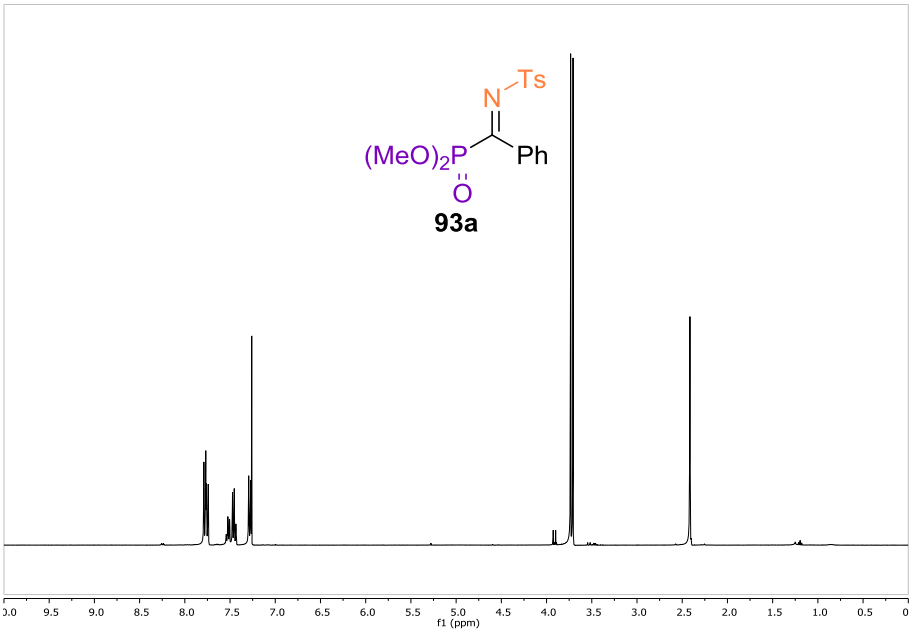


Figure 17. ^{1}H-NMR of α-ketiminophosphonate **49a**.

In addition, the ^{13}C-NMR spectrum of **49a** shows as the most characteristic chemical shifts the doublet corresponding to the methoxy groups at δ = 54.9 ppm which, in the same way that in

^{1}H-NMR spectrum, is coupled to the phosphorus atom, and another doublet for the iminic carbon, which appears at δ = 177.5 ppm with a coupling constant of $^{1}J_{PC}$ = 197.8 Hz (Figure 18). Furthermore, in these imines, most of the aromatic carbons are coupled to the phosphorus atom two to five bonds distance showing a complex pattern in the aromatic region.

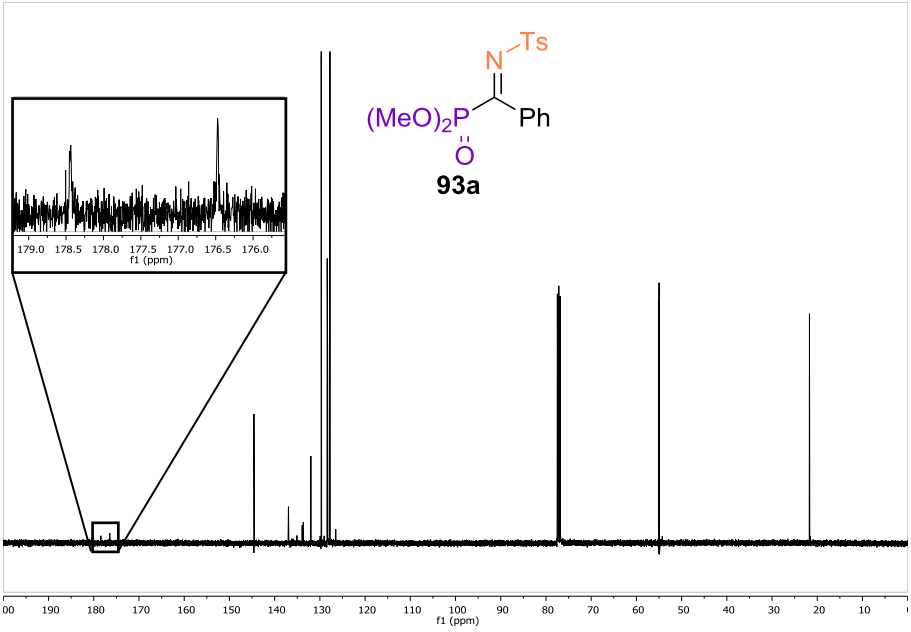


Figure 18. ^{13}C-NMR of α-ketiminophosphonate **49a**.

The *E* configuration of the imine double bond was stablished on the basis of COSY, NOE and HOESY experiments. Both doublets assigned to aromatic ortho CH of tosyl and phenyl groups at δ = 7.79 and 7.76 ppm respectively showed NOE effect. Consecuently, the two

doublets assigned to the aromatic protons of *N*-tosyl substituent at δ = 7.79 and 7.31 ppm did not show NOE effect with the doublet at δ = 3.72 ppm, corresponding to the methoxy hydrogens of the phosphonate group, and neither showed HOE effect with phosphorus signal at δ = 5.7 ppm in ^{31}P-NMR spectrum (Figure 19).

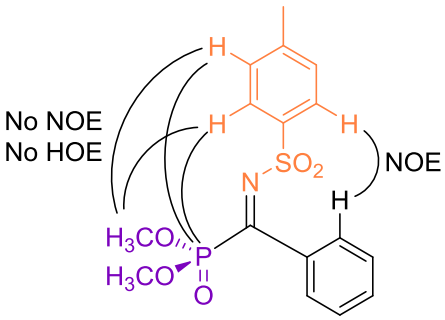


Figure 19. Determination of the imine *E* configuration of imine **49a**.

In summary, efficient methodologies for the synthesis of α-phosphorylated aldimines **71** and ketimines **49** have been developed and, using them, several valuable α-iminophosphonate derivatives have been prepared. In the following chapters of this Ph.D. Thesis, their synthetic applications as electrophiles in asymmetric catalysis will be explored, in order to synthesize biologically attractive trisubstituted and tetrasubstituted α-aminophosphonates.

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Chapter 2

Friedel-Crafts reactions of α-aldiminophosphonates with indole derivatives

It is well known that indole unit is a ubiquitous structural motif in nature that is frequently found in the structure of many proteins, in the form of the essential α-amino acid tryptophan (**95**), as well as in numerous biologically active compounds such as pharmaceuticals, agrochemicals or alkaloids like roxindole (**96**), Reserpine (**97**) or the insecticide **98** (Figure 20).[77]

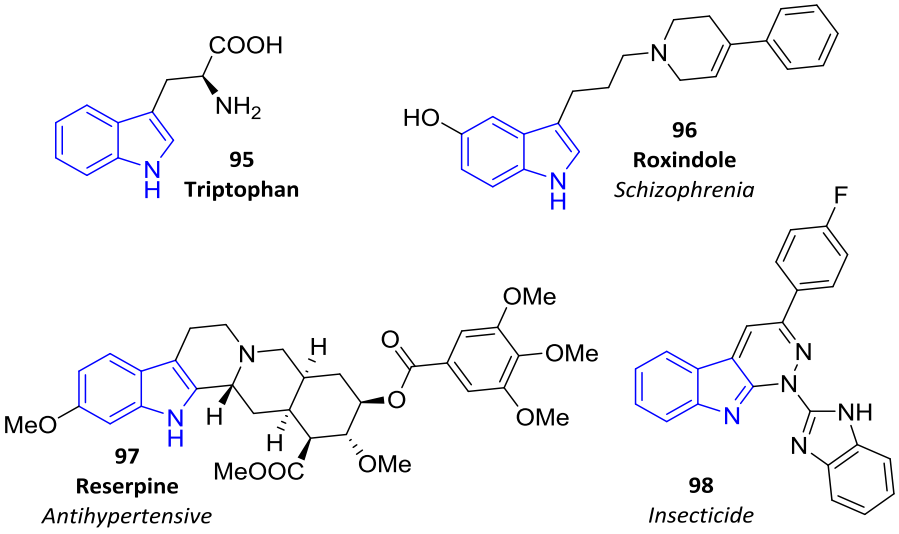
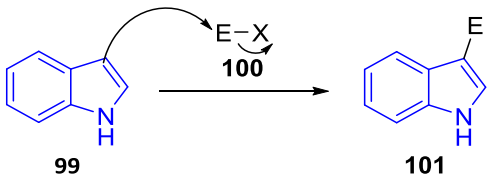


Figure 20. Some bio relevant indole containing molecules.

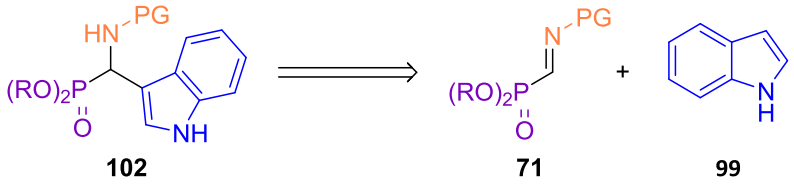
In fact, indole framework is known to associate with multiple receptors and enzymes with high affinity and, for that reason, it is considered as one of the most important of all privileged structures in medicinal sciences.[78]

With respect to its chemical reactivity, indole is an electron rich aromatic heterocycle containing ten π-electrons that govern its reactivity and, therefore, it shows an intrinsic nucleophilic character.[79] Electrophilic aromatic substitution, usually at C-3, is the typical method chosen for the functionalization of indole ring (Scheme 25) and asymmetric Friedel-Crafts reaction is the most direct way to the enantioselective synthesis of functionalized indole derivatives.[80]



Scheme 25. Electrophilic substitution reaction on the indole ring.

Medicinal chemistry has been one of the main focuses of our research group during the last years and, due to the interest of both, indole and α-aminophosphonate moieties, we thought that the development of an enantioselective synthetic protocol for the addition of biologically attractive indole derivatives to our α- phosphorated imines would be of great interest (Scheme 26).



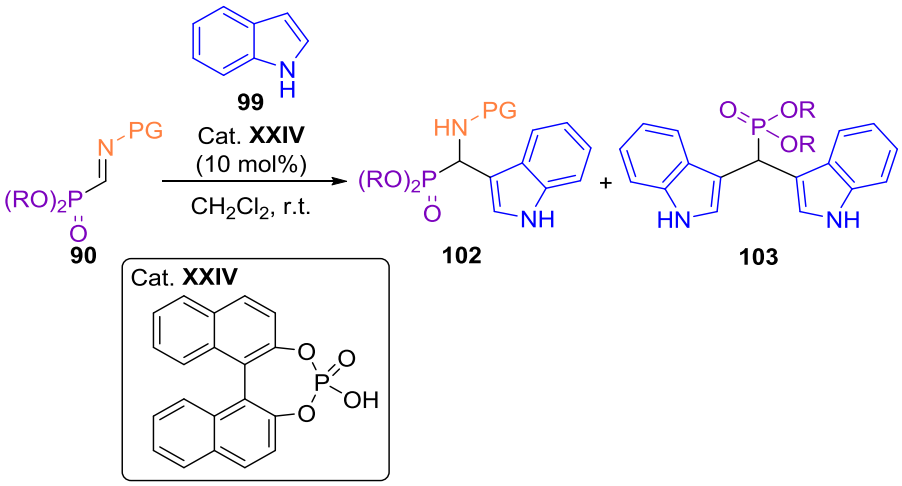
Scheme 26. Retrosynthesis of trisubstituted α-aminophosphonates.

As far as we know, up to date, there are only a few examples of enantioselective nucleophilic additions to α-phosphorylated aldimines, most of them reported by Kobayashi´s group between 2004 and 2006.[50-52] It should be noted that all these references were achieved using Cu-complexes as catalyst and there are not examples reported of organocatalytic asymmetric nucleophilic additions to α-phosphorylated aldimines.

First of all, some of our α-aldiminophosphonates **71** were tested in the Friedel-Crafts reaction with indoles (Table 4). We found that, when trityl (Trt) and tosyl (Ts) protecting groups were used in our substrates the bisindole derivative **103**, resulting from a double addition of indole to the imines with the loss of trityl amine or tosylamide, were obtained (Table 4, Enties 1-3). However, when 2,2,2-trichloroethoxycarbonyl (Troc) protecting group was used in the imine, the desired indolyl phosphoglycines **102a** and **102b** were isolated with good yields, regardeless the substituent on the phosphonate moiety (Table 4, entries 4, 5). The use of phenylcarbonyl

(Bz) protecting group affords, in a similar way, α-aminophosphonate **102c** (Table 4, Enty 6).

Table 4. Reactivity optimization of Friedel-Crafts reaction.



Entry	Comp.	PG	R	Conv. 102/103 (%)	Yield (%)
1	**103a**	Trt	Et	0/50	n.d.
2	**103b**	Trt	^{i}Pr	0/50	n.d.
3	**103b**	Ts	^{i}Pr	0/46	n.d.
4	**102a**	Troc	Et	100/0	70
5	**102b**	Troc	^{i}Pr	100/0	73
6	**102c**	Bz	^{i}Pr	100/0	69

Thus, a strong dependence of the reaction product on the protecting group of the imine was evidenced. According to these results, it seems that while good leaving groups and/or bulky moieties as protecting groups of imines **71** lead to bisindole products **103**, more

planar and less bulky groups like amides and carbamates afford indolyl phosphoglycines **102**.

Once the reaction was optimized, the obtained products **102** were fully characterized by NMR, IR and HRMS. The most significant signals of indolyl phosphoglycine **102c** in the ^{1}H-NMR spectrum are the chemical shifts corresponding to the proton of the stereogenic carbon, which appears as a double doublet at δ = 6.13 ppm because of its coupling with both, NH group of the amide and with the phosphorus atom, with coupling constant values of $^{3}J_{HH}$ = 9.7 Hz and $^{2}J_{PH}$ = 20.5 Hz respectively (Figure 21).

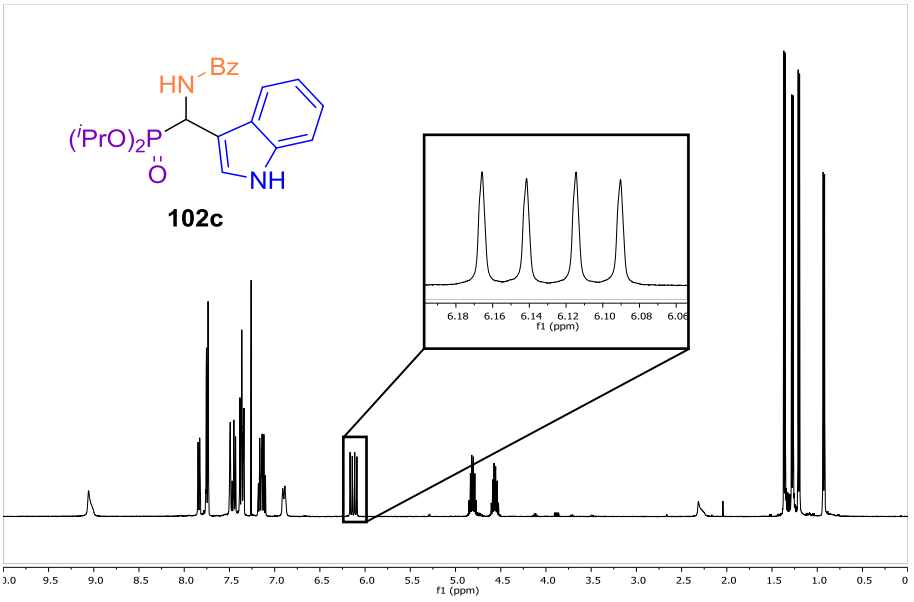


Figure 21. ^{1}H-NMR of compound **102c**.

Consequently, the NH group of α-aminophosphonate **102c** also appears at δ = 6.90 ppm as a doublet because of the coupling constant of $^{3}J_{HH}$ = 9.7 Hz with the vicinal CH group. Other typical chemical shifts of this α-aminophosphonate are the signals of phosphonate substituents. Due to the chiral carbon present in this structure, the isopropyl groups in indolyl phosphoglycine **102c** are diastereotopic and, for this reason, the ^{1}H-NMR spectrum shows two different multiplets for the each of the CH groups in the interval of δ = 4.98-4.43 ppm and two pair of doublets corresponding to the methyl groups between δ = 1.36 and δ = 0.93 ppm with coupling constants of $^{3}J_{HH}$ = 6.2 Hz.

With respect to the ^{13}C-NMR spectrum, the stereogenic carbon shows a doublet at δ = 43.3 ppm with a coupling constant to the phosphorus atom of $^{1}J_{PC}$ = 163.5 Hz (Figure 22). In addition, the same pattern of diastereotopic signals can be observed for isopropyl groups, showing two doublets at δ = 72.3 ppm and δ = 71.9 ppm for the CH groups, with coupling constants of $^{2}J_{PC}$ = 7.3 and 7.6 Hz respectively, and four doublets at δ = 24.4, 24.3, 24.0 and 23.5 ppm with coupling constants of $^{3}J_{PC}$ = 3.5, 3.2, 5.0 and 5.2 Hz for the methyl groups. Furthermore, most of the signals of the indole ring and the carbon of the amide exhibit coupling with the phosphorus atom.

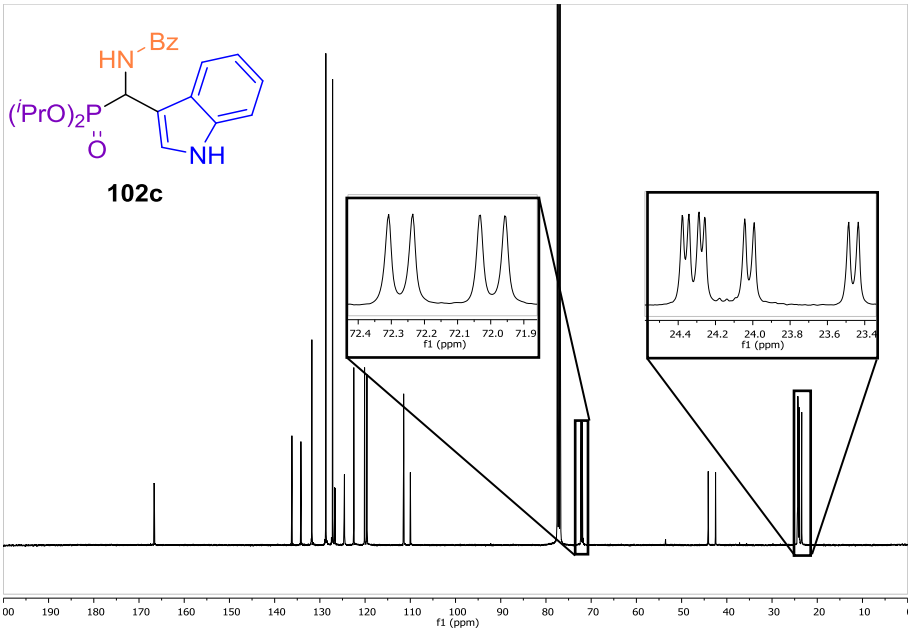


Figure 22. ^{13}C-NMR of compound **102c**.

Since the optimization of the reaction condtions for the Friedel-Craft process have shown that Troc and Bz protected imines selectively afford indolyl phosphoglycines **102**, in order to evaluate the asymmetric version of the reaction, several chiral catalysts were tested. Taking into account that Brønsted acid based catalysts like chiral thioureas and phosphoric acids have demonstrated their ability to catalyze the electrophilic substitution reaction on the indole ring, we first tested thiourea alkaloids **XXV-XXVI** and BINOL and VAPOL derived phosphoric acids **XXVII**-**XXXIV** (Figure 23) in the Friedel-Crafts reaction of indole (**99**) and α-iminophosphonate **71a**.

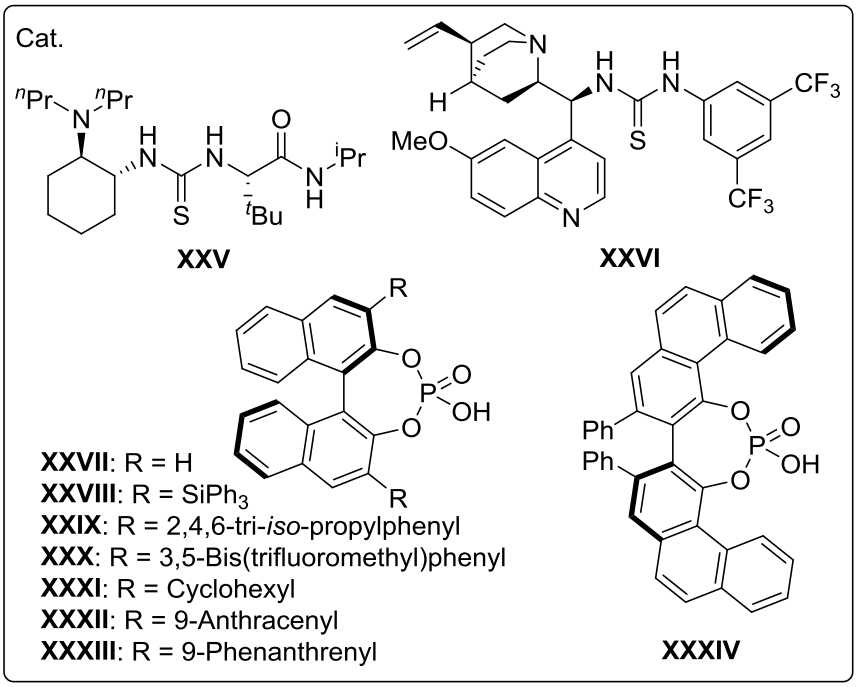
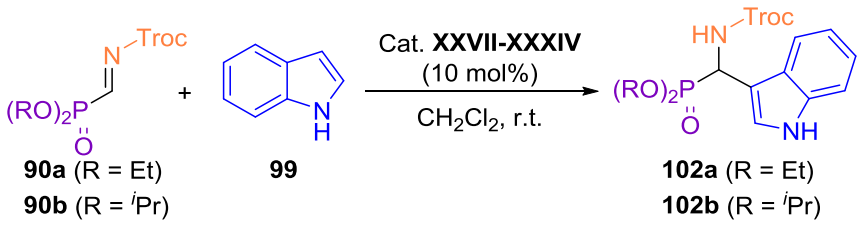


Figure 23. Catalysts tested in the asymmetric Friedel-Crafts reaction.

Thioureas **XXV-XXVI** did not afford high conversions and were instantaneously discarded for this reaction (Table 5, entries 1, 2), but using BINOL and VAPOL derived substituted phosphoric acids **XXVIII-XXXIV** full conversion and poor to moderate enantioselectivities were first obtained using diethyl α-iminophosphonate **71a** as substrate (Table 5, entries 3-10).

Table 5. Catalyst optimization for the Friedel-Crafts reaction.



90a (R = Et)
90b (R = ^{i}Pr)

99

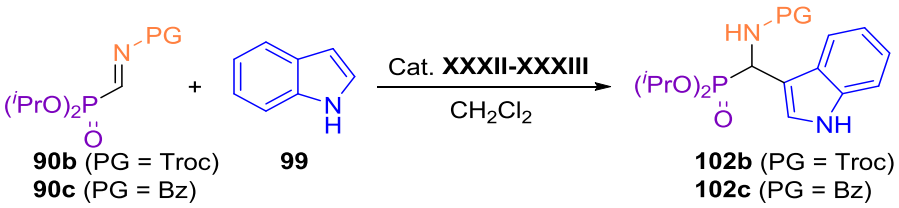
102a (R = Et)
102b (R = ^{i}Pr)

Entry	Cat.	R	Conv. (%)	T (h)	ee (%)
1	**XXV**	Et	5	24	n.d.
2	**XXVI**	Et	5	24	n.d.
3	**XXVII**	Et	100	12	0
4	**XXVIII**	Et	100	12	45
5	**XXIX**	Et	100	12	29
6	**XXX**	Et	100	12	62
7	**XXXI**	Et	100	12	40
8	**XXXII**	Et	100	12	42
9	**XXXIII**	Et	100	12	32
10	**XXXIV**	Et	100	12	17
11	**XXVII**	^{i}Pr	100	12	0
12	**XXVIII**	^{i}Pr	100	12	41
13	**XXIX**	^{i}Pr	100	12	47
14	**XXX**	^{i}Pr	100	12	55
15	**XXXI**	^{i}Pr	100	12	40
16	**XXXII**	^{i}Pr	100	12	70
17	**XXXIII**	^{i}Pr	100	12	70
18	**XXXIV**	^{i}Pr	100	12	19

In previous works it has been established a direct relationship between the size of the phosphorus substituent and the enantiomeric excesses observed for the addition of nucleophiles to α-iminophosphonates,[54, 56] and in all the cases isopropyl substituted phosphonates were far superior to other alkyl or aromatic substituents. For this reason, we carried out the reaction with diisopropyl phosphonate **90b** (Table 5, entries 11-18), obtaining the best results when large planar substituents where used in the phosphoric acid catalyst (Table 5, entries 16-17).

Then, in order to improve the enantiomeric excesses, a study of the effect of the protecting group of the imine on the enantioselectivity of the process was performed (Table 6). Despite of the slight drop on the enantioselectivity when *N*-benzoyl protected imine **90c** and catalyst **XXXII** were used with respect to the results obtained for Troc protected imine **90b** (Table 6, entries 1, 3), an increase of enantioselectivity was observed using catalyst **XXXIII** (Table 6, entries 2, 4).

Table 6. Optimization of the reaction conditions of asymmetric Friedel-Crafts reaction.



90b (PG = Troc)
90c (PG = Bz)

99

102b (PG = Troc)
102c (PG = Bz)

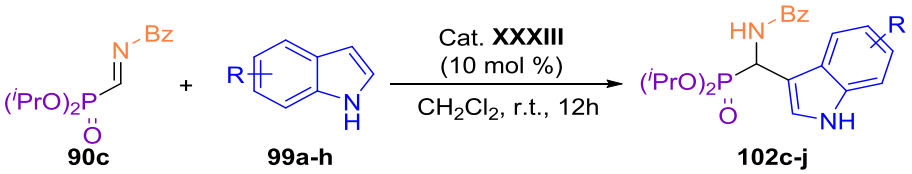
entry	Cat.	PG	Cat. load. (%)	T (°C)	t (h)	Conv. (%)	ee (%)
1	**XXXII**	Troc	10	r.t.	12	100	70
2	**XXXIII**	Troc	10	r.t	12	100	70
3	**XXXII**	Bz	10	r.t	12	100	60
4	**XXXIII**	Bz	10	r.t	12	100	75
5	**XXXIII**	Bz	10	0	48	81	58
6	**XXXIII**	Bz	10	-20	48	75	40
7	**XXXIII**	Bz	10	-40	48	70	20
8	**XXXIII**	Bz	10	40	12	0	n.d.
9	**XXXIII**	Bz	5	r.t	12	85	62
10	**XXXIII**	Bz	20	r.t	48	100	75

Other attempts to improve the enantioselectivity at different temperatures were unsuccessful, since lower enantiomeric excesses and conversions were obtained below to room temperature (Table 6, entries 5-7), probably due to the low solubility of the substrate or the catalyst. Curiously, the reaction performed in refluxing dichloromethane afforded a complex mixture, derived presumably from degradation of the unstable α-iminophosphonate substrate **90c** (Table 6, entry 8). Moreover, while a decrease in the catalyst loading

resulted in a drop in both conversion and enantioselectivity (Table 6, entry 9), an increase in the amount of the catalyst unfortunately did not have any effect at all in the reaction performance (Table 6, entry 10).

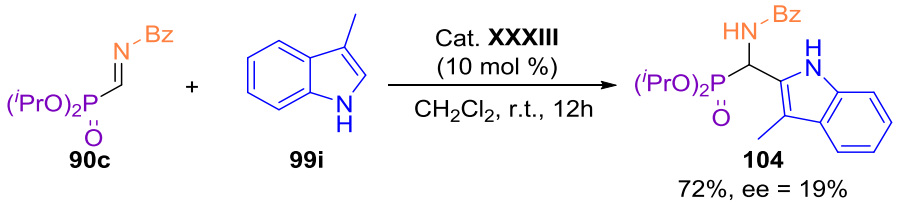
Given that, further attempts of improvement by optimization of the solvent were unsuccessful (CH_2Cl_2, $CHCl_3$, CCl_4, $ClCH_2CH_2Cl$, toluene, THF, Et_2O, DMF, DME and CH_3CN were checked), the generalization of the phosphoric acid catalyzed Friedel-Crafts reaction to several substituted indoles was performed using phenylcarbonyl protected di-isopropyl α-iminophosphonate **90c** and catalyst **XXXIII** (Table 7). Slight differences can be observed for 5, 6 or 7 substituted indole substrates, with enantiomeric excesses ranging from 68 to 82 %. The reaction can also be accomplished with indoles bearing strong and weak deactivating substituents (Table 7, entries 2-4) as well as with weakly and strongly activated indole substrates (Table 7, entries 5-7).

Table 7. Scope of the Friedel-Crafts reaction.



Entry	Comp.	R	t (h)	Yield (%)	ee (%)
1	**102c**	H	12	69	75
2	**102d**	5-NO_2	12	64	68
3	**102e**	5-F	12	70	70
4	**102f**	6-F	12	68	70
5	**102g**	5-CH_3	12	72	75
6	**102h**	5-OCH_3	12	73	80
7	**102i**	7-OCH_3	12	75	82
8	**102j**	2-Me	18	70	39

Interestedly, the substitution on the C-2 of indole unit had an adverse effect on the enantioselectivity (Table 7, entry 8). In addition, using 3-methyl substituted indole **99i**, electrophilic substitution reaction at the position 2 of indole ring was observed, although with a low enantiomeric excess (Scheme 27). The results obtained for indolyl phosphoglycines **102j** and **104** may indicate that an excess of steric hindrance by introducing substitution at the pyrrole unit may have a negative effect into the enantioselectivity of the process.



Scheme 27. Friedel-Crafts reaction of 3-substituted indole **99i**.

In order to determine the absolute configuration of the stereogenic carbon of the major enantiomer we tried to crystallize an enantioenriched mixture. After several crystallizations, only crystals of the racemic mixture of indolyl phosphoglycine **102f** were obtained (Figure 24) with the major enantiomer remaining in the solution. Therefore, X-ray diffraction spectrum was not useful to determine the absolute configuration but served to confirm without doubt the structure of α-aminophosphonates **102** prepared.

Next, the enantioenriched fraction of the major enantiomer of indolyl phosphoglycine **102h** was analysed by Vibrational Circular Dichroism. However, due to the wide conformational space in compounds **102**, no satisfactory correlation between the empirical and theoretical spectra was obtained.

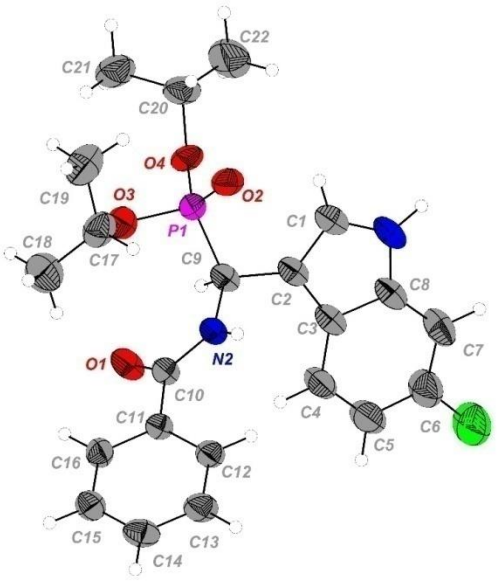
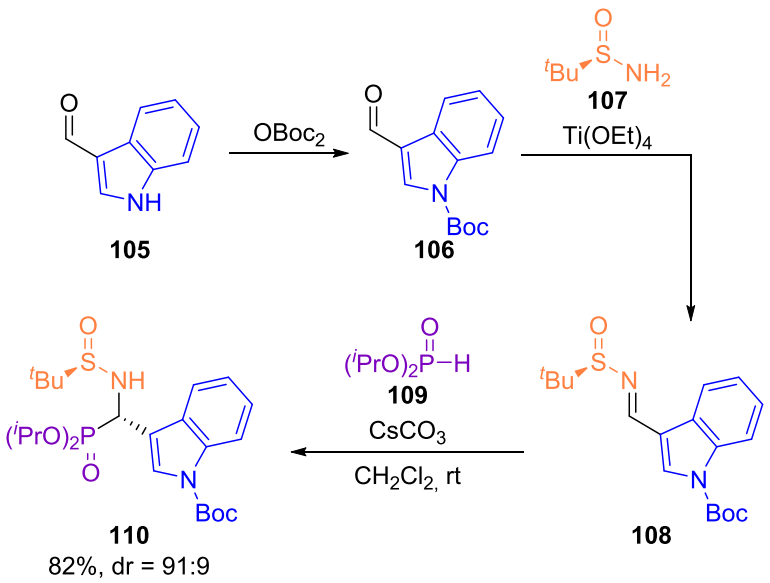


Figure 24. X-Ray diffraction structure of racemic α-aminophosphonate **102f**. (*S*) Enantiomer is shown.

For this reason, we decided to perform an alternative synthesis of α-aminophosphonates **102** so we can compare the stereochemistry of the compounds obtained by both routes and determine the absolute configuration of our products. Thus, we used the modified diastereoselective methodology reported by Ellman[81] and Yuan[82] for the preparation of α-aminophosphonate **110** using *tert*-butylsulfinyl group as chiral auxiliary.

Following this methodology, sulfinylimine substrate **108** was synthesized by the condensation of (*R*)-*tert*-butylsulfinamide (**107**) and

Boc protected indole 3-carboxaldehyde **106**. The addition of diisopropylphosphite (**109**) to sulfinylimine **108**, in the presence of an excess of a caesium carbonate, afforded indolyl phosphoglycine **110** in very good yield and diastereoselectivity (dr = 91:9) (Scheme 28).



Scheme 28. Synthetic methodology for the diastereoselective synthesis of α-aminophosphonate **110**.

It should be noted that the basicity of indolyl group had to be deactivated with an electron withdrawing protecting group such as Boc, since imines holding benzyl-protected indole moieties did not react with dialkylphosphites at all.

According to the literature,[81, 82] the base would remove the proton of the hydrogen posphite while the metallic cation activates both reagents, the imine and the phosphite (Figure 25). The diastereoselectivity of the reaction has proved to be strongly dependent on the size of the carbonate. In fact, following original Yuan´s method,[82] and using potassium carbonate as base, lower diastereoselectivity was observed (dr = 62:38).

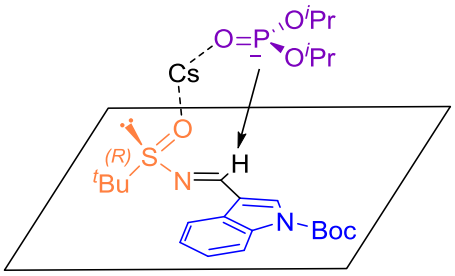


Figure 25. Proposed transition state for the synthesis of **110**.

The mayor diasteroisomer of α-aminophosphonate **110** was isolated by crystallization and its absolute configuration was determined to be (*S*, *R*) by X-Ray diffraction (Figure 26).

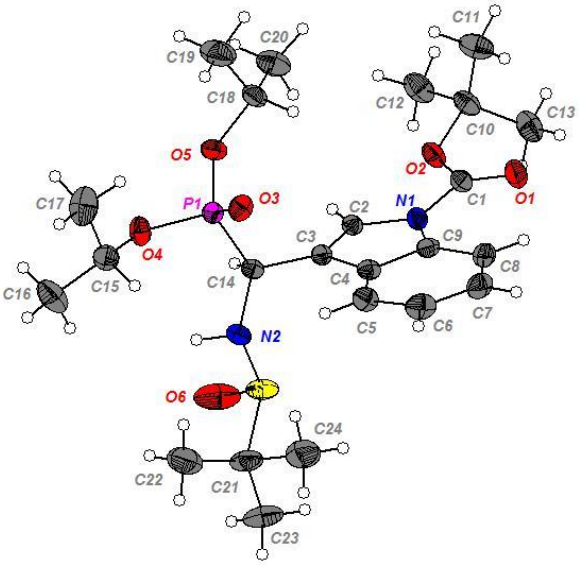
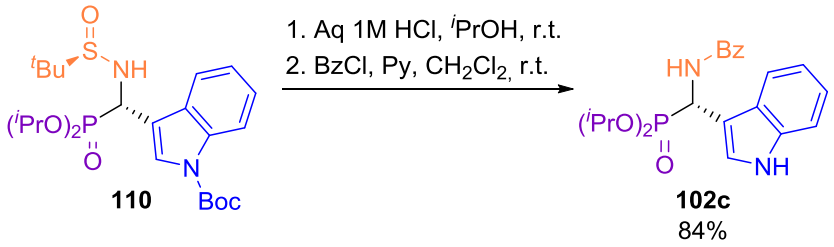


Figure 26. X-Ray diffraction structure of α-aminophosphonate **110.**

Next, in order to determine the absolute configuration obtained in the Friedel-Crafts reaction of our α-aminophosphonates **102**, the selective and simultaneous deprotection of amine and indole groups was performed under mild acidic media using the mother liquor of the crystallyzation. A subsequent *in situ* acylation of amine moiety with benzoyl chloride afforded our model indolyl phosphoglycine **102c** (Scheme 29).



Scheme 29. Synthesis of **102c** from **110**.

The comparison of the retention times in chiral HPLC with compound **102c** synthesized by the organocatalytic route showed that both compounds have the opposite configuration (Figure 27).

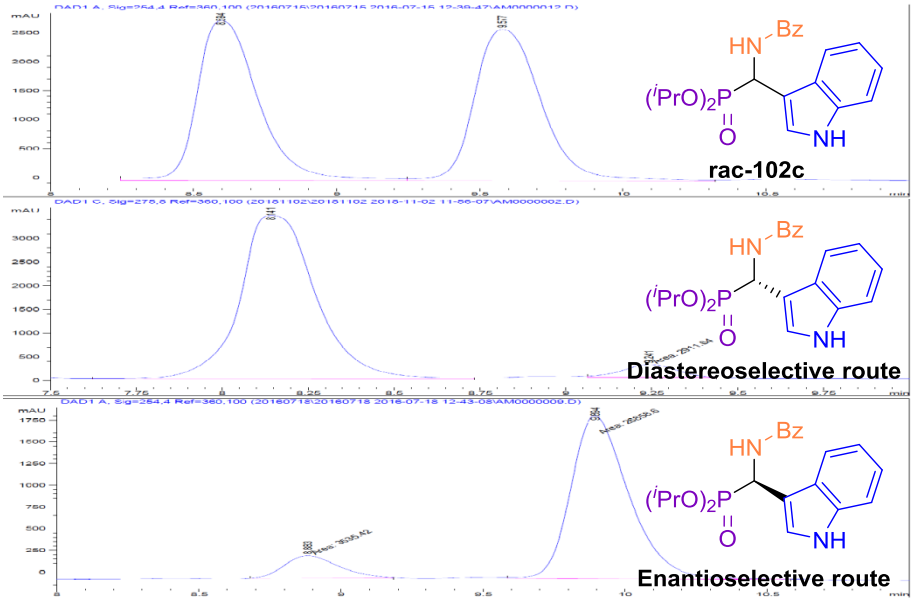


Figure 27. HPLC cromatogram comparation between diastereo and enantioselective routes to synthesize **102c**.

Therefore, an *R* absolute configuration of our indolyl phosphoglycines **102** was unambiguously stablished.

It is interesting that, under our optimized conditions, *N*-substituted indoles did not show any reaction with α-iminophosphonates. Bifunctional catalysis on indole by the Lewis basic site of phosphoric acids, has been discarded by some authors on the basis that some examples regarding *N*-substituted indoles have been reported.[83] However, the lack of reactivity of *N*-methylindole in our case and the absence or substantial decreasing of enantioselectivity in several others,[84] might indicate a crucial role of the NH group at the indole ring in the transition state. This NH moiety may establish a hydrogen bond with the phosphoryl oxygen of the catalyst. Similar activation has been proposed by other authors for the nucleophilic addition of indoles to nitroalkenes.[85]

Based upon these results and the models proposed for similar processes we suggest a tentative transition state where a bifunctional (double) activation of the imine and the indole by the phosphoric acid catalyst could happen. According to this model, the phosphoryl oxygen would establish a hydrogen bond with the indole NH proton, while a simultaneous second hydrogen bond between the phosphoric acidic proton and the imine nitrogen would activate the electrophile (Figure 28). Moreover, the fact that improved enantiomeric excesses are observed for aromatic substituted BINOL derived phosphoric acids,

might suggest a contribution of those aromatic substituents into the transition state by means of a π-stacking effect with the indole ring.

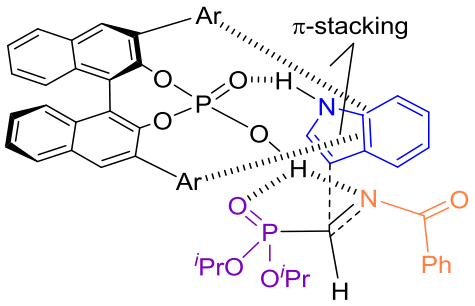


Figure 28. Tentative transition state for the Friedel-Crafts reaction of indole and α-iminophosphonates.

It should be noted that the opposite isomer of phosphoric acid catalyst **XXVIII** provides also the opposite enantiomer of indolyl phosphoglycines **102**, which is in agreement with the proposed transition state for this transformation.

To conclude this chapter, an efficient organocatalytic asymmetric route to provide access to enantioenriched indolyl phosphoglycines **102** has been developed, avoiding the formation of bis-(3-indolyl)methanes **103**. As far as we know, this is not only the first enantioselective functionalization of indole ring with non-cyclic α-aminophosphonates, but also the first organocatalyzed asymmetric reaction using α-phosphorylated aldimines. In addition, an alternative diastereoselective route to synthesize these products is also reported.

In the next chapter, the synthesis and potential applications of bis(3-indolyl) methanes **103** will be studied.

77) Some examples: (a) Sravanthi, T. V.; Manju, S. L. "Indoles - A promising scaffold for drug development" *Eur. J. Pharm. Sci.* **2016**, *91*, 1-10. (b) Saini, T.; Kumar, S.; Narasimhan, B. "Central Nervous System Activities of Indole Derivatives: An Overview" *Cent. Nerv. Syst. Agents Med. Chem.* **2015**, *16*, 19. (c) Netz, N.; Opatz, T. "Marine Indole Alkaloids" *Mar. Drugs* **2015**, *13*, 4814-4914. (d) Sharma, V.; Kumar, P.; Pathak, D. "Biological importance of the indole nucleus in recent years: A comprehensive review" *J. Heterocycl. Chem.* **2010**, *47*, 491-502.

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Chapter 3

Synthesis and antiproliferative evaluation of bis-(3-indolyl)methane phosphonates

The hybrid anticancer drug approach is an innovative synthetic strategy for the discovery of new biologically active hybrid molecules.[86] It is believed that the presence of two or more pharmacophores in a single unit not only synergizes their biological effect but also upsurge their ability to inhibit more than one biological target. Recently, the molecular hybrid approach has resulted in several novel chemical entities with improved anticancer activity and selectivity with reduced side effects.[87]

Some bis-indole family derivatives are of extraordinary significance in synthetic and medicinal chemistry, due to their wide occurrence in nature and their assorted biological activity.[88] Simple bis-(3-indolyl)methane (BIM) **111** and their derivatives (BIMs) **112-118** are nitrogen-containing heterocyclic compounds which structure can be found in many alkaloids isolated from natural sources (Figure 29).[89] In addition, numerous BIMs and their analogues show a wide range of biological and pharmacological activities,[90] including growth inhibition of numerous tumor types.[91]

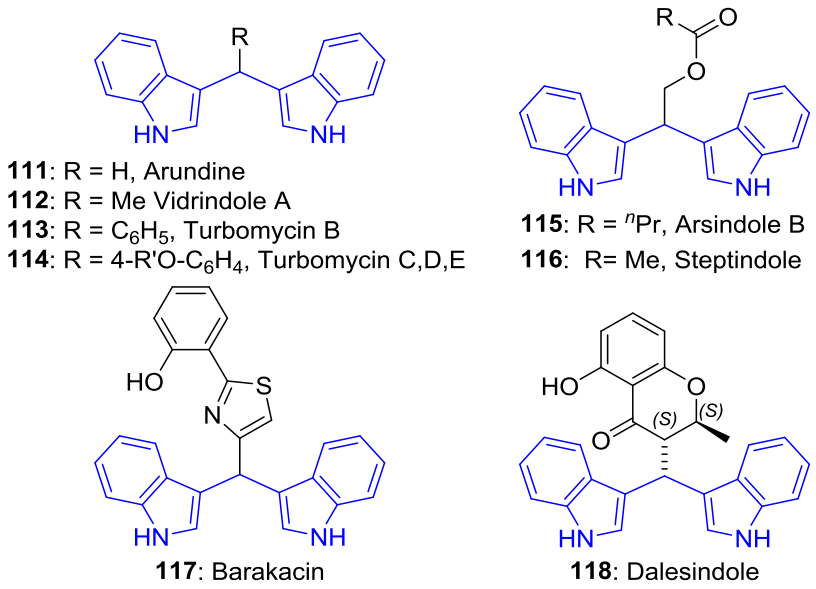
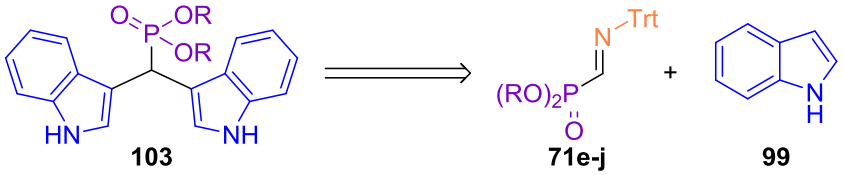


Figure 29. bis-(3-indolyl)methane derivatives.

In addition, as addressed before in the introduction of this thesis, the introduction of phosphorylated groups in bioactive molecules often result in an increase of their activity or in new bioactivities.[3] Considering the ability of phosphorylated molecules to inhibit enzymes and the biological properties of some BIM products as anti-tumour agents,[91] the design of an efficient synthetic route to prepare new hybrid bis-(3-indolyl)methane bearing a phosphorated group could be an interesting research goal in both, organic and medicinal chemistry.

Even though the most straightforward method for the preparation of BIM derivatives is the acid catalyzed Friedel-Crafts reaction between aldehydes and indoles, in our case, even though the synthesis of phosphorated BIMs would require the use of the formyl phosphonates, it was discarded because of the challenging methodology for their preparation. Nevertheles, in the previous chapter we have achieved a selective synthesis of bis-(3-indolyl)methane phosphonate derivatives when *N*-trityl and *N*-tosyl protected imines **71** are used (Table 4), we thought that the extension of this double addition reaction to several phosphonate and indole substrates would be of great interest. Particularly, the use of imines **71e-j** (Table 2) which, as we previously found, can be synthesized in a single step from the corresponding α-phosphoglycine derivatives, seems to be specially interesting (Scheme 30).

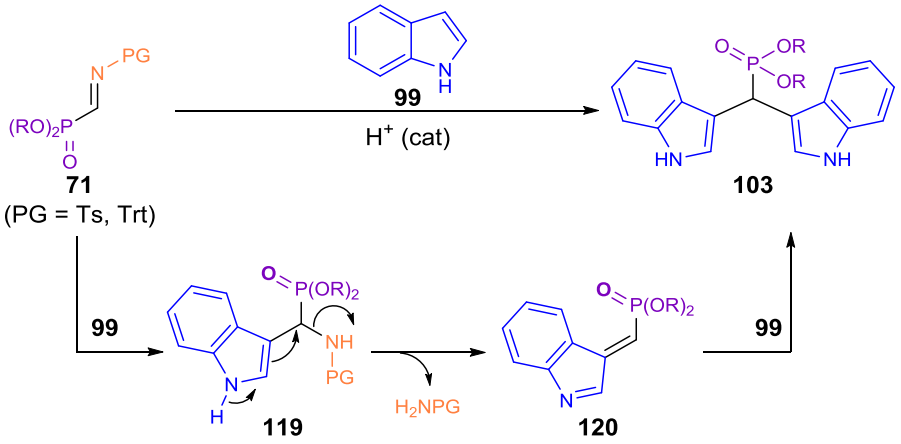


Scheme 30. Retrosynthesis of phosphorylated BIMs **103**.

The extension of this reaction could result in a new family of hybrid bis-(3-indolyl)methanes **103** with a phosphonate group in the BIM structure which is, as far as we know, unreported up to date.

This moiety may improve not only the antiproliferative properties with respect to other biologically active structures, but also represents an interesting challenge, due to the potential interest of these molecules in synthetic and medicinal chemistry. In this context, considering the experience of our research group in cytotoxicity essays, we decided to elaborate a structure-activity profile for these phosphorylated BIM derivatives.

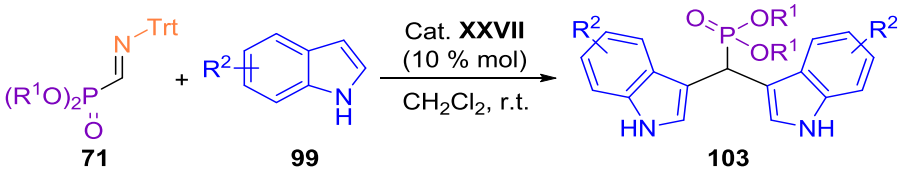
The double addition reaction of indole to aldehydes is well known since 19th century[92] and some authors have previously described this type of double addition of indole moieties to sulphonyl imines.[93] Based on these approaches, we propose the following mechanism for the reaction where, after the first addition of indole (**99**) to tosyl or trityl protected imines **71**, intermediate **119** yields azafulvene **120** by means of the elimination of a molecule of the corresponding amine or sulphonamide (Scheme 31). This new electrophilic species **120** undergoes a second acid catalyzed nucleophilic addition of indole (**99**) leading to the formation of BIM derivatives **103**.



Scheme 31. Proposed mechanism for the synthesis of BIMP products **103.**

In order to evaluate the effect of the size of the phosphorus substituents into the reactivity, we decided first to mix two equivalents of indole (**99**) with trityl protected imines **90** in the presence of a catalytic amount of racemic phosphoric acid catalyst **XXVII**. Following this procedure, imines **90e-i** provided in moderate yields the desired products **103** bearing alkyl phosphonates such as Me (Table 8, entry 3), Et (Table 8, entry 1), ^{i}Pr (Table 8, entry 2), ^{t}Bu (Table 8, entry 7) and Bn (Table 8, entry 10). Unfortunately, the reaction did not work properly when diphenyl α-iminophosphonate **90j** was used (Table 8, entry 22)

Table 8. Scope of the BIMPs **103**.



Entry	Comp.	R^1	R^2	Yield (%)
1	**103a**	Et	H	61
2	**103b**	^{i}Pr	H	60
3	**103c**	Me	H	59
4	**103d**	^{i}Pr	6-F	69
5	**103e**	^{i}Pr	5-F	67
6	**103f**	^{i}Pr	5-Me	62
7	**103g**	^{t}Bu	H	68
8	**103h**	^{t}Bu	5-F	69
9	**103i**	^{t}Bu	5-Me	72
10	**103j**	Bn	H	55
11	**103k**	Bn	6-F	65
12	**103l**	Bn	5-F	67
13	**103m**	Bn	5-CF_3	54
14	**103n**	Bn	6-CF_3	53
15	**103o**	Bn	5-MeO	57
16	**103p**	Bn	6-MeO	61
17	**103q**	Bn	5,6-MeO	58
18	**103r**	Bn	6-Me	64
19	**103s**	Bn	5-Me	65
20	**103t**	Bn	2-Me	63
21	**103u**	Bn	3-Me	n.r.
22	**103v**	Ph	H	n.r.

Then, the reaction was extended to several substituted indoles, affording the expected products in moderate to good yields. The reaction can be accomplished with a wide scope of activated and deactivated indole substrates with slight differences in their reactivity. The use of weakly activated substituents, such as methyl (Table 8, entries 6, 9, 18, 19) and weakly deactivated ones like fluorine (Table 8, entries 4, 5, 8, 11, 12) in the aromatic ring affords higher yields if compared with strongly activating methoxy (Table 8, entries 15-17) or deactivating trifluoromethyl groups (Table 8, entries 13, 14). The study of the effect of the substitution in the pyrrole unit was also performed and the product **103t** was obtained with 63 % yield starting from 2-methylindole (Table 8, entry 20). Unfortunately, the use of 3 substituted indole did not afford the desired product (Table 8, entry 21), probably due to the impossibility to generate the azafulvene intermediate **120** (Scheme 31).

All the bisindole products **103** were fully characterized by NMR, IR and HRMS. Using compound **103b** as example, in the ^{1}H-NMR spectrum, the hydrogen atom next to the phosphonate is shown as a doublet at δ = 5.04 ppm, coupled to the phosphorus atom with a coupling constant of $^{2}J_{PH}$ = 25.2 Hz. In addition, the signals of the isopropyl groups show only one multiplet at δ = 4.43 ppm for CH groups and two doublets at δ = 1.20 and δ = 0.72 ppm, both with a coupling constant of $^{3}J_{HH}$ = 6.2 Hz for methyl groups. Importantly, the

integrals of the indole proton shifts evidenced the presence of two molecules of indole in the sample (Figure 30).

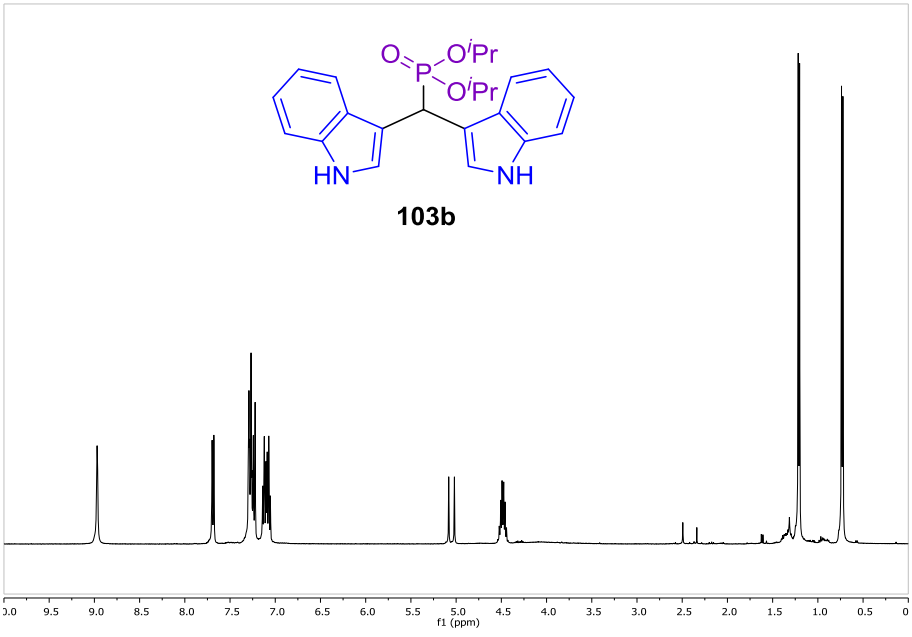


Figure 30. ^{1}H-NMR of compound **103b**.

Furthermore, the ^{13}C-NMR spectrum shows as the most characteristic signal, the doublet at δ = 32.4 ppm, corresponding to the carbon atom next to the phosphonate moiety, with a coupling constant of $^{1}J_{PC}$ = 145.4 Hz (Figure 31).

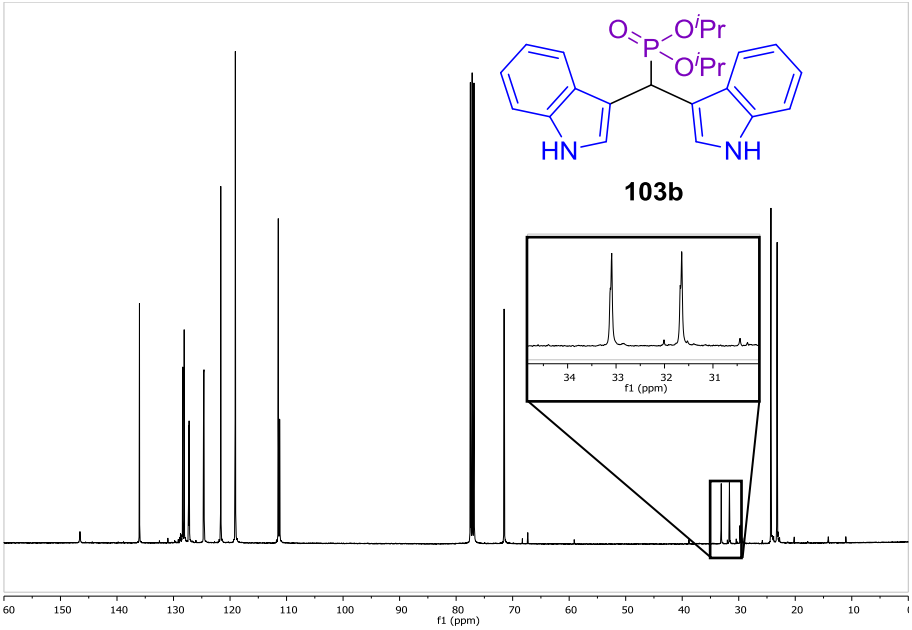
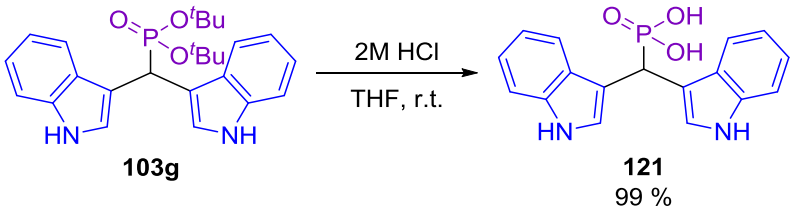


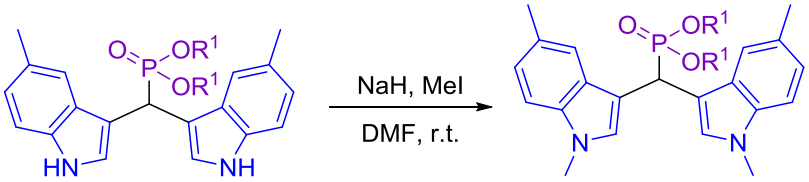
Figure 31 ^{13}C-NMR of compound **103b**

In order to increase the diversity of substituents in our substrates, the acidic hydrolysis of di-*tert*-butylphosphonate **103g** was performed using an aqueous solution of hydrochloric acid in THF, affording phosphonic acid derivative **121** in almost quantitative yield (Scheme 32).



Scheme 32. Hydrolysis of dimethylphosphonate **103g**.

For the same purpose, the alkylation of indolic nitrogen of isopropyl and *tert*-butylphosphonate derivatives **103f** and **103i** was performed in the presence of methyl iodide in *N*,*N*-dimethylformamide, using sodium hydride as base. In this way, bis-(3-*N*-methylindolyl) derivatives **122** and **123** were obtained in almost quantitative yields (Scheme 33). It should be noted that, as in the case of asymmetric Friedel-Crafts reaction, the direct synthesis of *N*-methylated BIMP derivatives **122** and **123** starting from *N*-methylindole is not feasible.



103f: R^1 = ^{i}Pr
103i: R^1 = ^{t}Bu

122: R^1 = ^{i}Pr 99 %
123: R^1 = ^{t}Bu 99 %

Scheme 33. *N*-methylation reactions of **103f** and **103i**.

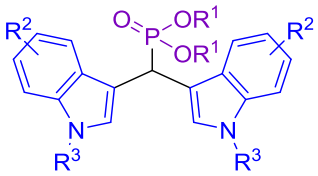
In addition, the alkylation reaction was tested for benzyl phosphonate substrate **103j**, but the presence of the slightly acidic benzylic hydrogens had an adverse effect on the reactivity and the final product could not be isolated.

With this collection of promising structures in our hands, the study of their biological activity was next considered. The *in vitro* cytotoxicity of our novel BIMP derivatives was evaluated by testing their antiproliferative activities against two human cancer cell lines:

A549 (human alveolar basal epithelial carcinoma) and SKOV03 (human ovarian carcinoma). Cell proliferation inhibitory activities of the bis-indol derivatives **103, 121-123** and chemotherapeutic doxorubicin are shown as IC_{50} values. Moreover, MRC-5 non-malignant lung fibroblasts were tested in order to study their selectivity[94] and it was demonstrated that none of the synthesized phosphorated compounds or doxorubicin exhibited any toxicity toward MRC-5 cells.

Regarding the effect of the substitution at the phosphonate ester group in BIM derivatives **103** on their cytotoxicity against SKOV03 cell line *in vitro*, it was evidenced that the presence of a bulky group, in general, resulted in an increased activity. Considering only substrates holding non-substituted indole moieties, IC_{50} values higher than 50 μM were observed for methyl or ethyl esters **103c** and **103a** (Table 9, entries 1,2), but these values dropped to 11.43±0.83 μM for isopropyl ester **103b** (Table 9, entry 3) and, interestingly, lower values of 1.06±0.30 μM and 1.26±0.13 μM were obtained for *tert*-butyl and benzyl esters **103g** and **103j** respectively (Table 9, entries 7, 10).

Table 9. Antiproliferative activity of BIMP derivatives **103**, **121-123** against lung and ovarian cancer cell lines. Part 1.



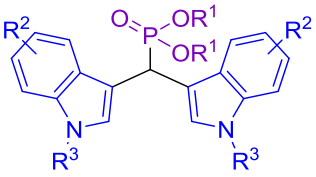
103, 121-123

Entry	Comp.	R^1	R^2	R^3	IC_{50} ovarian (μM)[a] (SKOV03)	IC_{50} lung (μM)[a] (A549)
1	**103c**	Me	H	H	>50	>50
2	**103a**	Et	H	H	>50	10.48±1.01
3	**103b**	^{i}Pr	H	H	11.43±0.83	1.06±0.30
4	**103d**	^{i}Pr	6-F	H	6.30±0.24	0.85±0.00
5	**103e**	^{i}Pr	5-F	H	3.52±0.37	0.58±0.09
6	**103f**	^{i}Pr	5-Me	H	7.78±0.47	0.41±0.13
7	**103g**	^{t}Bu	H	H	1.06±0.30	15.90±0.74
8	**103h**	^{t}Bu	5-F	H	0.65±0.05	11.30±0.08
9	**103i**	^{t}Bu	5-Me	H	9.01±0.58	**0.06±0.04**
10	**103j**	Bn	H	H	1.26±0.13	10.53±0.39
11	**103k**	Bn	6-F	H	7.78±0.47	0.22±0.15
12	**103l**	Bn	5-F	H	7.18±1.20	0.63±0.16
13	**103m**	Bn	5-CF_3	H	5.98±0.32	6.10±0.23
14	**103n**	Bn	6-CF_3	H	11.99±1.60	8.90±0.92
15	**103o**	Bn	5-MeO	H	6.77±1.03	1.05±0.58
16	**103p**	Bn	6-MeO	H	>50	7.45±0.35
17	**103q**	Bn	5,6-MeO	H	>50	(≈10)[b]

[a] Concentration corresponding to 50% growth inhibition.

[b] Approximate value due to systematic error in experimental.

Table 9. Continued.



103, 121-123

Entry	Comp.	R^1	R^2	R^3	IC_{50} ovarian (μM)[a] (SKOV03)	IC_{50} lung (μM)[a] (A549)
18	**103r**	Bn	6-Me	H	4.90±0.36	7.16±0.89
19	**103s**	Bn	5-Me	H	**0.06±0.02**	0.93±0.13
20	**103t**	Bn	2-Me	H	>50	10.79±2.52
21	**121**	H	H	H	>50	>50
22	**122**	^{i}Pr	5-Me	Me	11.91±1.84	>50
23	**123**	^{t}Bu	5-Me	Me	>50	>50
24	**Dox.**	-	-	-	0.00184±0.00022	0.48±0.017

[a] Concentration corresponding to 50% growth inhibition.

Although practically the same pattern was observed for A549 cell line, in this case the best result was observed for isopropyl ester **103b** with IC_{50} values of 1.06±0.30 μM (Table 9, entry 3). In contrast to this tendency, phosphonic acid derivative **121** did not show any cytotoxicity in any of the tested cell lines (Table 9, entry 21). It should be noted that simple bis-(3-indolyl)methane Arundine **111** (Figure 29) has been reported to have no cytotoxic activity *in vitro* against A549 cell line.[95]

Next, the effect of the substitution at the indole ring on the cytotoxicity of BIMPs against both cell lines was investigated. Although generally, the effect of fluorine on the biological activity of organic compounds is difficult to predict, it is well known that the introduction of fluorine substituents in bioactive molecules very often leads to increased activities.[96] For this reason, first we tested the *in vitro* cytotoxicity of fluorine substituted BIMP derivatives against both cell lines. In the case of SKOV03 cell line, high cytotoxicity is observed for 6- and 5-fluoro substituted indole moieties in isopropyl esters **103d**, **103e** (Table 9, entries 4, 5), *tert*-butyl ester **103h** (Table 9, entry 8) and benzyl ester derivatives **103k** and **103l** (Table 9, entries 11, 12).

Alternatively, in the case of A549 cell line, substitution of indole ring with fluorine atoms has a higher cytotoxic effect since, IC_{50} values of 0.85±0.007 μM and 0.58±0.09 μM were revealed for isopropyl ester derivatives **103d** and **103e** (Table 9, entries 4, 5). The values increased for *tert*-butyl ester derivative **103h** with an IC_{50} value of 11.30±0.08 μM (Table 9, entry 8), and they dropped to 0.22±0.15 μM and 0.63±.16 μM for benzyl ester derivatives **103k** and **103l** (Table 9, entries 11, 12). Surprisingly, the introduction of a trifluoromethyl group into the indole ring has a negative effect into the cytotoxicity of BIMs neither on SKOV03 cell line nor when they were tested in A549 cell line (Table 9, entries 13, 14).

It is known that, a methoxy group in an aromatic ring, is a widespread motif in drugs and natural products. For that reason, next we analyzed the effect of the introduction of methoxy groups in the skeleton of indole ring in benzyl ester BIMP derivatives. Respect to the antiproliferative activity *in vitro* in SKOV03 cell line, while 5-methoxy substituted BIMP substrate **103o** showed an IC_{50} value of 6.77±1.03μM (Table 9, entry 15), substitution in the 6-position resulted in a complete loss of the cytotoxic properties for 6-methoxy and 5,6-dimethoxy BIMPs **103p** and **103q** (Table 9, entries 16, 17). Moreover, when the cytotoxicity of those methoxy-substituted BIMP substrates was tested in A549 cell line, a slight increase in the activity was observed for 5-methoxy and 6-methoxy substituted BIMPs **103o** and **103p** with IC_{50} values of 1.05±0.58 μM and 7.45±0.35 μM (Table 9, entries 15, 16).

In addition, it is also stablished that the introduction of methyl groups into a bioactive structure results in an increase of its lipophilic character often improving its capability to cross cell membranes.[97] In general, the methyl group in the indole ring of our BIMP substrates **103f**, **103i**, **103r-t** (Table 9, entries 6, 9, 18-20) presented interesting cytotoxic effects and particularly, substitution with methyl group in 5-possition has a very significant impact into the cytotoxicity of BIMP derivatives. For instance, *tert*-butyl ester derivative **103i** showed an IC_{50} value of 9.01±0.58 μM in SKOV03 cell line and an improved value of 0.06±0.04 μM in A549 cell line (Table 9, entry 9). In accordance,

benzyl ester derivative **103s** with a methyl group in 5-position showed an improved cytotoxicity in the nanomolar range when tested against the SKOV03 cell line, with an IC_{50} value of 0.06±0.02 μM and a significant effect in the A549 cell line with an IC_{50} value of 0.93±0.13 μM (Table 9, entry 19).

Finally, in order to determine the importance of NH group in the indole moiety, *N*-methylindole derivatives **122** and **123** were also tested. In this case, an increase of IC_{50} values to 11.91±1.84 μM and >50 μM was observed in SKOV03 and A549 cell lines respectively for isopropyl ester derivative **122** with respect to the corresponding BIMP product **103f** bearing a NH group (Table 9, entries 6, 22), and an absolute lack of toxicity was observed in both cell lines for *tert*-butyl ester derivative **123** when it was compared with BIMP **103i** (Table 9, entries 9, 23). This result suggests a significant role of NH group in the cytotoxic activity of BIMPs.

In summary, this new synthetic methodology proves to be very efficient for the selective preparation of BIM phosphonates **103**, avoiding the use of undesirable formylphosphonates. This strategy allows the generation of assorted structural diversity in the resultant scaffold, depending on the starting phosphonate and commercialy available indole substrates. Moreover, the obtained BIM phosphonates showed *in vitro* cytotoxicity, inhibiting the growth of human tumor cell lines A549 (human alveolar basal epithelial

carcinoma) and SKOV03 (human ovarian carcinoma) without exhibing any toxicity toward MRC-5 non-malignant lung fibroblasts. Substrates **103i** and **103s** presented very promising IC_{50} values of 0.06 µM.

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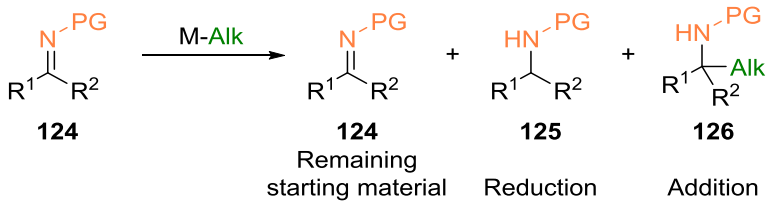
Chapter 4
Nucleophilic addition of organometalic reagents to α-ketiminophosphonates. *

*This part of the Ph. D was hold in in the Stratingh Institute for Chemistry of the University of Groningen.

The generation of tetrasubstituted carbon stereocenters is known to be a challenging task in synthetic organic chemistry, even more when the main goal is to generate them in a catalytic asymmetric way. In this context, the use of lithium, magnesium and zinc based organometallic reagents, discovered in the second half of XVIII and early XIX centuries, has been one of the most straightforward methods to add carbon nucleophiles to carbonylic compounds or imines. The high reactivity of most of the organometallic reagents makes them an excellent choice, not only for asymmetric additions to activated substrates, like aldehydes and aldimines but also for the addition to less reactive ketones, affording enantioenriched tertiary alcohols.[98] In contrast, the analogous reaction with ketimines is still a big challenge due to the poorer electrophilicity of the substrates and the more difficult discrimination between both faces on the prochiral species.

In particular, so far the only examples of enantioselective metal catalyzed nucleophilic additions to α-ketiminophosphonates have been reported using cyclic substrates.[59, 60] It should be noted that most of the reported references with ketimines are related to arylation,[99] alkynylation[100, 58] and allylation,[101] but there are even fewer references

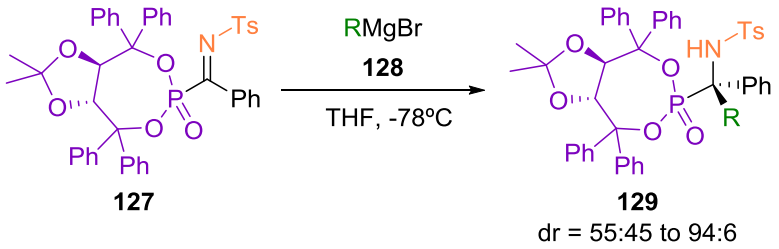
regarding the enantioselective alkylation of ketimines. The lower reactivity of ketimines in comparison with the corresponding ketones usually implies not only low conversions but also increases the risk of β-hydride elimination as an undesirable side reaction, leading to the racemic reduction of the imine (Scheme 34).



Scheme 34. Addition of organometallic reagents to imines.

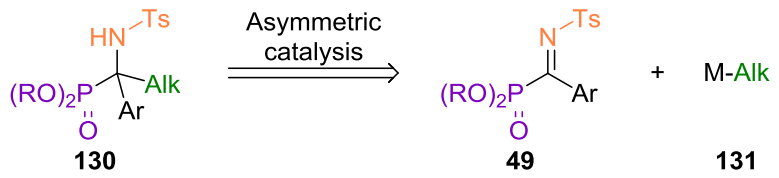
Having all of this in mind, it is not surprising to find that the references regarding the addition of aliphatic organometallic reagents are mostly limited to a few examples of methylation and ethylation of ketimines, using organozinc and organoaluminium reagents.[102] Furthermore, the analogous reaction with ketimines using organomagnesium reagents, which have proved their capability to add enantioselectively to ketones,[103] is still almost unexplored.[104]

Some years ago, our group reported the nucleophilic addition of Grignard reagents to α-ketiminophosphonates and a few examples of the diastereoselective version of this reaction using TADDOL derived α-ketiminophosphonate **127** (Scheme 35).[55]



Scheme 35. Diastereoselective addition of Grignard reagents to α-ketiminophosphonates **127**.

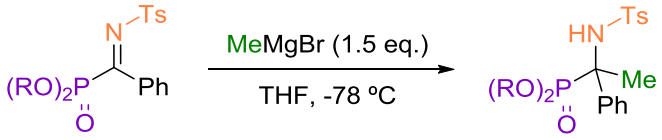
Some advances in enantioselective addition of Grignard reagents to imines have been reported during the last years and, considering the small amount of references in the bibliography concerning the enantioselective alkylation of ketimines, we thought that the development of a catalytic asymmetric protocol for the addition of alkyl organometallic reagents to our α-phosphorylated ketimines **49** would be an important contribution to the field (Scheme 36).



Scheme 36. Enantioselective alkylation of α-ketiminophosphonates.

Therefore, first the reactivity of imines **49** was investigated and, in order to evaluate the influence of the substituent at the phosphorus atom, the addition of methylmagnesium bromide to different phosphonate derived ketimines was analyzed. The reaction successfully worked for dialkyl phosphonates **49a-d** (Table 10, entries 1-4), but when diphenyl phosphonate **49e** was used as substrate a complex mixture was obtained and desired product could not be isolated (Table 10, entry 5). Although the reaction worked properly using dibenzyl phosphonate **49d** (Table 10, entry 4), the staring imine was found to be more susceptible to hydrolysis processes during the storage, and therefore it was discarded for the next experiments. In order to reduce the steric hindrance on the imine, methyl ketimino-phosphonate **49a** was selected for the following optimization essays.

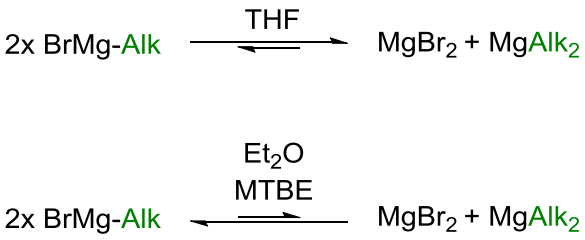
Table 10. Grignard addition to various α-iminophosphonates.



49 **132a-136a**

Entry	R	Imine	Prod.	time (h)	Conv. (%)
1	Me	**49a**	**132a**	<1	100
2	Et	**49b**	**133a**	<1	100
3	^{i}Pr	**49c**	**134a**	<1	100
4	Bn	**49d**	**135a**	<1	100
5	Ph	**49e**	**136a**	2	n.d.

In previous work in our research group, nucleophilic additions of Grignard reagents were carried out in THF at -78°C with excellent yields.[55] However, in THF, the Schlenk equilibrium of Grignard reagents is driven to the formation of dialkylmagnesium species (Scheme 37), that are much more reactive than organomagnesium bromides and, consequently, makes even more difficult to get any stereocontrol on the process.

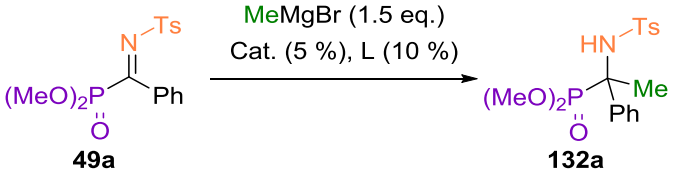


Scheme 37. Schlenk equilibrium of Grignard reagents in presence of different ethers.

In fact, there are not too many reported examples of enantioselective Grignard additions in THF, and most of them make use of linear ethers like Et_2O and MTBE, or not coordinating solvents such as CH_2Cl_2 or toluene. Since the background reaction has proved to be very fast for these imines (Table 10) and, considering the additional challenge to control the enantioselectivity of the process in THF, the reactivity of our substrates was studied in various other solvents (Table 11). Following the optimal conditions for similar processes previously described, CH_2Cl_2 and toluene were first tested

(Table 11, entries 2, 3) obtaining similar fast reactivity to the previous tests in THF (Table 11, entry 1).

Table 11. Optimization of the reaction conditions.



Entry	Solvent	T (°C)	time (h)	Cat.	L	Conv. (%)
1	THF	-78	<1	-	-	100
2	CH_2Cl_2	-78	<1	-	-	100
3	Toluene	-78	<1	-	-	100
4	MTBE	-78	24	-	-	30
5	MTBE	-78	24	CuBr·SMe_2	PPh_3	18
6	MTBE	-40	6	-	-	27
7	MTBE	-r.t.	6	-	-	44
8	MTBE/CH_2Cl_2 1:1	-78	5	-	-	63
9	MTBE/CH_2Cl_2 1:1	-78	<1	CuBr·SMe_2	PPh_3	100
10	MTBE/CH_2Cl_2 9:1	-78	6	CuBr·SMe_2	PPh_3	97

It should be noted that these imines are typically purified by crystallization in Et_2O, and their solubility is also low in other linear ethers even at room temperature. For this reason, we thought that this could be a convenient strategy to slow down the reaction enough to get a good enantioselectivity under catalyzed conditions and therefore, MTBE was checked as solvent (Table 11, entry 4). However,

very low conversion was observed after 24 h when the reaction was performed in MTBE at low temperature. With these results in hand, next $CuBr{\cdot}SMe_2$ was added as catalyst in the reaction using triphenylphosphine as racemic ligand, but surprisingly, the conversion was found to be even lower than without it (Table 11, entry 5).

Next, a study of the effect of the temperature on the reaction was performed (Table 11, entries 4, 6, 7). Despite the better results obtained at higher temperatures, the presence of several unknown side products made impossible to get a good yield of the final product. At this point, a mixture of MTBE and CH_2Cl_2 was tested in order to improve the solubility and, at the same time, reduce the reactivity of the imine as much as possible. As expected, good conversion and reasonable reaction times were found in this case (Table 11, entry 8). Here again, the effect of the Cu (I) catalyst was investigated, obtaining in this case excellent conversion and fast reaction (Table 11, entry 9). The use of a minimal amount of dichloromethane results in a similar conversion rates and slightly higher reaction times, making the reaction conditions optimal for the study of the enantioselectivity (Table 11, entry 10).

Chiral bisphosphines have proved to be excellent ligands for copper catalyzed nucleophilic additios of organometallic reagents. For this reason, some chiral bisphosphine-based ligands were tested in the reaction (Figure 32).

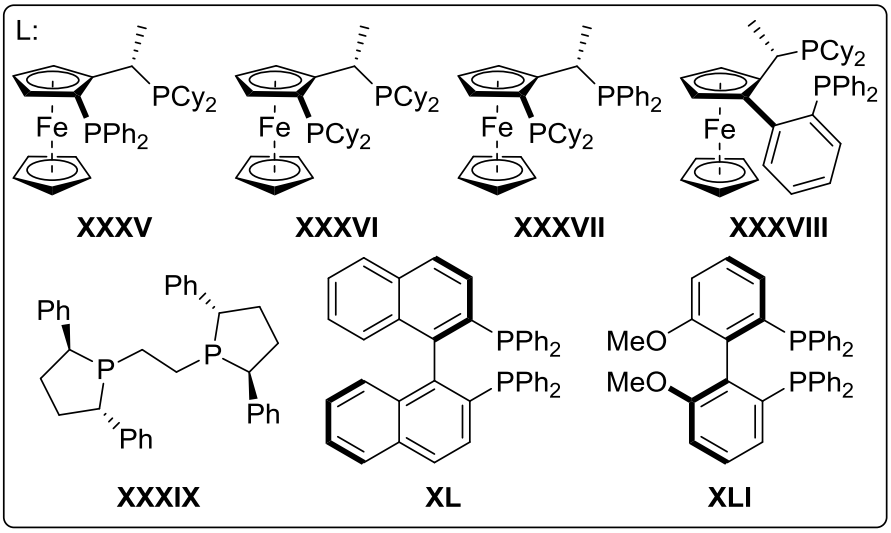
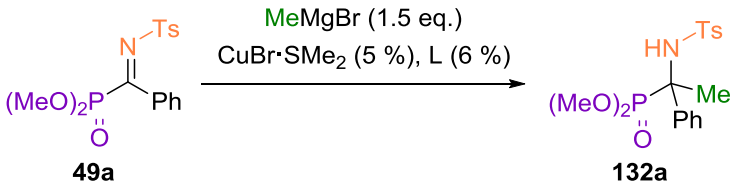


Figure 32. Tested bisphosphine chiral ligands.

The screening was started with ferrocenyl moiety containing biphosphines like JosiPHOS family **XXXV-XXXVII** and WalPHOS (**XXXVIII**) ligands. In addition, BPE (**XXXIX**), BINAP (**XL**) and MeOBIPHEP (**XLI**) ligands were also tested. However, none of these ligands provided relevant enantioslectivity (Table 12).

Table 12. Screening of bisphosphine ligands.



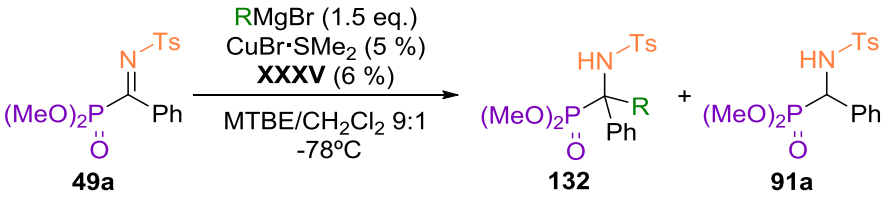
49a **132a**

Entry	Solvent	T (°C)	time (h)	L	Conv. (%)	ee (%)
1	MTBE/CH_2Cl_2 9:1	-78	6	**XXXV**	98	2
2	MTBE/CH_2Cl_2 9:1	-78	6	**XXXVI**	96	0
3	MTBE/CH_2Cl_2 9:1	-78	6	**XXXVII**	97	2
4	MTBE/CH_2Cl_2 9:1	-78	6	**XXXVIII**	97	4
5	MTBE/CH_2Cl_2 9:1	-78	6	**XXXIX**	95	0
6	MTBE/CH_2Cl_2 9:1	-78	6	**XL**	95	3
7	MTBE/CH_2Cl_2 9:1	-78	6	**XLI**	79	2
8	MTBE	-50	24	**XXXV**	77	2

Although the conversion ratios were found to be excellent, the stereoselectivity of the process in all cases was lower than 10 % no matter which ligand was used. For this reason we again tested the effect of the temperature in the enantioselectivity of the reaction in MTBE using JosiPHOS **XXXV** as chiral ligand at -50 °C (Table 12, entry 8). In this case acceptable conversion was obtained, but the selectivity was similar to the previous cases. In view of that all the tested ligands gave comparable enantioselectivities, the subsequent tests were carried out using Josiphos **XXXV** as chiral ligand.

Afterwards, a study of the effect of the Grignard reagents in the reactivity and enantioselectivity was investigated, employing ethyl and isobutyl Grignard reagents on the reaction instead of methylmagnesium bromide.

Table 13. Extension of the reaction to other Grignard reagents.



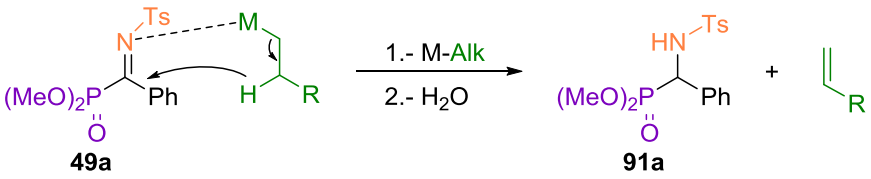
Entry	R	time (h)	Prod.	Conv. (%)	132/91a[b] ratio	ee 132 (%)
1	Et[a]	<1	**132b**	96	70/26	-
2	Et	1	**132b**	83	60/23	0
3	^{i}Bu[a]	<1	**132c**	77	14/63	-
4	^{i}Bu	1	**132c**	66	33/33	0
5	Np[a]	2	**132d**	74	74/0	-
6	Np	2	**132d**	73	73/0	0

[a] No catalyst or ligand were used.

[b] Measured by ^{31}P-NMR.

As expected, the product resulting from the reduction of the imine was recovered in an increasing ratio when bulkier Grignard reagents were used without catalyst (Table 13, entries 1, 3). When the same reactions were carried out using the catalytic system, better addition/reduction ratios were observed, but it was not still good

enough for both, reactivity and enantioselectivity (Table 13, entries 2, 4). Indeed, a high ratio of reduction product was found, not only for isobutylmagnesium bromide, which is a bulky group, but also for the smaller ethyl alkyl chain. The formation of the reduction product can only happen when hydrogen atoms are present in the β-position of the organometallic reagent. Certanly, when the addition of Grignard reagent is less favored because of higher steric hindrance on the imine, the ratio of β-hydride transfer product increases with respect to the addition product. Moreover, the stability of the final alkene obtained in this process makes easier to obtain the reduction product with isobutylmagnesium bromide than with ethyl Grignard reagent (Scheme 38).



Scheme 38. β-Hydride transfer mechanism.

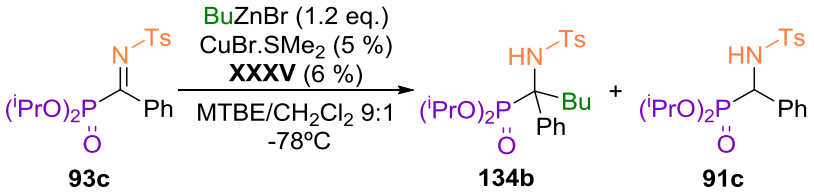
In order to elude the reduction of imine **49a**, neopentylmagnesium bromide was used (Table 13, entries 5, 6), but unfortunately, although the reduction product was avoided, these Grignard reagents were also found to be too reactive and no enantioselectivity was observed in any case.

Considering that in previous works bulkier phosphonates usually gave better enantiomeric excesses, isopropyl α-iminophosphonate **49c** was tested as substrate with different Grignard reagents. Unfortunately, no relevant increase on the eneantioselectivity was observed, and the amount of reduction product was found to be even higher.

In view that Grignard reagents were not useful for our goal, the use of less reactive alkylzinc bromides was then proposed. It should be noted that organozinc halides are typically used for Negishi type couplings,[105] but there are not many examples of enantioselective 1,2 nucleophilic additions to carbonyl or imine compounds and, as far as we know, all the reported asymmetric additions of organozinc bromides require a stoichiometric amount of the chiral ligand in order to get any enantioselectivity.[106] Although the use of alkylzinc bromides seems to be a bad idea for a nucleophilic addition to ketimines due to the low reactivity of both, nucleophile and electrophile, our imines **49** had proved to be too reactive for enantioselective additions of Grignard reagents and therefore, the use of a less reactive nucleophile could be a good choice in this particular case. Accordingly, butylzinc bromide was prepared *in situ* by mixing dry $ZnBr_2$ with butyllithium in MTBE and stirring at 0 °C for 30 min before adding the following reagents.

Surprisingly, when the reaction was tested, just a small amount of the reduction product was found and the conversion to the desired product was found to be above 70 % (Table 14, entry 1).

Table 14. Optimization of the reaction for BuZnBr.



Entry	time (h)	Conv. (%)	134b/91c ratio	ee 134b (%)
1	4	78	75/3	0
2	20	21	21/0	-
3[a,b]	15	82	69/13	-
4[b]	1	99	96/3	-

[a] BuLi was used as nucleophile instead of BuZnBr.

[b] No ligand was used.

In order to make sure that the background reaction was not as fast as the catalyzed one, the non-catalyzed reaction and the direct addition of butyl lithium were tested. After 20 hours, the conversion of uncatalyzed reaction was found to be very low (Table 14, entry 2). Moreover, the reaction with just organolithium reagent provided higher conversion, and the proportion of the reduction product was also increased (Table 14, entry 3). In order to better understand the role of each component of the reaction, it was carried out with Cu(I)

catalyst but without using any ligand (Table 14, entry 4). The fact that in this essay the reaction worked even faster than with the ligand and the conversion of the reaction was also found to be better, along with the absence of any stereocontrol on these tests, made us think about the capability of the Cu (I) catalyst to act as a Lewis acid in this reaction, making it faster but without inducing any enantioselectivity.

In summary, in this chapter, the nucleophilic addition of several organometallic alkyl chains to our α-phosphorylated imines has been explored. Even though the initial challenge to selectively obtain the addition product instead of the reduced imine has been successfully overcome, the enantioselectivities were found to be very low.

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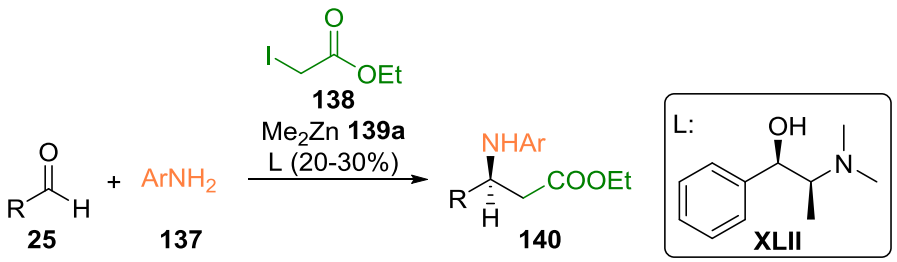
Chapter 5

Enantioselective aza-Reformatksy reaction of α-ketiminophosphonates

Following the approach of chapter 4 regarding metal catalyzed additions to α-ketiminophosphonates in order to generate tetrasubstituted α-aminophosphonates, and having in mind the interesting results obtained with organozinc reagents, asymmetric Reformatsky reaction of α-ketiminophosphonates was set as a new objective.

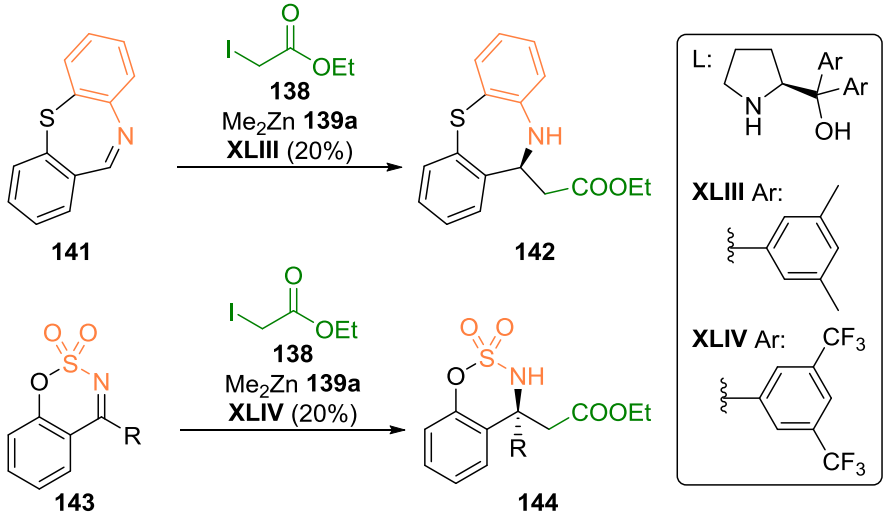
In this regard, Reformatsky reaction is a valuable synthetic process that is widely used for the effective formation of C-C bonds.[107] This transformation consists in a nucleophilic addition, in general to aldehyde or ketone substrates, of a zinc enolate, which is generated *in situ* from a metal insertion into activated carbon halides.[108] The discovery that organozinc species **139** can be used as the metal source,[109] offered more convenient homogenous conditions for this reaction and, since then, many efforts have been made in developing catalytic systems for the enantioselective Reformatsky reaction using ketones and aldehydes.[110] Imines are also suitable substrates for this reaction, providing access to β-amino acid derivatives in a simple synthetic protocol.

The first catalytic enantioselective aza-Reformatsky reaction was reported by Cozzi in 2006 using *in situ* preformed aldimines and 20-30% of *N*-methylephedrine **XLII** as chiral ligand (Scheme 39).[111]



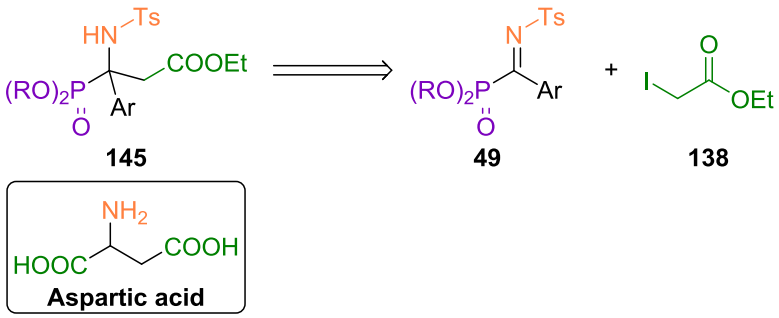
Scheme 39. First catalytic imino-Reformatsky reaction.

Although not strictly catalytic, more recently Ando *et al.* have reported the synthesis of α,α-difluoro-β-lactams by an aza-Reformatsky protocol promoted by a 75% of chiral aminoalcohol ligands.[112] More recently, Pedro and Vila *et al.* have performed successful imino-Reformatsky processes with cyclic aldimines **141** and **143** (R = H)using a 20% of prolinol derived ligands **XLIII** and **XLIV** (Scheme 40).[113] Remarkably, their catalytic system is equally effective when cyclic ketimines **143** (R = Alk) are used as substrates, which allow the synthesis of quaternary cyclic β-aminoesters **144** (R = Alk) with excellent enantioselectivities.



Scheme 40. Aza-Reformatsky reaction to cyclic imines.

As mentioned before, due to the poor electrophilic character of ketimine carbons and the additional steric hindrance on the substrate, the formation of tetrasubstituted carbons from ketimines is always a challenging task. In addition, the enantiotopic faces of ketimines are not as easily discriminated as those of aldimines when asymmetric synthesis is sought.[114] This drawbacks are specially serious if acyclic imines are used as substrates. In this case, we were intrigued about the possibility of accessing to phosphorated analogues of aspartic acid holding tetrasubstituted carbons, using α-ketiminophosphonates as electrophile substrates in an asymmetric aza-Reformatsky reaction (Scheme 41). As far as we know there are not examples of such reaction using acyclic ketimines as substrates.



Scheme 41. Retrosynthesis of tetrasubstituted phosphorated analogues of aspartic acid.

Based in the zinc intermediates proposed by Noyori[115] and inspired by the mechanisms for other enantioselective Reformatsky processes proposed by Cozzi[111] and Feringa,[116] initially we chose several diols like BINOL derivatives **XLV-XLVII** or VAPOL **XLVIII** and pseudoephedrine β-aminoalcohol **XLIX** as chiral inductors in the aza-Reformatsky reaction of α-ketiminophosphonates (Figure 33).

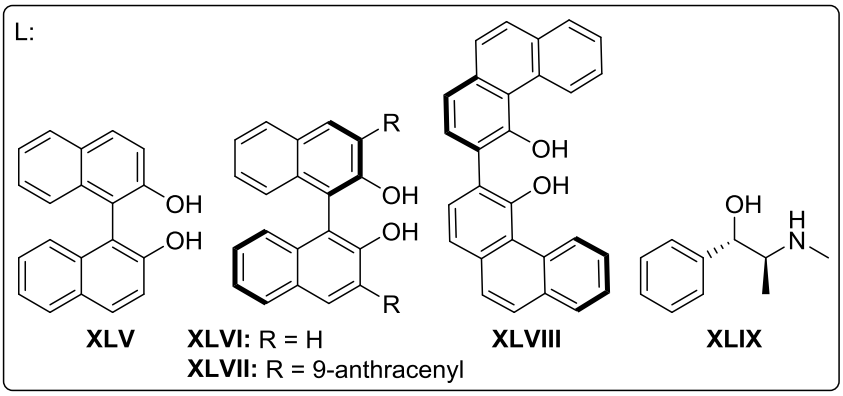


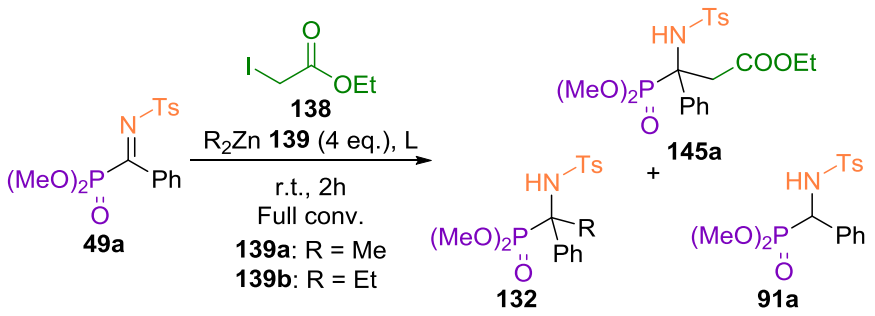
Figure 33. Ligands tested in the aza-Reformatsky reaction.

For the optimization of the reaction conditions, first we studied the reaction of dimethyl iminophosphonate **49a** with ethyl iodoacetate **138** in the presence of an organozinc reagent and a catalytic amount of racemic BINOL **XLV**. Besides the desired product **145a**, compounds **132** and **91a** were observed in the reaction mixture, resulting from a direct nucleophilic addition of organozinc reagent or the reduction of imine bond, respectively (Table 15).

When diethylzinc **139b** was used, the reaction proceeded fast but unfortunately only reduced α-aminophosphonate **91a** was observed (Table 15, entry 1). Switching to dimethylzinc **139a** as the metal source, only the addition product of the organozinc reagent was found instead of the reduction one, and no Reformatsky product could be observed in the reaction media (Table 15, entry 2). In some of the previous researches on dialkylzinc reagents **139** mediated Reformatsky reaction, the presence of oxygen in the reaction media was proposed as crucial factor in the reaction performance.[111, 113, 116] For this reason, the use of dry air atmosphere instead of nitrogen was considerated. Unluckily, the same result than with inert atmosphere (Table 15, entry 1) was obtained when diethylzinc **139b** was used (Table 15, entry 3), but when dimethylzinc **139a** was tested in these new conditions, the formation of aza-Reformatsky product **145a** was mainly observed together with a 10% of 1,2-addition product **132** (Table 15, entry 4). Although the same ratio **145a:132** was obtained when the reaction was performed in low polar or strong polar solvents

such as toluene or *N*,*N*-dimethylformamide, respectively (Table 15, entries 5-6), the amount of Reformatsky product **145a** could be increased using tetrahydrofuran or acetonitrile as solvents (Table 15, entries 7-8).

Table 15. Optimization of the reaction conditions.



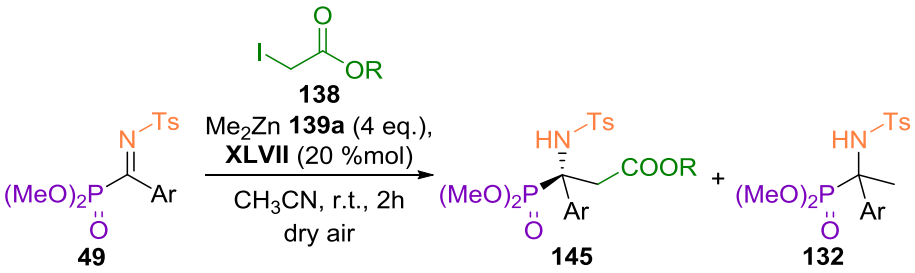
Entry	Solvent	ZnR_2	L	L Loading (%)	145a/132/91a ratio	ee (%)
1	CH_2Cl_2	**139b**	**XLV**	20	0/0/100	-
2	CH_2Cl_2	**139a**	**XLV**	20	0/100/0	-
3[a]	CH_2Cl_2	**139b**	**XLV**	20	0/0/100	-
4[a]	CH_2Cl_2	**139a**	**XLV**	20	90/10/0	-
5[a]	Toluene	**139a**	**XLV**	20	90/10/0	-
6[a]	DMF	**139a**	**XLV**	20	90/10/0	-
7[a]	THF	**139a**	**XLV**	20	95/5/0	-
8[a]	CH_3CN	**139a**	**XLV**	20	97/3/0	-
9[a]	CH_3CN	**139a**	**XLVI**	20	97/3/0	64
10[a]	CH_3CN	**139a**	**XLVII**	20	97/3/0	99
11[a]	CH_3CN	**139a**	**XLVIII**	20	97/3/0	38
12[a]	CH_3CN	**139a**	**XLIX**	20	97/3/0	97
13[a]	CH_3CN	**139a**	**XLVII**	15	97/3/0	78
14[a]	CH_3CN	**139a**	**XLVII**	10	97/3/0	19

[a] Dry air atmosphere was tested instead of N_2.

Next, we tested enantiopure (*R*)-BINOL (**XLVI**) as chiral ligand, under the optimal reaction conditions, but only modest enantioselectivity was obtained (Table 15, entry 9). To our delight, when anthracenyl substituted BINOL ligand **XLVII** was used in the same conditions, very high enantioselectivity was observed (Table 15, entry 10). Surprisingly, the use of (*S*)-VAPOL (**XLVIII**) resulted in decreased enantiomeric excess compared to simple (*R*)-BINOL (**XLVI**) (Table 15, entry 11). Finally, we also tested β-amino alcohol derivative **XLIX**, that showed very good enantioselection as well (Table 15, entry 12). Unfortunately, when lower catalyst loading were used a drastic decrease on enantioselectivities were observed (Table 15, entries 13, 14).

With the optimal reaction conditions in our hands, then we extended the scope of the enantioselective aza-Reformatsky reaction to differently substituted α-ketiminophosphonates **49** (Table 16). Good yields and excellent enantiomeric excesses were obtained in all the cases. The reaction tolerates the presence of *para* and *meta* alkyl substituents at the aromatic ring (Table 16, entries 2, 3) as well as strong electron donating groups at the *para* position of the aromatic imine (Table 16, entry 4).

Table 16. Scope of the enantioselective aza-Reformatsky reaction.



Entry	Comp.	Ar	R	Yield (%)	145/132 ratio	ee 145 (%)
1	**145a**	Ph	Et	91	97/3	99
2	**145b**	4-Me-C_6H_4	Et	86	99/1	94
3	**145c**	3-Me-C_6H_4	Et	91	>99/<1	93
4	**145d**	4-$SCCl_3$-C_6H_4	Et	87	98/2	95
5	**145e**	4-F-C_6H_4	Et	89	97/3	93
6	**145f**	4-Cl-C_6H_4	Et	88	97/3	>99
7	**145g**	4-Br-C_6H_4	Et	91	>99/<1	>99
8	**145h**	3-F-C_6H_4	Et	89	99/1	>99
9	**145i**	3-Cl-C_6H_4	Et	90	97/3	93
10	**145j**	2-F-C_6H_4	Et	93	>99/<1	>99
11	**145k**	3,4-Cl_2-C_6H_3	Et	86	98/2	99
12	**145l**	3,4-F_2-C_6H_3	Et	91	98/2	99
13	**145m**	2,4-F_2-C_6H_3	Et	93	>99/<1	94
14	**145n**	C_6F_5	Et	92	>99/<1	98
15	**145o**	3-Cl-4-MeO-C_6H_3	Et	81	>99/<1	97
16	**145p**	4-NO_2-C_6H_4	Et	85	97/3	99
17	**145q**	4-CF_3-C_6H_4	Et	87	98/2	93
18	**145r**	4-biphenyl	Et	90	>99/<1	99
19	**145s**	5-Cl-2-thienyl	Et	82	98/2	98
20	**145t**	Ph	Bn	92	97/3	96

Several halogen substituted aromatic ketimines were also successfully used in the reaction, including *para* substituted aromatic rings containing fluorine, chlorine or bromine (Table 16, entries 5-7), *meta* substituted aromatic rings holding fluorine and chlorine (Table 16, entries 8, 9) as well as *ortho*-fluorophenyl substituted ketimines (Table 16, entry 10). Moreover, dichloro- and difluoro-phenyl substituted imines showed excellent enantioselectivities (Table 16, entries 11-13) and even perfluorophenyl substituted substrates were tested with success using the catalytic system (Table 16, entry 14). Furthermore, an excellent result was observed for imine holding an aromatic ring that is disubstituted with chlorine and a strong electron donating methoxy group (Table 16, entry 15). Besides, good reactivity and excellent enantioselectivity is also obtained using aromatic imines substituted with electron withdrawing groups such as *p*-nitro or *p*-trifluoromethyl substituents (Table 16, entries 16, 17). The reaction can be also extended to the use of imines holding biphenyl or heteroaromatic substituents (Table 16, entries 18, 19). In addition, in order to further deprotect selectively the ester group, benzyl iodoacetate was used as substrate in the aza-Reformatsky reaction with our α-iminophosphonate substrates, again with an excellent result (Table 16, entry 20).

All of these Reformatsky products were fully characterized by NMR, IR and HRMS. α-Aminophosphonate **145o** is selected as example (Figure 35). The most characteristic signals of **145o** in the ^{1}H-NMR

spectrum are two doublets at δ = 3.55 and δ = 3.52 ppm, corresponding to the methoxy groups of the phosphonate ester that show a P-H coupling with phosphorus atom with a coupling constant of $^{3}J_{PH}$ = 10.7 Hz. The fact that these signals appears as two doublets instead of one make evident the presence of a chiral stereocenter in the molecule due to the diastereotopic character of methoxy groups (Figure 34).

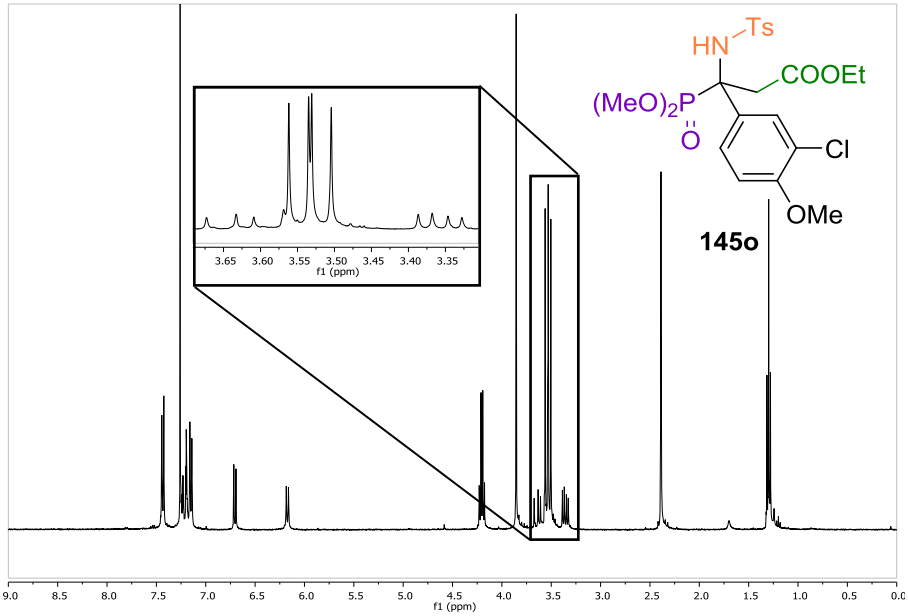


Figure 34. ^{1}H-NMR spectra of compound **145o**.

Because of the proximity to the stereocenter, the protons of the methylene group are also diastereotopic and are shown as two doublet doublets at δ = 3.62 and δ = 3.36 ppm. The multiplicity of the signals can be explained because of the coupling with the geminal proton with a coupling constant of $^{2}J_{HH}$ = 16.1 Hz, along with different

couplings constants of $^{3}J_{PH}$ = 7.5 Hz and $^{3}J_{PH}$ = 25.7 Hz with the phosphorus atom.

With respect to the ^{13}C-NMR spectrum, most of the signals between one to five bonds distance to the phosphorus atom are coupled to it with variable constants depending on the number of bonds of each carbon to the phosphorus atom (Figure 35). The signal of the stereogenic carbon at one bond distance to the phosphorus appears at δ = 61.3 ppm as a doublet with a coupling constant of $^{1}J_{PC}$ = 155.4 Hz. Here again, the methoxy groups of the phosphonate ester are shown as two different doublets at δ = 54.7 and 54.3 ppm because of their diastereotopic character and display coupling constants of $^{2}J_{PC}$ = 7.3 and 7.7 Hz respectively.

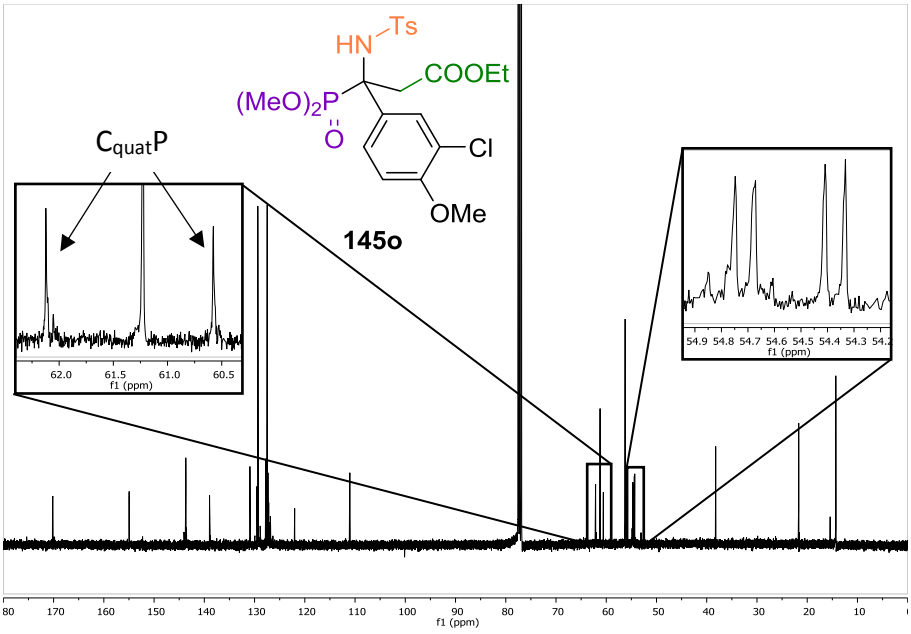
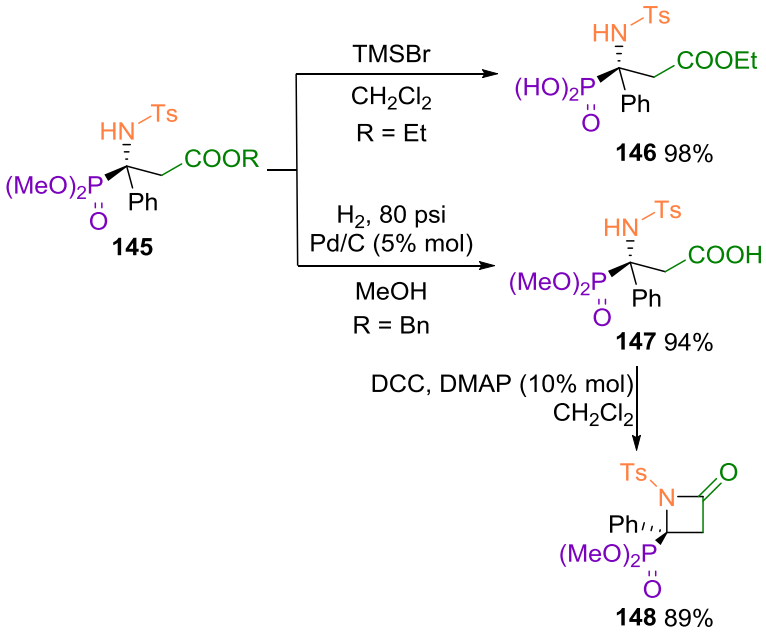


Figure 35. ^{13}C-NMR spectra of compound **145o**.

Next, with the purpose of illustrating the applications of these enantioenriched Reformatsky substrates, some transformations of the α-aminophosphonate derivatives were performed. For instance selective deprotection of the phosphonate group of **145a** can be easily accomplished in a few hours in the presence of trimethylsilyl bromide, to afford α-aminophosphonic acid derivative **146** in very good yield (Scheme 42).



Scheme 42. Synthetic applications of Reformatsky products **145**.

For the selective deprotection of the ester group, we chose benzyl ester **145t** as substrate. A vigorous stirring of this compound under hydrogen atmosphere in the presence of a catalytic amount of palladium yielded the expected phosphorylated β-amino acid

derivative **147** in excellent yield. In addition, the activation of carboxylic group in **147** with *N*, *N*-dicyclohexylcarbodiimide in the presence of 4-dimethyaminopyridine led to the formation of phosphorated β-lactam derivative **148** bearing a tetrasubstituted stereocenter.

Once the scope of the reaction was completed, the synthetic potential of our asymmetric methodology was evaluated. For this purpose, a multi-gram scale reaction for the synthesis of the model α-aminophosphonate **145a** was performed. Thus, 1.0 grams of ketimine **49a** reacted with benzyl iodoacetate in the presence of 20 mol % of BINOL ligand **XLVII** to afford 1.2 g of the aza-Reformatsky product **145t** in 84% yield and 86 % ee.

In order to determine the absolute configuration of the stereogenic carbon of the major enantiomer in our substrates, next, using enantioenriched compound **145t**, substancial amount of enantiopure β-lactam **148** was prepared using the previously described synthetic route (Scheme 42). The X-Ray diffraction analysis provided unequivocally the structure and an absolute *S* configuration for the stereogenic carbon (Figure 36). The absolute configuration of other products **145-147** was assumed by analogy.

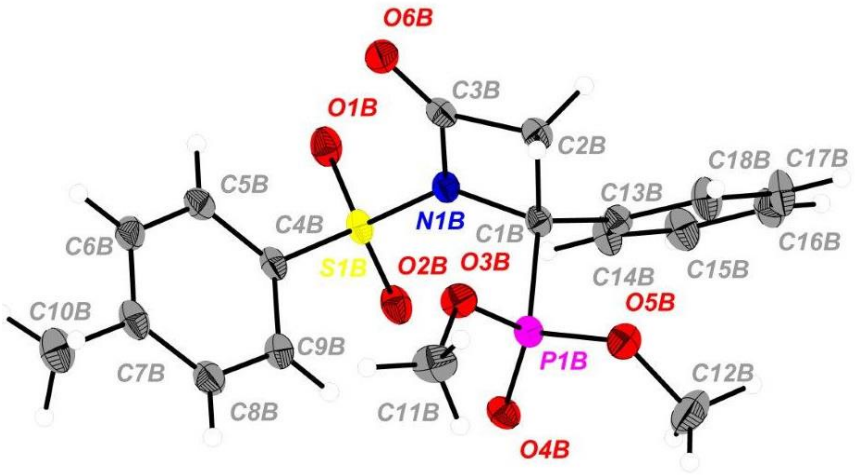
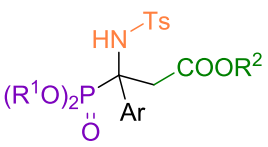


Figure 36. X-Ray diffraction structure of β-lactam **148.**

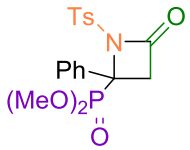
Since some α-aminophosphonic acid derivatives have proved to be effective as anticancer agents,[7] and having all of these new α-aminophosphonates in hand, the *in vitro* cytotoxicity of phosphorated aspartic acid derivatives **145-147** was evaluated by testing their antiproliferative activities against two human cancer cell lines: A549 (human alveolar basal epithelial carcinoma) and SKOV03 (human ovarian carcinoma). Cell proliferation inhibitory activities of aza-Reformatksy products **145** and their derivatives **146-148** are shown as IC_{50} values (Table 17). Remarkably, the model α-aminophosphonate **145a** bearing a simple phenyl group (Table 17, entry 1) showed cytotoxic activity against A549 cell line, with an IC_{50} of 2,66±0,26 μM but no antiproliferative effect was found for SKOV03 cancer cell line.

Regarding the effect of some substituents at the aromatic ring on the activity against lung cell line, it was observed that the presence of lipophilic fluorinated group in **145e** results in lower toxicity against A549 cell line with an IC_{50} value of 7,15±0,24 μM (Table 17, entry 2), while disubstituted 3-chloro-4-methoxyphenyl group in the structure of α-aminophosphonate **145o** displays an increased cytotoxicity with an IC_{50} value of 1,44±0,15 μM (Table 17, entry 3).

Table 17. Antiproliferative activity of compounds **145-148** against lung and ovarian cancer cell lines.



145-147



148

Entry	Comp.	R^1	R^2	Ar	IC_{50} lung (μM)[a] (A549)	IC_{50} ovarian (μM)[a] (SKOV03)
1	**145a**	Me	Et	Ph	2,66±0,26	>50
2	**145e**	Me	Et	4-F-C_6H_4	7,15±0,24	>50
3	**145o**	Me	Et	3-Cl-4-MeO -C_6H_3	1,44±0,15	>50
4	**145q**	Me	Et	4-CF_3- C_6H_4	20,3±1,14	9,8±0,60
5	**146**	H	Et	Ph	20,25±1,79	>50
6	**147**	Me	H	Ph	20,61±1,05	>50
7	**148**	-	-	-	>50	>50

[a] Concentration corresponding to 50% growth inhibition.

Moreover, these substrates **145e** and **145o** did not show antiproliferative activity against SKOV03 line (Table 17, entries 2, 3).

Trifluoromethyl substituted α-aminophosphonate **145q** exhibits lower cytotoxicity against A549 cell line than compounds **145a,e,o** with an IC_{50} value of 20,3±1,14 μM but, surprisingly, shows a moderate antiproliferative activity against SKOV03 cell line with an IC_{50} value of 9,8±0,60 μM (Table 17, entry 4).

Deprotection of either, phosphonate or ester groups results in an important decrease on the cytotoxic activity against A549 cancer cell line and IC_{50} values of 20,25±1,79 and 20,61±1,05 μM are shown for compounds **146** and **147** respectively (Table 17, entries 5, 6). Moreover, no cytotoxic effect was observed for both compounds against SKOV03 cell line. Finally, β-lactam **148** was found to be non-cytotoxic against both cancer cell lines (Table 17, entry 7).

In summary, we report here the first example of an enantioselective aza-Reformatsky reaction using acyclic ketimines as electrophile substrates. Phosphorated analogs of aspartic acid holding tetrasubstituted carbons, are efficiently obtained with excellent enantioselectivity using α-ketiminophosphonates with a simply functionalized BINOL ligand as the chiral inductor. In addition, besides that phosphorus-containing enantiopure tetrasubstituted β-lactams have not been reported so far, we describe here the first asymmetric synthesis of phosphorylated β-lactams using a catalytic approach. Finally, promising results of these compounds as selective antiproliferative agents for lung cancer cells are also presented.

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Conclusions

A wide range of α-iminophosphonate substrates can be effectively prepared by formal oxidation of the corresponding α-aminophosphonates. These imines show an assorted reactivity towards nucleophiles.

α-Phosphorylated aldimines have demonstrated to be useful intermediates for the selective synthesis of phosphorus containing indoles and bisindoles, depending on the protecting group of the imine. The use of amides (PG = Bz) and carbamates (PG = Troc) as protecting group of the imine affords indolyl phosphoglycines while bulkier groups like amines (PG = Trt) or sulfonamides (PG= Ts) yield bisindole products.

An organocatalytic asymmetric version of Friedel-Crafts reaction is successfully achieved using amides (PG = Bz) as protecting groups and substituted BINOL phosphoric acid derivatives as catalyst, obtaining enantiomeric excesses from 68 to 82 %. In addition, an alternative synthetic route to obtain these enantioenriched indolyl phosphoglycines can also be used, through an efficient diastereoselective methodology, thus allowing the determination of the absolute configuration of indolyl phosphoglycines.

A wide range of bis(3-indolyl)methane phosphonates can be prepared using a bulky amine (PG = Trt) as protecting group of the imine in the Friedel-Crafts reaction. These compounds have demonstrated to be highly active and selective against lung and ovarian cancer cells with respect to non malignant cell lines, showing IC_{50} values up to 0.06 μM for both tested cell lines.

α-Phosphorylated ketimines can be successfully used for the addition of organometallic alkyl chains, effectively avoiding the β-hydride elimination by using organozinc bromides as nucleophiles. Even though the reaction mostly yields the desired addition product, the obtained enantioselectivities are very low.

The aza-Reformatsky reaction of acyclic ketimines has proved to be useful for the preparation of phosphorated analogs of aspartic acid holding chiral tetrasubstituted carbons. The use of dimethylzinc as catalyst and dry air instead of inert atmosphere have demonstrated to be crucial in order to obtain the desired products. In addition, the enantioselective version of this reaction is achieved using BINOL derivatives as chiral ligands, allowing to obtain enantioselectivities up to 99 %. In addition, preliminary results indicate that these compounds have promising antiproliferative effect against lung cancer cell lines.

Se han preparado una gran variedad de α-iminofosfonatos de forma eficiente mediante oxidación formal de los correspondientes α-aminofosfonatos. Estas iminas han mostrado tener reactividad variada frente a nucleófilos.

Las aldiminas α-fosforadas han demostrado ser intermedios útiles para la preparación selectiva de indoles y bisindoles fosforados en función del grupo protector utilizado en la imina. El uso de amidas (GP = Bz) y carbamatos (GP = Troc) como grupos protectores de las iminas permite obtener indolil fosfoglicinas, mientras que grupos más voluminosos como aminas (GP = Trt) o sulfonamidas (GP = Ts) dan lugar a bisindoles fosforados.

Se ha logrado llevar a cabo la version organoctalitica asimétrica de la reacción de Friedel-Crafts utilizando amidas (GP = Bz) como grupos protectores y ácidos fosfóricos quirales derivados de BINOL como catalizadores, permitiendo obtener excesos enantioméricos de 68 a 82 %. Además, utilizando una metodología diastereoselectiva altamente eficiente, se ha desarrollado una ruta alternativa para la preparación de estas indolil fosfoglicinas enantioenriquecidas que ha permitido determinar la configuración absoluta de las mismas.

Se han preparado una amplia variedad de bis indole fosforados utilizando una amina voluminosa (GP = Trt) como grupo protector de

la imina en la reacción de Friedel-Crafts. Estos compuestos han demostrado ser altamente activos y selectivos frente a células cancerosas de pulmón y ovario en comparación con líneas celulares no malignas, mostrando valores de IC_{50} de hasta 0.06 μM para las líneas celulares utilizadas.

Las cetiminas α-fosforadas han sido empleadas con éxito como electrófilos en la adicción de reactivos organometálicos alifáticos, logrando evitar la eliminación del hidrógeno en la posición β cuando se utilizan bromuros de alquilzinc como nucleófilos. A pesar de que la reacción da lugar al producto deseado, la enantioselectividad del proceso es muy limitada.

La reacción aza-Reformatsky sobre cetiminas fosforadas acíclicas ha demostrado ser útil para la preparación de derivados fosforados de ácido aspártico con un carbono tetrasustituido en su estructura. El uso de dimetilzinc como catalizador y aire seco en lugar de atmósfera interte han demostrado ser cruciales para la obtención de los productos deseados. Además, la versión enantioselectiva de esta reacción se ha llevado a cabo con éxito utilizando derivados de BINOL como ligandos quirales, permitiendo obtener excesos enantioméricos superiores al 99 %. Además, los resultados preliminares parecen indicar que estos compuestos tienen actividades antiproliferativas prometedoras frente a lineas celulares cancerosas de pulmón.

Experimental section

General methods and materials

NMR: ^{1}H (300 MHz), ^{13}C (75 MHz), ^{31}P NMR (120 MHz) and ^{19}F NMR (282 MHz) spectra were performed using a Varian Unity Plus spectrometer. ^{1}H (400 MHz), and ^{13}C (100 MHz) spectra were performed using a Bruker Avance 400 spectrometer. The most commonly used solvent was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in δ (ppm) relative to residual peak of the solvent for ^{1}H (δ = 7.26 ppm) and ^{13}C NMR (δ = 77.16 ppm) spectra, to an external reference of phosphoric acid (50 %) (δ = 0.0 ppm) for ^{31}P NMR spectra and to an external reference of $CFCl_3$ for ^{19}F NMR (δ = 0.0 ppm). ^{13}C NMR peak assignments were supported by DEPT. Coupling constants *(J)* are reported in Hertz. The multiplicity of each signal is represented by **s** (singlet), **d** (doublet), **dd** (double doblet), **t** (triplet), **q** (quartet) and **m** (multiplet).

IR: The spectra were registered using a Nicolet iS10 spectrophotometer from Thermo Scientific, working with the Smart iTR accessory and reporting the value of the peak in cm^{-1}. IR spectra were taken as neat solids or oils.

HRMS: The spectra were obtained by positive-ion electrospray ionization (ESI) using a LC-QTOF method.

Mp: Melting points were determined in digital measurement devices Büchi MPB-540 in opened capillary tubes.

Chromatography: Some reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F254 plates and visualized under ultraviolet light (λ = 254 nm). In addition, TLC plates were also visualized by heating them after contact with a solution prepared with potassium permanganate (3 g), potassium carbonate (20 g) and 5% sodium hydroxide aqueous solution (5 mL) in 300 mL of water. Column flash chromatography was used, utilizing silica gel (60 Å, 230-400 mesh ASTM) and adequate proportions of different solvents as eluents. In addition, CombiFlash (Teledyne Isco) chromatography was used for the purification of some compounds.

HPLC: In order to determine the enantiomeric excesses, HPLC Agilent 1100/1200 Series system was used, with a chiracel IA, chiracel IB and chiracel IC columns as stationary phase.

X-Ray diffraction analysis: The X-ray diffraction analysis experiments were conducted using difractometers for monocrystals.

Reagents and solvents: Reagents were purchased from different commercial suppliers (Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

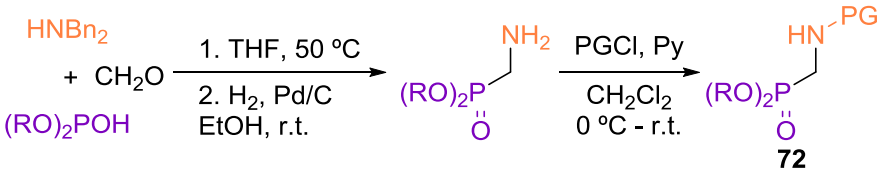
Solvents for extraction, chromatography and crystallization were technical grade. All solvents used in reactions were treated with dry molecular sieves as specified in the literature.[117]

Dimethylformamide (DMF) was treated with P_2O_5, stirred overnight and distilled before use. Et_3N and pyridine where dried with $CaCl_2$ and distilled before use. TsCl was purified by recrystallization in hexanes.

Chapter 1. Synthesis of α-iminophosphonates

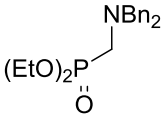
Synthesis of aldimines 71

General procedure for the synthesis of di-alkyl α-aminophosphonates 72 (Route A).



Step 1: Kabachnik-Fields reaction. Following a modified literature procedure,[75] a solution of di-alkyl phosphite (250.0 mmol), dibenzylamine (38.5 mL, 200.0 mmol) and 37 % aqueous formaldehyde (19.5 mL, 240.0 mol) in THF (100 mL) was stirred for 1 h at room temperature. The reaction was then heated at 50 °C overnight. The resulting solution was concentrated under reduced pressure and the crude residue was dissolved in hexanes (300 mL), washed with water (3 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated under vacuum to afford the desired product.

Diethyl (dibenzylaminomethyl)phosphonate.[75]

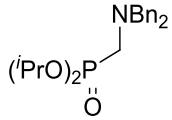


The general procedure was used affording 69.5 g (99 %) of pure diethyl (dibenzylaminomethyl)phosphonate as colorless oil.

^{1}H NMR and **^{13}C NMR** spectra data match the data reported in the literature.[75]

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.7 ppm.

Diisopropyl (dibenzylaminomethyl)phosphonate.



The general procedure was used affording 74.3 g (99 %) of pure diisopropyl (dibenzylaminomethyl)phosphonate as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, $^{3}J_{HH}$ = 8.0 Hz, 4H, 4xCH_{Ar}), 7.30 (t, $^{3}J_{HH}$ = 7.6 Hz, 4H, 4xCH_{Ar}), 7.21 (t, $^{3}J_{HH}$ = 7.6 Hz, 2H, 2xCH_{Ar}), 4.93–4.48 (m, 2H, 2xCH), 3.81 (s, 4H, 2xCH_2Ph), 2.86 (d, $^{2}J_{PH}$ = 10.5 Hz, 2H, CH_2P), 1.31 (t, $^{3}J_{HH}$ = 5.7 Hz, 12H, 4xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.8 (2x$C_{quat}CH_2$), 129.1 (4xC_{Ar}), 128.2 (4xC_{Ar}), 127.0 (2xC_{Ar}), 70.2 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH), 59.2 (d, $^{3}J_{PC}$ = 8.3 Hz, 2xCH_2Ph), 49.7 (d, $^{1}J_{PC}$ = 159.4 Hz, CH_2P), 24.2 (d, $^{3}J_{PC}$ = 3.3 Hz, 2xCH_3). 24.1 (d, $^{3}J_{PC}$ = 4.5 Hz, 2xCH_3) ppm.

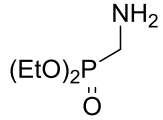
^{31}P NMR (120 MHz, $CDCl_3$) δ 24.9 ppm.

IR ν 1450 (CH_2), 1251 (P=O), 1220 (P-O-C), 1049 (P-O-C) cm^{-1}.

ESI-HRMS (Q-TOF) m/z: calcd. for $C_{21}H_{31}NO_3P$ $[M+H]^+$ 376.2036, Found 376.2042.

Step 2: Double debenzylation. Following a modified literature procedure, [75] a mixture of di-alkyl dibenzylaminomethylphosphonate (200.0 mmol), 37% aqueous hydrochloric acid (19.7 mL, 200.0 mmol) and 10% palladium on carbon (10.6 g, 10.0 mmol Pd) in ethanol (300 mL) was stirred for 6 hours under hydrogen pressure at 80 psi. A solution of NaOH 2M (100 mL, 200.0 mmol) was added, and the reaction mixture was filtered through celite. The volatiles were distilled off at reduced pressure, and the residue was dissolved in diethyl ether. The resulting solution was dried over $MgSO_4$ and concentrated at reduced pressure to afford the corresponding aminophosphonate.

Diethyl (aminomethyl)phosphonate.[118]

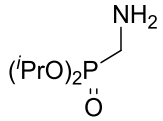


The general procedure was used affording 31.1 g (93 %) of diethyl aminomethylphosphonate as yellow oil.

^{1}H NMR and **^{13}C NMR** spectra data match the data reported in the literature.[118]

^{31}P NMR (120 MHz, $CDCl_3$) δ 27.4 ppm.

Diisopropyl (aminomethyl)phosphonate.



The general procedure was used affording 35.1 g (90 %) of diisopropyl aminomethylphosphonate as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (m, 2H, 2xCH), 2.91 (d, $^{3}J_{HH}$ = 10.1 Hz, 2H, CH_2P), 1.67 (broad s, 2H, NH_2), 1.30 (d, $^{3}J_{HH}$ = 6.2 Hz, 12H, 4xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) 70.3 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH), 38.6 (d, $^{1}J_{PC}$ = 149.3 Hz, CH), 23.9 (d, $^{3}J_{PC}$ = 4.2 Hz, 2xCH_3), 23.8 (d, $^{3}J_{PC}$ = 3.5 Hz, 2x CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.8 ppm.

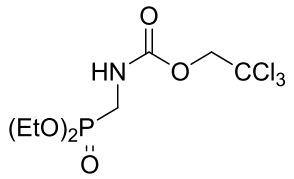
IR ν 3436, 3398 (N-H), 1243 (P=O), 1160 (P-O-C), 1045 (P-O-C) cm^{-1}.

ESI-HRMS (Q-TOF) m/z: calcd. for $C_7H_{18}NO_3P$ $[M+H]^+$ 196.1097; found 196.1094.

Step 3: Protection of amino group. Pyridine (3.6 mL, 44.0 mmol) was added to a solution di-alkyl aminomethylphosphonate (40.0 mmol) in CH_2Cl_2 (80 mL) at room temperature. The solution was cooled to 0°C and the corresponding chloride (44.0 mmol) was slowly added. The reaction was stirred at room temperature for 2h and was then washed with a 1M aqueous solution of HCl (2×30 mL). The combined organic layers were dried over $MgSO_4$ and volatiles were

distilled off at reduced pressure to yield the crude product, which was purified by crystallization.

2,2,2-Trichloroethyl ((diethoxyphosphoryl)methyl)carbamate (72a).



The general procedure was followed, affording 8.7 g (64 %) of **72a** as white solid after crystallization in Et_2O-pentane.

Mp: 62-63 ℃ (Et_2O-pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 1H, 1H, NH), 4.74 (s, 2H, CH_2CCl_3), 4.16 (m, 4H, 2x$C\underline{H}_2CH_3$), 3.65 (dd, $^2J_{PH}$ = 11.6 Hz, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2P), 1.34 (t, $^3J_{HH}$ = 7.0 Hz, 6H, 2x$C\underline{H}_3$) ppm.

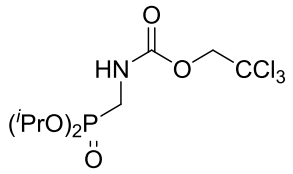
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.67 (d, $^3J_{PC}$ = 6.9 Hz, CO), 95.41 (CCl_3), 74.96 ($\underline{C}H_2CCl_3$), 62.90 (d, $^2J_{PC}$ = 6.6 Hz, 2x$\underline{C}H_2CH_3$), 36.99 (d, $^1J_{PC}$ = 158.1 Hz, CH_2P), 16.55 (d, $^3J_{PC}$ = 5.8 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.0 ppm.

IR ν 3224 (N-H), 1729 (C=O), 1264 (P=O), 1049 (P-O-C), 1027 (P-O-C) (cm^{-1}).

ESI-HRMS (Q-TOF) m/z: calcd. for $C_8H_{16}Cl_3NO_5P$ $[M+H]^+$ 341.9825; found 371.9831.

2,2,2-Trichloroethyl ((diisopropyloxyphosphoryl)methyl)carbamate (72b).



The general procedure was followed, affording 9.3 g (63 %) of **72b** as a white solid after crystallization in Et_2O-pentane.

Mp: 72-75 ℃ (Et_2O-pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (broad s, 1H, NH), 4.72 (s, 2H, CH_2CCl_3), 4.71 (m, 2H, 2xCH), 3.57 (dd, $^2J_{PH}$ = 11.9 Hz, $^3J_{HH}$ = 5.9 Hz, 2H, CH_2P), 1.30 (t, $^3J_{HH}$ = 6.0 Hz, 12H, 4xCH_3) ppm.

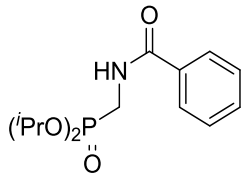
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) 154.7 (d, $^3J_{PC}$ = 7.9 Hz, CO), 95.4 (CCl_3), 74.9 ($\underline{C}H_2CCl_3$), 71.7 (d, $^2J_{PC}$ = 6.8 Hz, CH), 38.0 (d, $^1J_{PC}$ = 159.5 Hz, CH_2P), 24.1 (d, $^3J_{PC}$ = 3.9 Hz, 2xCH_3), 24.0 (d, $^3J_{PC}$ = 4.7 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 20.8 ppm.

IR ν 3391 (N-H), 1714 (C=O), 1213 (P=O), 1018 (P-O-C), 1005 (P-O-C) (cm^{-1}).

ESI-HRMS (Q-TOF) m/z: calcd. for $C_{10}H_{20}Cl_3NO_5P$ $[M+H]^+$ 370.0139; Found 370.0147.

Diisopropyl (benzamidomethyl)phosphonate (72c).



The general procedure was followed, affording 7.7 g (64 %) of **72c** as a white solid after crystallization in AcOEt-hexanes.

Mp: 87-89 ℃ (AcOEt-hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar}), 7.55 – 7.40 (m, 3H, 3xCH_{Ar}), 6.53 (broad s, 1H, NH), 4.72 (m, 2H, 2xCH), 3.88 (dd, $^{2}J_{PH}$ = 13.2 Hz, $^{3}J_{HH}$ = 5.7 Hz, 2H, CH_2P), 1.34 (t, $^{3}J_{HH}$ = 6.7 Hz, 12H, 4xCH_3) ppm.

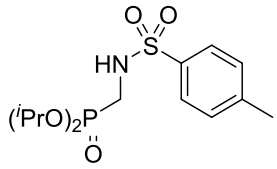
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.4 (d, $^{3}J_{CP}$ = 6.7 Hz, CO), 134.1 ($C_{quat}CO$), 131.9 (C_{Ar}), 128.8 (2xC_{Ar}), 127.1 (2xC_{Ar}), 71.7 (d, $^{2}J_{PC}$ = 6.7 Hz, 2xCH), 36.4 (d, $^{1}J_{PC}$ = 157.5 Hz, CH_2P), 24.2 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xCH_3), 24.1 (d, $^{3}J_{PC}$ = 6.5 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3279 (N-H), 1753 (C=O), 1245 (P=O), 1197 (P-O-C), 1102 (P-O-C) cm^{-1}.

ESI-HRMS (Q-TOF) m/z: calcd. for $C_{14}H_{22}NO_4PNa$ $[M+Na]^+$ 322.1179; found 322.1191.

Diisopropyl (((4-methylphenyl)sulfonamido)methyl)phosphonate (72d).



The general procedure was followed, affording 9.9 g (71 %) of **72d** as a yellow solid after crystallization in Et_2O-pentane.

Mp: 99-100 °C (Et_2O-pentane).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.73 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 7.32 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 4.84 (dd, $^3J_{PH}$ = 11.4 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, NH), 4.71 (m, 2H, 2xCH), δ 3.17 (dd, $^2J_{PH}$ = 14.3 Hz, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2P), 2.43 (s, 3H, CH_3 Ts), 1.31 (t, 12H, 4xCH_3) ppm.

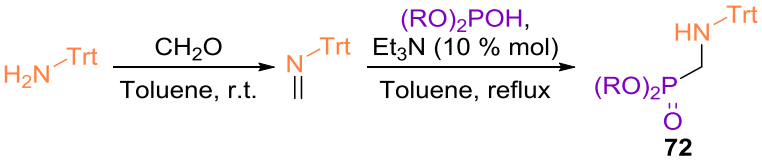
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.9 ($C_{quat}CH_3$ Ts), 135.5 (C_{quat}S Ts), 129.8 (2xCH_{Ar}), 127.3 (2xCH_{Ar}), 71.9 (d, $^2J_{PC}$ = 6.7 Hz, 2xCH), 39.30 (d, $^1J_{PC}$ = 158.2 Hz, CH_2P), 23.9 (d, $^3J_{PC}$ = 4.0 Hz, 2xCH_3), 23.8 (d, $^3J_{PC}$ = 4.8 Hz, 2xCH_3), 21.5 (CH_3 Ts) ppm.

^{31}P RMN (120 MHz, $CDCl_3$) δ 19.9 ppm.

IR ν 339 (N-H), 1704 (O=S=O), 1243 (P=O), 1160 (P-O-C), 1045 (P-O-C) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{14}H_{24}NO_5PSNa$ $[M+Na]^+$ 372.1005, found 372.1012.

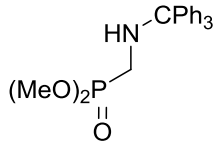
General procedure for the synthesis of di-alkyl α-aminophosphonates 72 (Route B).



72

According to previously described procedure,[76] 37 % aqueous formaldehyde (0.8 mL, 10.0 mmol) was added to a solution of tritylamine (1.3 g, 5.0 mmol) in toluene (20 mL) and the reaction mixture was stirred for 20 h at room temperature. Then, water was removed using a Dean-Stark and the corresponding hydrogen phosphate (6 mmol) and triethylamine (69.6 µL, 0.5 mmol) were added. The reaction was stirred under reflux in toluene overnight and the volatiles were distilled off at reduced pressure to yield the crude product as clear liquid, which was crystallized from toluene-pentane**.**

Dimethyl ((tritylamino)methyl)phosphonate (72e).[76]



The general procedure was followed, affording 1.8 g (95 %) of **72e** as a white solid. No reliable HRMS was obtained.

Mp: 200-204 °C (Toluene-pentane). Lit.[76] 210-211 °C ($CHCl_3$-MeOH).

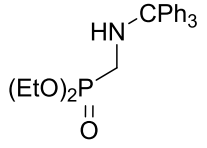
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $^3J_{HH}$ = 7.7 Hz, 6H, 6xCH_{Ar} *o*-Ph), 7.30 (m, 6H, 6xCH_{Ar} *m*-Ph), 7.22 (m, 3H, 3xCH_{Ar} *p*-Ph), 3.83 (d, $^3J_{PH}$ = 10.7 Hz, 6H, 2xCH_3O), 2.54 (d, $^2J_{PH}$ = 13.9 Hz, 2H, CH_2P), 2.05 (broad s, 1H, NH) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.8 (3xC_{quat} Ph), 128.6 (6xC_{Ar}), 128.2 (6xC_{Ar}), 126.7 (3xC_{Ar}), 71.6 (d, $^3J_{PC}$ = 19.1 Hz, CPh_3), 53.1 (d, $^2J_{PC}$ = 6.6 Hz, 2xCH_3), 39.3 (d, $^1J_{PC}$ = 160.1 Hz, CH_2P) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 30.9 ppm.

IR ν 3309 (N-H), 1267 (P=O), 1191 (P-O-C), 1096 (P-O-C) cm^{-1}.

Diethyl ((tritylamino)methyl)phosphonate (72f).[76]



The general procedure was followed, affording 1.9 g (92 %) of **72f** as a white solid. No reliable HRMS was obtained.

Mp: 116-117 °C (Toluene-pentane). Lit.[76] 115-117 °C ($CHCl_3$-MeOH).

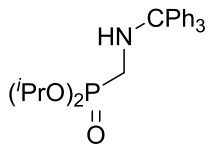
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, $^{3}J_{HH}$ = 8.0 Hz, 6H, 6xCH_{Ar} *o*-Ph), 7.30 (m, 6H, 6xCH_{Ar} *m*-Ph), 7.21 (m, 3H, 3xCH_{Ar} *p*-Ph), 4.22 (m, 4H, 2x$\underline{C}H_2CH_3$), 2.52 (d, $^{2}J_{PH}$ = 13.8 Hz, 2H, CH_2P), 2.04 (broad s, 1H, NH), 1.38 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, 2xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.0 (3xC_{quat} Ph), 128.7 (6xC_{Ar}), 128.1 (6xC_{Ar}), 126.7 (3xC_{Ar}), 71.5 (d, $^{3}J_{PC}$ = 19.1 Hz, CPh_3), 62.3 (d, $^{2}J_{PC}$ = 6.6 Hz, 2x$\underline{C}H_2CH_3$), 39.9 (d, $^{1}J_{PC}$ = 160.2 Hz, CH_2P), 16.7 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 28.4 ppm.

IR ν 3315 (N-H), 1262 (P=O), 1185 (P-O-C), 1089 (P-O-C) cm^{-1}.

Diisopropyl ((tritylamino)methyl)phosphonate (72g).



The general procedure was followed, affording 2.0 g (91 %) of **72g** as a white solid. No reliable HRMS was obtained.

Mp: 74-76 ℃ (Toluene-pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, $^{3}J_{HH}$ = 7.6 Hz, 6H, 6xCH_{Ar} *o*-Ph), 7.32 (m, 6H, 6xCH_{Ar} *m*-Ph), 7.21 (m, 3H, 3xCH_{Ar} *p*-Ph), 4.78 (m, 2H, 2xCH), 2.46 (d, $^{2}J_{PH}$ = 14.0 Hz, 2H, CH_2P), 2.06 (broad s, 1H, NH), 1.37 (d, $^{3}J_{HH}$ = 6.2 Hz, 12H, 4xCH_3) ppm.

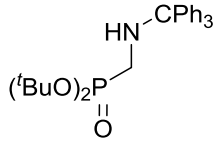
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.1 (3xC_{quat} Ph), 128.7 (6xC_{Ar}), 128.1 (6xC_{Ar}), 126.6 (3xC_{Ar}), 71.5 (d, $^{3}J_{PC}$ = 19.2 Hz, CPh_3), 70.8 (d, $^{2}J_{PC}$ = 6.8

Hz, 2xCH), 40.7 (d, $^{1}J_{PC}$ = 161.3 Hz, CH_2P), 24.3 (d, $^{3}J_{PC}$ = 5.3 Hz, 2xCH_3), 24.2 (d, $^{3}J_{PC}$ = 6.3 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.4 ppm.

IR ν 3317 (N-H), 1269 (P=O), 1194 (P-O-C), 1105 (P-O-C) cm^{-1}.

Di-*tert*-butyl ((tritylamino)methyl)phosphonate (72h).



The general procedure was followed, affording 2.3 g (97 %) of **72h** as colorless oil. No reliable HRMS was obtained.

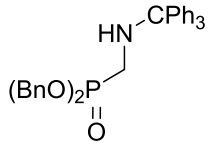
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, $^{3}J_{HH}$ = 7.7 Hz, 6H, 6xCH_{Ar} *o*-Ph), 7.27 (m, 6H, 6xCH_{Ar} *m*-Ph), 7.17 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, , 3xCH_{Ar} *p*-Ph), 2.35 (dd, $^{2}J_{PH}$ = 13.5 Hz, $^{3}J_{HH}$ = 8.1 Hz, 2H, CH_2P), 1.95 (broad s, 1H, NH), 1.49 (s, 18H, 6xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.5 (3xC_{quat} Ph), 128.8 (6xC_{Ar}), 128.0 (6xC_{Ar}), 126.5 (3xC_{Ar}), 82.2 (d, $^{2}J_{PC}$ = 8.8 Hz, 2x$\underline{C}(CH_3)_3$), 71.4 (d, $^{3}J_{PC}$ = 18.8 Hz, CPh_3), 43.1 (d, $^{1}J_{PC}$ = 163.2 Hz, CH_2P), 30.6 (d, $^{3}J_{PC}$ = 4.0 Hz, 6xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 19.3 ppm.

IR ν 3295 (N-H), 1271 (P=O), 1190 (P-O-C), 1098 (P-O-C) cm^{-1}.

Dibenzyl ((tritylamino)methyl)phosphonate (72i).



The general procedure was followed, affording 2.5 g (95 %) of **72i** as a white solid. No reliable HRMS was obtained.

Mp: 104-105 °C (Toluene-pentane).

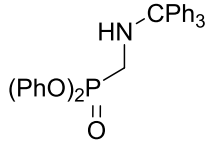
^{1}H NMR (300 MHz, $CDCl_3$) 7.55 – 7.02 (m, 25H, 25xCH_{Ar}), 5.37 – 4.88 (m, 4H, 2xCH_2Ph), 3.00 (m, 1H, NH), 2.51 (d, $^{2}J_{PH}$ = 13.5 Hz, 2H, CH_2P) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.9 (3xC_{quat} Ph), 136.5 (d, $^{3}J_{PC}$ = 5.9 Hz, 2x$C_{quat}CH_2$), 128.8 – 128.5 (m, 6xC_{Ar} Ph + 6xC_{Ar} Bn), 128.1 (6xC_{Ar} Ph + 4xC_{Ar} Bn), 126.7 (3xC_{Ar} Ph), 71.5 (d, $^{3}J_{PC}$ = 19.4 Hz, CPh_3), 67.9 (d, $^{2}J_{PC}$ = 6.7 Hz, 2xCH_2Ph), 40.3 (d, $^{1}J_{PC}$ = 160.5 Hz, CH_2P) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 29.4 ppm.

IR ν 3303 (N-H), 1258 (P=O), 1203 (P-O-C), 1101 (P-O-C) cm^{-1}.

Diphenyl ((tritylamino)methyl)phosphonate (72j).



The general procedure was followed, affording 2.6 g (96 %) of **72j** as a white solid. No reliable HRMS was obtained.

Mp: 125-127 °C (Toluene-pentane).

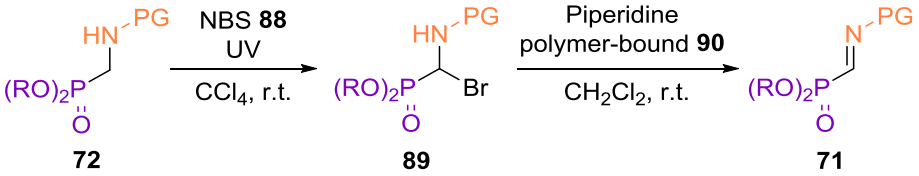
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 5H, 5xCH_{Ar}), 7.41 – 7.17 (m, 20H, 20xCH_{Ar}), 2.94 (dd, $^{2}J_{PH}$ = 13.6 Hz, $^{3}J_{HH}$ = 7.9 Hz, 3H, CH_2), 2.21 (broad s, 1H, NH) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.41 (d, $^{2}J_{PC}$ = 8.9 Hz, 2xC_{quat}O), 144.60 (3xC_{quat} Ph), 129.90 (4xC_{Ar} *m*-OPh), 128.58 (6xC_{Ar}), 128.21 (6xC_{Ar}), 126.80 (3xC_{Ar}), 125.31 (2xC_{Ar} *p*-OPh), 120.59 (d, $^{3}J_{PC}$ = 4.4 Hz, 4xC_{Ar} *o*-OPh), 71.64 (d, $^{3}J_{PC}$ = 19.9 Hz, CPh_3), 40.09 (d, $^{1}J_{PC}$ = 161.3 Hz, CH_2) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.6 ppm.

IR ν 3319 (N-H), 1269 (P=O), 1192 (P-O-C), 1095 (P-O-C) cm^{-1}.

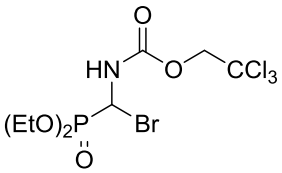
General procedure for the synthesis of aldimines 71a-d.



Step 1: Halogenation. *N*-Bromosuccinimide (0.9 g, 5.0 mmol) was added to a solution of the corresponding α-aminomethylphosphonate **72** (5.0 mmol) in CCl_4 (10 mL). The mixture was stirred in a quartz flask under UV light until observing the disappearance of starting α-aminomethylphosphonate by ^{31}P RMN. Then, the mixture was filtered to yield the desired product **89** as a clear solution.

Aminophosphonates **89** could not be fully characterized due to fast dehalogenation of the substrates. **89b** and **89c** were found to be slightly more stable and were partially characterized by ^{1}H NMR and ^{13}C NMR.

2,2,2-Trichloroethyl (bromo(diethoxyphosphoryl)methyl)carbamate (89a).[49]

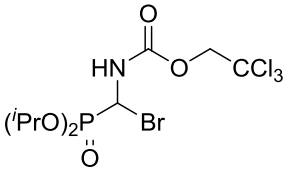


The general procedure was followed stirring the reaction under UV light for 2 h to afford 1.9 g (92 %) of **89a** as a colorless oil. No reliable HRMS was obtained due to fast dehalogenation of substrate.

^{1}H NMR spectra data matchs the data reported in the literature.[49]

^{31}P NMR (120 MHz, $CDCl_3$) δ 11.8 ppm.

2,2,2-Trichloroethyl (bromo(diisopropyloxyphosphoryl)methyl)carbamate (89b).



The general procedure was followed stirring the reaction under UV light for 2 h to afford 2.1 g (95 %) of **89b** as a colorless oil. No reliable HRMS was obtained due to fast dehalogenation of substrate.

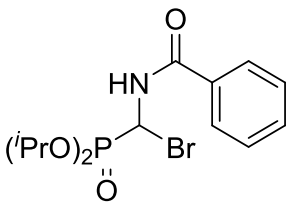
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H, NH), 6.02 (dd, $^{3}J_{HH}$ = 11.7 Hz, $^{3}J_{HH}$ = 8.8 Hz, 1H, CHP), 5.05 – 4.57 (m, 4H, 2xCH + CH_2CCl_3), 1.57 – 1.10 (m, 12H, 4xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) 154.0 (d, $^{3}J_{PC}$ = 15.9 Hz, CO), 94.9 (CCl_3), 75.2 (CH_2), 74.4 (d, $^{2}J_{PC}$ = 7.2 Hz, $\underline{C}HCH_3$), 73.8 (d, $^{3}J_{PC}$ = 7.0 Hz, $\underline{C}HCH_3$),

51.5 (d, $^{1}J_{PC}$ = 194.0 Hz, CHP), 24.4 (d, $^{3}J_{PC}$ = 2.7 Hz, CH_3), 24.3 (d, $^{3}J_{PC}$ = 3.1 Hz, CH_3), 23.7 (d, $^{3}J_{PC}$ = 6.0 Hz, CH_3), 23.6 (d, $^{3}J_{PC}$ = 6.5 Hz, CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 10.9 ppm.

Diisopropyl (benzamidobromomethyl)phosphonate (89c).



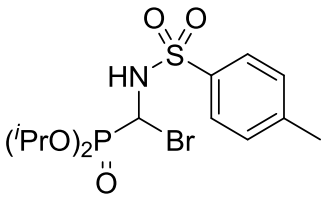
The general procedure was followed stirring the reaction under UV light for 12 h to afford 1.8 g (95 %) of **89c** as a colorless oil. No reliable HRMS was obtained due to fast dehalogenation of substrate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, $^{3}J_{HH}$ = 10.9 Hz, $^{3}J_{PH}$= 5.2 Hz, 1H, NH), 7.93 (m, 2H, 2xCH_{Ar}), 7.54 (m, 1H, CH_{Ar}), 7.45 (m, 2H, 2xCH_{Ar}), 6.36 (dd, $^{3}J_{HH}$ = 10.9 Hz, $^{3}J_{PH}$ = 9.0 Hz, 1H, CHP), 4.85 (m, 2H, 2xCH), 1.39 (d, $^{3}J_{HH}$ = 6.2 Hz, 6H, 2xCH_3), 1.32 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.28 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0 (d, $^{3}J_{PC}$ = 10.1 Hz, CO), 132.8 ($\underline{C}_{quat}CO$), 132.68 (C_{Ar}), 128.8 (2xC_{Ar}), 128.01 (2xC_{Ar}), 74.3 (d, $^{2}J_{PC}$ = 7.2 Hz, $\underline{C}HCH_3$), 73.6 (d, $^{2}J_{PC}$ = 7.2 Hz, $\underline{C}HCH_3$), 58.3 (d, $^{1}J_{PC}$ = 194.8 Hz, CHP), 24.6 (d, $^{3}J_{PC}$ = 2.7 Hz, CH_3), 24.4 (d, $^{3}J_{PC}$ = 3.3 Hz, CH_3), 23.9 (d, $^{3}J_{PC}$ = 5.4 Hz, CH_3), 23.8 (d, $^{3}J_{PC}$ = 6.1 Hz, CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 11.9 ppm.

Diisopropyl (bromo((4-methylphenyl)sulfonamido)methyl)phosphonate (89d).



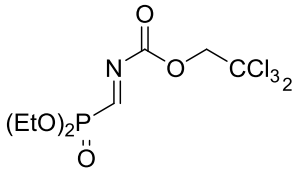
The general procedure was followed stirring the reaction under UV light for 4 h to afford 1.9 g (89 %) of **89d** as a yellowish oil. No reliable HRMS, ^{1}H and ^{13}C RMN were obtained due to fast dehalogenation of substrate.

^{31}P NMR (120 MHz, $CDCl_3$) δ 9.8 ppm.

Step 2: Elimination. A mixture of bromomethylphosphonate **89** (0.5 mmol), piperidinomethyl polystyrene (0.5 g) and $MgSO_4$ was stirred in CH_2Cl_2 (5 mL) for 30-40 min using a mechanical stirring plate. The reaction was filtered through a syringe filter to afford a clear solution of pure α-iminophosphonate, which formation was determined by ^{31}P NMR.

Aldimines **71a-d** could not be fully characterized due to their high reactivity and moisture sensitivity and were immediately used in the following synthetic step without further purification.

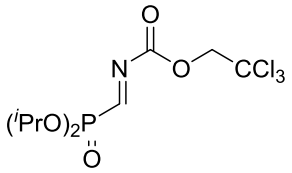
2,2,2-Trichloroethyl (*E*)-((diethoxyphosphoryl)methylene)carbamate (71a).



The general procedure was followed to afford **71a** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 1.7 ppm.

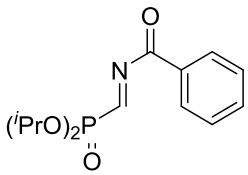
2,2,2-Trichloroethyl (*E*)-((diisopropoxyphosphoryl)methylene)carbamate (71b).



The general procedure was followed to afford **71b** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 0.9 ppm.

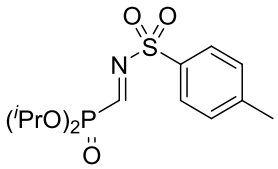
Diisopropyl (*E*)-((benzoylimino)methyl)phosphonate (71c).



The general procedure was followed to afford **71c** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 2.8 ppm.

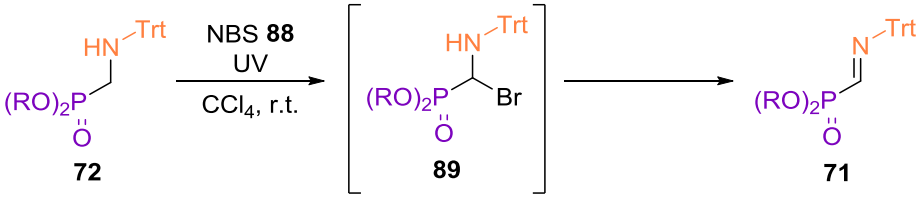
Diisopropyl (*E*)-((tosylimino)methyl)phosphonate (71d).



The general procedure was followed to afford **71d** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 0.6 ppm.

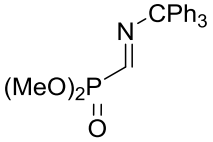
General procedure for the synthesis of aldimines 71e-j.



N-Bromosuccinimide (0.9 g, 5.0 mmol) was added to a solution of the corresponding α-aminomethylphosphonate (5.0 mmol) in CCl_4 (10 mL). The mixture was stirred in a quartz flask under UV light until observing the disappearance of starting α-aminomethylphosphonate by ^{31}P RMN. Then, the mixture was filtered to yield the desired aldimine as a clear solution, which was immediately used in the following reactions.

Aldimines **71e-j** could not be fully characterized due to their high reactivity and moisture sensitivity and were immediately used in the following synthetic step without further purification.

Dimethyl (*E*)-((tritylimino)methyl)phosphonate (71e).



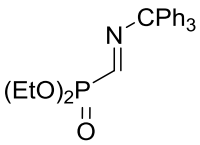
The general procedure was followed stirring the reaction under UV light for 45 min to afford **71e** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, $^{2}J_{PH}$ = 64.6 Hz, 1H, CHP), 7.32 – 7.23 (m, 12H, 12xCH_{Ar}), 7.15 (m, 3H, 3xCH_{Ar}), 3.90 (d, $^{3}J_{PH}$ = 10.8 Hz, 6H, 2xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.8 (d, $^{1}J_{PC}$ = 219.9 Hz, CN), 147.3 – 140.7 (m, 3xC_{quat}), 130.8 – 126.7 (m, 15xC_{Ar}), 81.8 (d, $^{3}J_{PC}$ = 31.2 Hz, CPh_3), 53.8 (d, $^{2}J_{PC}$ = 6.5 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 10.1 ppm.

Diethyl (*E*)-((tritylimino)methyl)phosphonate (71f).

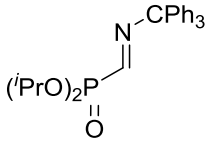


The general procedure was followed stirring the reaction under UV light for 70 min to afford **71f** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, $^{2}J_{PH}$ = 64.2 Hz, 1H, CHP), 7.34 – 7.22 (m, 12H, 12xCH_{Ar}), 7.15 (m, 3H, 3xCH_{Ar}), 4.26 (m, 4H, 2xCH_2), 1.38 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 8.0 ppm.

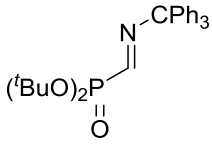
Diisopropyl (*E*)-((tritylimino)methyl)phosphonate (71g).



The general procedure was followed stirring the reaction under UV light for 90 min to afford **71g** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 6.5 ppm.

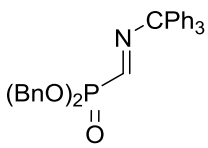
Di-*tert*-butyl (*E*)-((tritylimino)methyl)phosphonate (71h).



The general procedure was followed stirring the reaction under UV light for 90 min to afford **71h** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 0.9 ppm.

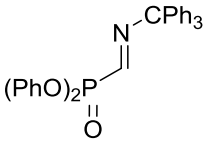
Dibenzyl (*E*)-((tritylimino)methyl)phosphonate (71i).



The general procedure was followed stirring the reaction under UV light for 90 min to afford **71i** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ 8.4 ppm.

Diphenyl (*E*)-((tritylimino)methyl)phosphonate (71j).

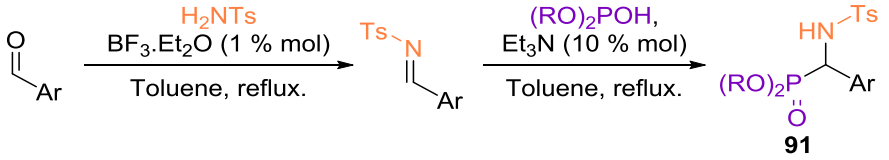


The general procedure was followed stirring the reaction under UV light for 9 h to afford **71j** as a clear solution after filtration. Full conversion was determined by ^{31}P NMR.

^{31}P NMR (120 MHz, $CDCl_3$) δ -0.5 ppm.

Synthesis of ketimines 49

General procedure for the synthesis of di-alkyl α-aminophosphonates 91.

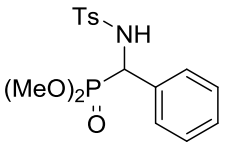


Aminophosphonates **91** were prepared following a literature procedure.[54] To a solution of *p*-toluensulfonamide (8.6 g, 50.0 mmol) and an excess of the corresponding aromatic aldehyde in toluene (100 mL) was added boron trifluoride etherate (61.7 µL, 0.5 mmol). The solution was refluxed using a Dean-Stark until water evolution stopped (0.9 mL, 20-24 h). The resulting solution was cooled to -20 ℃ and crystals were obtained. When crystallization was not observed, 25 mL of hexanes were added at room temperature. The resulting solid was collected by filtration, washed with cold toluene (50 mL) and hexanes (50 mL) and dried under low pressure to afford pure *N*-tosyl arylimines that were used in the next step without further purification.

Then, to a suspension of the corresponding *N*-tosyl arylimine (25.0 mmol) and the corresponding dialkyl phosphite (30.0 mmol) in toluene (50 mL), triethylamine (0.4 mL, 2.5 mmol) was added. The solution was stirred and refluxed in toluene 20-24 h until disappearance of *N*-tosylimine. The solution was cooled to -20 ℃ and the resulting crystals were collected by filtration, washed with cold

toluene (30 mL) and hexanes (30 mL) and dried under low pressure to afford pure *N*-tosyl α-aminophosphonates **91**.

Dimethyl (((4-methylphenyl)sulfonamido)(phenyl)methyl)phosphonate (91a).[54]



The general procedure was followed to give 16.3 g (89 %) of **91a** as a white solid.

Mp: 163-164 °C (Toluene). Lit.[54] 163-164 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.20 (d, $^{3}J_{HH}$ = 7.2 Hz, 2H, 2xCH_{Ar}), 7.17 – 7.07 (m, 3H, 3xCH_{Ar} Ph), 7.03 – 6.92 (m, 3H, 2xCH_{Ar} *m*-Ts + NH), 4.83 (dd, $^{2}J_{PH}$ = 24.1 Hz, $^{3}J_{HH}$ = 9.7 Hz, 1H, CHP), 3.86 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, OCH_3), 3.39 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, OCH_3), 2.26 (s, 3H, CH_3 Ts) ppm.

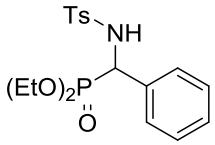
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.0 ($C_{quat}CH_3$Ts), 137.8 (d, $^{2}J_{PC}$ = 1.7 Hz, C_{quat}S Ts), 133.4 (C_{quat}CH), 129.1 (2xC_{Ar} Ts), 128.4 (d, $^{4}J_{PC}$ = 2.1 Hz, 2xC_{Ar} *m*-Ph), 128.3 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC_{Ar} *o*-Ph), 128.1 (d, $^{5}J_{PC}$ = 2.8 Hz, C_{Ar} *p*-Ph), 127.1 (2xC_{Ar} Ts), 55.0 (d, $^{1}J_{PC}$ = 157.0 Hz, CHP), 54.7 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.1 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 21.5 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.0 ppm.

IR ν 3433(N-H), 1331 (O=S=O), 1236 (P=O), 1173 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{21}NO_5PS$ $[M+H]^+$ 370.0878, found 370.0874.

Diethyl (((4-methylphenyl)sulfonamido)(phenyl)methyl)phosphonate (91b).[54]



The general procedure was followed to give 16.7 g (84 %) of **91b** as a white solid.

Mp: 126-127 °C (Toluene). Lit.[54] 126-127 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.20 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H, 2×CH_{Ar}), 7.14 - 7.08 (m, 3H, 3×CH_{Ar}), 6.97 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.85 (broad s, 1H, NH), 4.80 (dd, $^{3}J_{HH}$ = 9.6 Hz, $^{2}J_{PH}$ = 24.3 Hz, 1H, CHP), 4.28-4.18 (m, 2H, CH_2), 3.87 (m, 1H, C$\underline{H}_a$H$_b$), 3.61 (m, 1H, CH$_a$$\underline{H}_b$), 2.27 (s, 3H, CH_3 Ts), 1.35 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.04 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3) ppm.

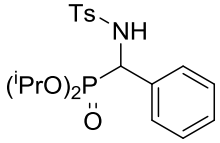
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.3 ($C_{quat}CH_3$ Ts), 138.0 (d, $^{4}J_{PC}$ = 1.7 Hz, C_{quat}S Ts), 133.5 (C_{quat}CH), 128.6 (2xC_{Ar} Ts), 128.3 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC_{Ar} *o*-Ph), 127.9 (d, $^{4}J_{PC}$ = 1.9 Hz, 2xC_{Ar} *m*-Ph), 127.5 (d, $^{5}J_{PC}$ = 2.6 Hz, C_{Ar} *p*-Ph), 126.8 (2x C_{Ar} Ts), 64.0 (d, $^{2}J_{PC}$= 7.0 Hz, CH_2), 63.4 (d, $^{2}J_{PC}$= 7.0 Hz, CH_2), 55.3 (d, $^{1}J_{PC}$= 157.5 Hz, CHP), 21.2 (CH_3 Ts), 16.3 (d, $^{3}J_{PC}$= 5.9 Hz, $CH_2\underline{C}H_3$), 15.9 (d, $^{3}J_{PC}$= 5.6 Hz, $CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 20.7 ppm.

IR ν 3316 (N-H), 1330 (O=S=O), 1236 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{25}NO_5PS$ $[M+H]^+$ 398.1191, found 398.1197.

Di*isopropyl* (((4-methylphenyl)sulfonamido)(phenyl)methyl)phosphonate (91c).[54]



The general procedure was followed to give 18.5 g (82 %) of **91c** as a white solid.

Mp: 189-190 °C (Toluene). Lit.[54] 189-190 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.20 (d, $^{3}J_{HH}$ = 7.0 Hz, 2H, 2×CH_{Ar}), 7.11 - 7.02 (m, 3H, 3×CH_{Ar}), 6.93 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.78 (broad s, 1H, NH), 4.85 (m, 1H, C<u>H</u>CH_3), 4.74 (dd, $^{3}J_{HH}$ = 9.5 Hz, $^{2}J_{PH}$ = 24.6 Hz, 1H, CHP), 4.37 (m, 1H, C<u>H</u>CH_3), 2.26 (s, 3H, CH_3 Ts), 1.39 (m, 6H, 2×CHC<u>H</u>$_3$), 1.22 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CHC<u>H</u>$_3$), 0.78 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CHC<u>H</u>$_3$) ppm.

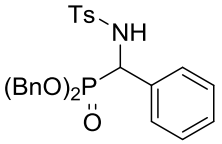
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.4 ($C_{quat}CH_3$ Ts), 138.6 (d, $^{4}J_{PC}$ = 2.1 Hz, C_{quat}S Ts), 134.2 (C_{quat}CH), 128.9 (d, $^{3}J_{PC}$ = 5.0 Hz, 2xC_{Ar} *o*-Ph), 128.8 (2xC_{Ar} Ts), 128.0 (d, $^{4}J_{PC}$ = 2.0 Hz, 2xC_{Ar} *m*-Ph), 127.6 (d, $^{5}J_{PC}$ = 2.7 Hz, C_{Ar} *p*-Ph), 127.2 (2xC_{Ar}Ts), 73.1 (d, $^{2}J_{PC}$= 7.3 Hz, <u>C</u>HCH_3), 72.7 (d, $^{2}J_{PC}$= 7.4 Hz, <u>C</u>HCH_3), 56.3 (d, $^{1}J_{PC}$= 160.3 Hz, CHP), 24.6 (d, $^{3}J_{PC}$= 3.1 Hz, CH<u>C</u>H_3), 24.4 (d, $^{3}J_{PC}$= 3.0 Hz, CH<u>C</u>H_3), 24.0 (d, $^{3}J_{PC}$= 5.7 Hz, CH<u>C</u>H_3), 23.0 (d, $^{3}J_{PC}$= 6.0 Hz, CH<u>C</u>H_3), 21.5 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 19.1ppm.

IR ν 3319 (NH), 1334 (O=S=O), 1231 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{29}NO_5PS$ $[M+H]^+$ 426.1504, found 426.1499.

Dibenzyl (((4-methylphenyl)sulfonamido)(phenyl)methyl)phosphonate (91d).[54]



The general procedure was followed to give 21.4 g (82 %) of **91d** as a white solid.

Mp: 142-143 °C (Toluene). Lit.[54] 142-143 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.11 - 7.02 (m, 16H, 15×CH_{Ar} +NH), 6.88 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 5.19 (dd, $^3J_{PH}$ = 7.1 Hz, $^1J_{HH}$ = 11.6 Hz, 1H, C$\underline{H}_a$H$_b$), 5.10 (dd, $^3J_{PH}$ = 8.9 Hz, $^1J_{HH}$ = 11.6 Hz, 1H, CH$_a$$\underline{H}_b$), 4.95 (dd, $^3J_{HH}$ = 9.8 Hz, $^2J_{PH}$ = 24.4 Hz, 1H, CHP), 4.78 (dd, $^3J_{PH}$ = 7.3 Hz, $^1J_{HH}$ = 11.8 Hz, 1H, C$\underline{H}_a$H$_b$), 4.48 (dd, $^3J_{PH}$ = 8.9 Hz, $^1J_{HH}$ = 11.8 Hz, 1H, CH$_a$$\underline{H}_b$), 2.23 (s, 3H, CH_3 Ts) ppm.

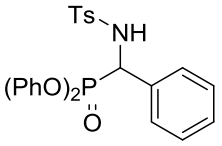
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.4 ($C_{quat}CH_3$ Ts), 138.2 (d, $^4J_{PC}$ = 1.9 Hz, C_{quat}S Ts), 135.9 (d, $^3J_{PC}$ = 6.3 Hz, $C_{quat}CH_2$), 135.5 (d, $^3J_{PC}$ = 5.7 Hz, $C_{quat}CH_2$), 133.2 (C_{quat}CH), 128.8 (2×C_{Ar}), 128.5 – 128.4 (m, 4×C_{Ar}), 128.4 (2×C_{Ar}), 128.3 (d, $^3J_{PC}$ = 6.5 Hz, 2xC_{Ar} *o*-Ph), 128.3 (2×C_{Ar}), 128.1 (2×C_{Ar}), 127.7 (C_{Ar}), 127.6 (2×C_{Ar}), 126.9 (2×C_{Ar}), 69.2 (d, $^2J_{PC}$= 7.1 Hz, CH_2Ph), 68.4 (d, $^2J_{PC}$= 7.1 Hz, CH_2Ph), 54.4 (d, $^1J_{PC}$= 158.4 Hz, CHP), 21.1 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.6 ppm.

IR ν 3312 (NH), 1338 (O=S=O), 1233 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{28}H_{29}NO_5PS$ $[M+H]^+$ 522.1504, found 522.1500.

Diphenyl (((4-methylphenyl)sulfonamido)(phenyl)methyl)phosphonate (91e).[54]



The general procedure was followed to give 21.0 g (85 %) of **91e** as a white solid.

Mp: 211-212 °C (Toluene). Lit.[54] 211-212 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.32 - 7.07 (m, 13H, 13×CH_{Ar}), 6.94 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.74 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 6.30 (broad s, 1H, NH), 5.19 (dd, $^3J_{HH}$ = 9.7 Hz, $^2J_{PH}$ = 24.7 Hz, 1H, CHP), 2.25 (s, 3H, CH_3 Ts) ppm.

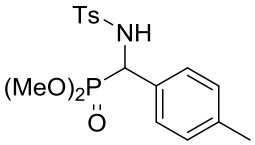
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.1 (d, $^2J_{PC}$ = 10.7 Hz, $C_{quat}O$), 149.9 (d, $^2J_{PC}$ = 10.1 Hz, $C_{quat}O$), 143.2 ($C_{quat}CH_3$ Ts), 137.4 (d, $^4J_{PC}$ = 1.6 Hz, $C_{quat}S$ Ts), 132.5 ($C_{quat}CH$), 129.7 (2×C_{Ar}), 129.6 (2×C_{Ar}), 129.2 (2×C_{Ar}), 128.5 (3×C_{Ar}), 128.3 (d, $^3J_{PC}$ = 6.2 Hz, 2xC_{Ar}), 127.0 (2xC_{Ar}), 125.5 (C_{Ar}), 125.3 (C_{Ar}), 120.7 (d, $^3J_{PC}$ = 4.1 Hz, 2×C_{Ar}), 120.2 (d, $^3J_{PC}$ = 4.3 Hz, 2×C_{Ar}), 55.3 (d, $^1J_{PC}$= 160.0 Hz, CHP), 21.4 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 13.2 ppm.

IR ν 3312 (NH), 1330 (O=S=O), 1233 (P=O), 1161 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{26}H_{25}NO_5PS$ $[M+H]^+$ 494.1191, found 494.1188.

Dimethyl (((4-methylphenyl)sulfonamido)(p-tolyl)methyl)phosphonate (91f).[119]



The general procedure was followed to give 16.9 g (88 %) of **91f** as a white solid.

Mp: 185-187 °C (Toluene). Lit.[119] 187-189 (AcOEt-hexanes).

^{1}H NMR (400 MHz, DMSO) δ 8.76 (dd, $^3J_{HH}$ = 10.3, $^3J_{PH}$ = 2.2 Hz, 1H, NH), 7.45 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} o-Ts), 7.13 – 7.05 (m, 4H, 4xCH_{Ar}), 6.90 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} m-Ts), 4.74 (dd, $^2J_{PH}$ = 24.0 Hz, $^3J_{HH}$ = 10.3 Hz, 1H, CHP), 3.64 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 3.41 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.24 (s, 3H, CH_3 Ts), 2.18 (s, 3H, CH_3) ppm.

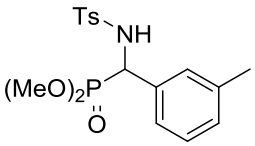
^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 142.2 ($C_{quat}CH_3$ Ts), 138.4 (d, $^4J_{PC}$ = 2.0 Hz, C_{quat}S Ts), 136.7 (d, $^5J_{PC}$ = 2.9 Hz, $C_{quat}CH_3$), 131.0 (C_{quat}CH), 128.9 (2xC_{Ar} Ts), 128.3 (d, $^4J_{PC}$ = 2.1 Hz, 2xC_{Ar} m-CH_3), 128.1 (d, $^3J_{PC}$ = 5.9 Hz, 2xC_{Ar} o-CH_3), 126.5 (2xC_{Ar} Ts), 53.7 (d, $^2J_{PC}$ = 7.1 Hz, CH_3O), 53.6 (d, $^1J_{PC}$ = 157.1 Hz, CHP), 53.2 (d, $^2J_{PC}$ = 7.0 Hz, CH_3O), 20.8 (CH_3 Ts), 20.6 (d, $^6J_{PC}$ = 0.7 Hz, CH_3) ppm.

^{31}P NMR (120 MHz, DMSO) δ 23.4 ppm.

IR ν 3427(N-H), 1328 (O=S=O), 1238 (P=O), 1155 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{23}NO_5PS$ $[M+H]^+$ 384.1029, found 384.1037.

Dimethyl (((4-methylphenyl)sulfonamido)(m-tolyl)methyl)phosphonate (91g).



The general procedure was followed to give 16.1 g (84 %) of **91g** as a white solid.

Mp: 119-120 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} o-Ts), 7.03 – 6.95 (m, 4H, 2xCH_{Ar} m-Ts + 2xCH_{Ar}), 6.95 – 6.86 (m, 2H, 2xCH_{Ar}), 6.65 (broad s, 1H, NH), 4.76 (dd, $^2J_{PH}$ = 24.0 Hz, $^3J_{HH}$ = 9.7 Hz, 1H, CHP), 3.84 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.40 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.27 (s, 3H, CH_3 Ts), 2.10 (s, 3H, CH_3) ppm.

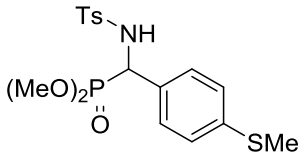
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.9 ($C_{quat}CH_3$ Ts), 138.1 (d, $^4J_{PC}$ = 2.1 Hz, C_{quat}S Ts), 137.9 (d, $^4J_{PC}$ = 1.5 Hz, $C_{quat}CH_3$), 133.1 (C_{quat}CH), 129.0 (2xC_{Ar} Ts), 128.9 – 128.8 (m, 2xC_{Ar} Ph), 128.4 (d, $^4J_{PC}$ = 2.3 Hz, C_{Ar} Ph), 127.2 (2xC_{Ar} Ts), 125.4 (d, $^3J_{PC}$ = 6.0 Hz, C_{Ar} Ph), 54.9 (d, $^1J_{PC}$ = 156.6 Hz, CHP), 54.6 (d, $^2J_{PC}$ = 7.0 Hz, CH_3O), 54.1 (d, $^2J_{PC}$ = 7.0 Hz, CH_3O), 21.5 (CH_3 Ts), 21.2 (CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.1 ppm.

IR ν 3439(N-H), 1331 (O=S=O), 1230 (P=O), 1164 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{23}NO_5PS$ $[M+H]^+$ 384.1029, found 384.1033.

Dimethyl (((4-methylphenyl)sulfonamido)(4-(methylthio)phenyl)methyl)phosphonate (91h).



The general procedure was followed to give 18.3 g (88 %) of **91h** as a white solid.

Mp: 198-200 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (broad s, $^{3}J_{HH}$ = 9.3 Hz, 1H, NH), 7.39 (d, $^{3}J_{HH}$ = 7.4 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.08 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *m*-SCH_3), 6.87 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} o-SCH_3), 6.83 (d, $^{3}J_{HH}$ = 7.4 Hz, 2H, 2xCH_{Ar} m-Ts), 4.77 (dd, $^{2}J_{PH}$ = 24.1 Hz, $^{3}J_{HH}$ = 9.9 Hz, 1H, CHP), 3.86 (d, $^{3}J_{PH}$ = 11.0 Hz, 3H, CH_3O), 3.39 (d, $^{3}J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.32 (s, 3H, CH_3 Ts), 2.19 (s, 3H, CH_3S) ppm.

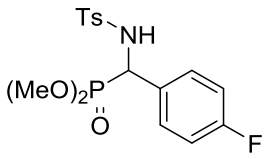
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.6($C_{quat}CH_3$ Ts), 138.4 (d, $^{5}J_{PC}$ = 3.3 Hz, $C_{quat}S$ CH_3), 138.0 (d, $^{4}J_{PC}$ = 1.7 Hz, $C_{quat}S$ Ts), 129.8 ($C_{quat}CH$), 128.8 (2xC_{Ar} Ts), 128.7 (d, $^{3}J_{PC}$ = 6.0 Hz, 2xC_{Ar} *m*-SCH_3), 126.9 (2xC_{Ar} Ts), 125.8 (d, $^{4}J_{PC}$ = 2.0 Hz, 2xC_{Ar} *o*-SCH_3), 54.7 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.6 (d, $^{1}J_{PC}$ = 159.0 Hz, CHP), 53.8 (d, $^{2}J_{PC}$ = 7.2 Hz, CH_3O), 21.2 (CH_3 Ts), 15.5 (CH_3S) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.8 ppm.

IR ν 3439(N-H), 1335 (O=S=O), 1240 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{23}NO_5PS_2$ $[M+H]^+$ 416.0750, found 416.0724.

Dimethyl ((4-fluorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91i).[119]



The general procedure was followed to give 17.6 g (91 %) of **91i** as a white solid.

Mp: 207-209 °C (Toluene). Lit.[119] 209-210 (AcOEt-hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.17 (m, 2H, 2xCH_{Ar}), 6.93 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.73 (t, $^{3}J_{HH/HF}$ = 8.6 Hz, 2H, 2xCH_{Ar} *m*-F), 5.33 (broad s, 1H, NH), 4.78 (d, $^{2}J_{PH}$ = 23.6 Hz, 1H, CHP), 3.82 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.43 (d, $^{3}J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.25 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3 (dd, $^{1}J_{FC}$ = 247.1 Hz, $^{5}J_{PC}$ = 3.4 Hz, CF), 142.4 ($C_{quat}CH_3$ Ts), 139.0 (d, $^{4}J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 130.3 (C_{quat}CH), 130.1 (dd, $^{3}J_{FC}$ = 8.0 Hz, $^{3}J_{PC}$ = 6.2 Hz, 2xC_{Ar} *m*-F), 129.0 (2xC_{Ar} Ts), 127.0 (2xC_{Ar} Ts), 115.1 (dd, $^{2}J_{FC}$ = 21.6 Hz, $^{4}J_{PC}$ =1.7 Hz, 2xC_{Ar} *o*-F), 54.8 (d, $^{1}J_{PC}$ = 159.9 Hz, CHP), 54.6 (d, $^{2}J_{PC}$ = 7.2 Hz, CH_3O), 53.9 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 21.4 (CH_3 Ts) ppm.

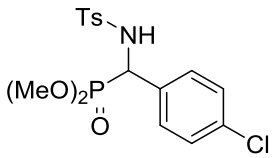
^{31}P NMR (120 MHz, $CDCl_3$) δ 23.0 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.8 ppm.

IR ν 3443(N-H), 1341 (O=S=O), 1256 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{20}FNO_5PS$ $[M+H]^+$ 388.0779, found 388.0783.

Dimethyl ((4-chlorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91j).[120]



The general procedure was followed to give 18.0 g (89 %) of **91j** as a white solid.

Mp: 198-200 °C (Toluene). Lit.[120] 203-205 (AcOEt-hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, $^{3}J_{HH}$ = 10.1 Hz, $^{3}J_{PH}$ = 4.2 Hz, 1H, NH), 7.44 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.14 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{PH}$ =2.1 Hz, 2H, 2xCH_{Ar} *m*-Cl), 7.02 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, 2xCH_{Ar} *o*-Cl), 6.97 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 4.82 (dd, $^{2}J_{PH}$ = 24.5 Hz, $^{3}J_{HH}$ = 10.1 Hz, 1H, CHP), 3.92 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.46 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.28 (s, 3H, CH_3) ppm.

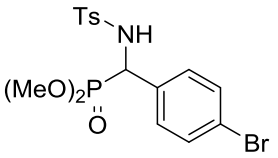
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.25 ($C_{quat}CH_3$ Ts), 137.87 (d, $^{4}J_{PC}$ = 1.9 Hz, C_{quat}S Ts), 134.06 (d, $^{5}J_{PC}$ = 3.6 Hz, CCl), 131.99 (C_{quat}CH), 129.71 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC_{Ar} *m*-Cl), 129.12 (2xC_{Ar} Ts), 128.46 (d, $^{4}J_{PC}$ = 2.2 Hz, 2xC_{Ar} *o*-Cl), 127.11 (2xC_{Ar} Ts), 55.03 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.48 (d, $^{1}J_{PC}$ = 158.4 Hz, CHP), 54.02 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 21.46 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.5 ppm.

IR ν 3436(N-H), 1331 (O=S=O), 1239 (P=O), 1158 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{20}ClNO_5PS$ $[M+H]^+$ 404.083, found 404.0487.

Dimethyl ((4-bromophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91k).



The general procedure was followed to give 21.2 g (96 %) of **91k** as a white solid.

Mp: 227-228 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.21 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, 2xCH_{Ar}), 7.05 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{PH}$ = 2.1 Hz, 2H, 2xCH_{Ar}), 7.02 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.77 (dd, $^{3}J_{HH}$ = 9.6 Hz, $^{3}J_{PH}$ = 5.2 Hz, 1H, NH), 4.77 (dd, $^{2}J_{PH}$ = 24.2 Hz, $^{3}J_{HH}$ = 9.6 Hz, 1H, CHP), 3.86 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.47 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 2.33 (s, 3H, CH_3) ppm.

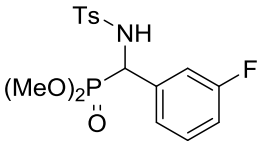
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.6($C_{quat}CH_3$ Ts), 137.67 (C_{quat}S Ts), 132.6 (C_{quat}CH), 131.6 (d, $^{4}J_{PC}$ = 2.3 Hz, 2xC_{Ar} *o*-Br), 129.9 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC_{Ar} *m*-Br), 129.3(2xC_{Ar} Ts), 127.2(2xC_{Ar} Ts), 122.4 (d, $^{5}J_{PC}$ = 3.7 Hz, CBr), 54.8 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 54.5 (d, $^{1}J_{PC}$ = 156.8 Hz, CHP), 54.1 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 21.6(CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.3 ppm.

IR ν 3449(N-H), 1331 (O=S=O), 1236 (P=O), 1157 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for$C_{16}H_{19}BrNO_5PSNa$ $[M+Na]^+$ 471.9777, found 471.9772.

Dimethyl ((3-fluorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91l).



The general procedure was followed to give 16.6 g (87 %) of **91l** as a white solid.

Mp: 163-165 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $^{3}J_{HH}$ = 10.2 Hz, 1H, NH), 7.47 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.06 – 6.92 (m, 5H, 5xCH_{Ar}), 6.79 (m, 1H, CH_{Ar}), 4.85 (dd, $^{2}J_{PH}$ = 24.6 Hz, $^{3}J_{HH}$ = 10.2 Hz, 1H, CHP), 3.92 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.43 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.23 (s, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.5 (dd, $^{1}J_{FC}$ = 246.7, $^{4}J_{PC}$ = 2.6 Hz, CF), 143.0 ($C_{quat}CH_3$ Ts), 137.97 (d, $^{4}J_{PC}$ = 1.9 Hz, C_{quat}S Ts), 136.0 (d, $^{3}J_{FC}$ = 7.3 Hz, C_{quat}CH), 129.8 (dd, $^{3}J_{FC}$ = 8.2 Hz, $^{4}J_{PC}$ = 2.3 Hz, C_{Ar} *m*-F), 129.0 (2xC_{Ar}Ts), 127.1 (2xC_{Ar}Ts), 124.2 (dd, $^{3}J_{PC}$ = 6.2 Hz, $^{4}J_{FC}$ = 2.9 Hz, C_{Ar} *p*-F), 115.3 (dd, $^{2}J_{FC}$ = 22.8, $^{3}J_{PC}$ = 5.6 Hz, C_{Ar} *o*-F), 114.8 (dd, $^{2}J_{FC}$ = 21.2 Hz, $^{5}J_{PC}$ = 3.0 Hz, C_{Ar} *o*-F), 55.0 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 54.7 (dd, $^{1}J_{PC}$ = 158.5 Hz, $^{4}J_{FC}$ = 1.8 Hz, CHP), 54.1 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 21.4 (CH_3 Ts) ppm.

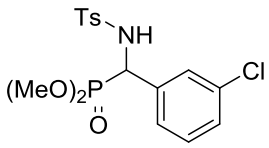
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.4 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -113.5 ppm.

IR ν 3425(N-H), 1332 (O=S=O), 1242 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{20}FNO_5PS$ $[M+H]^+$ 388.0779, found 388.0783.

Dimethyl ((3-chlorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91m).[120]



The general procedure was followed to give 17.0 g (84 %) of **91m** as a white solid.

Mp: 144-146 °C (Toluene). Lit.[120] 145-147 (AcOEt-hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (broad s, 1H, NH), 7.43 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.18 – 7.07 (m, 2H, 2xCH_{Ar}), 7.05 – 6.94 (m, 2H, 2xCH_{Ar}), 6.91 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.80 (dd, $^{2}J_{PH}$ = 24.8 Hz, $^{3}J_{HH}$ = 10.0 Hz, 1H, CHP), 3.93 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.43 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 2.21 (s, 3H, CH_3) ppm.

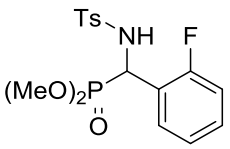
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.0 ($C_{quat}CH_3$ Ts), 137.8 (d, $^{4}J_{PC}$ = 1.8 Hz, C_{quat}S Ts), 135.2 (C_{quat}CH), 134.2 (d, $^{4}J_{PC}$ = 2.5 Hz, CCl), 129.5 (d, $^{4}J_{PC}$ = 2.4 Hz, C_{Ar} *m*-Cl), 128.9 (2xC_{Ar} Ts), 128.3 (d, $^{3}J_{PC}$ = 5.9 Hz, C_{Ar} *m*-Cl), 127.8 (d, $^{5}J_{PC}$ = 2.9 Hz, C_{Ar} *p*-Cl), 127.0 (2xC_{Ar}Ts), 126.6 (d, $^{3}J_{PC}$ = 5.8 Hz, C_{Ar} *p*-Cl), 55.0 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 54.77 (d, $^{1}J_{PC}$ = 159.1 Hz, CHP), 54.1 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 21.3 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.4 ppm.

IR ν 3417(N-H), 1326 (O=S=O), 1238 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{16}H_{20}ClNO_5PS$ $[M+H]^+$ 404.0483, found 404.0489.

Dimethyl ((2-fluorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91n).



The general procedure was followed to give 17.6 g (92 %) of **91n** as a white solid.

Mp: 184-185 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.37 (m, 1H, CH_{Ar}), 7.11 (m, 1H, CH_{Ar}), 7.03 – 6.93 (m, 3H, 2xCH_{Ar} *m*-Ts + NH), 6.90 – 6.78 (m, 2H, 2xCH_{Ar}), 5.20 (dd, $^{2}J_{PH}$ = 24.6 Hz, $^{3}J_{HH}$ = 10.3 Hz, 1H, CHP), 3.92 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.49 (d, $^{3}J_{PH}$= 10.8 Hz, 3H, CH_3O), 2.25 (s, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.8 (dd, $^{1}J_{FC}$ = 247.6 Hz, $^{3}J_{PC}$ = 6.6 Hz, CF), 143.2($C_{quat}CH_3$ Ts), 137.3 (d, $^{4}J_{PC}$ = 1.6 Hz, C_{quat}S Ts), 129.9 – 129.7 (m, 2xC_{Ar}), 129.2 (2xC_{Ar} Ts), 127.1 (2xC_{Ar} Ts), 124.4 – 124.3 (m, C_{Ar}), 121.2 (d, $^{2}J_{FC}$ = 13.9 Hz, C_{quat} *o*-F), 115.2 (dd, $^{2}J_{FC}$ = 22.2 Hz, $^{4}J_{PC}$ = 2.3 Hz, C_{Ar} *o*-F), 55.0 (d, $^{2}J_{PC}$ = 7.1 Hz CH_3O), 54.1 (d, $^{2}J_{PC}$= 7.1 Hz CH_3O), 47.7 (dd, $^{1}J_{PC}$ = 160.7 Hz, $^{3}J_{FC}$ = 3.2 Hz, CHP), 21.5 (CH_3 Ts) ppm.

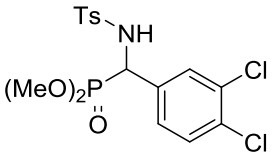
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.1 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -117.8 ppm.

IR ν 3446(N-H), 1334 (O=S=O), 1236 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{20}FNO_5PS$ $[M+H]^+$ 388.0779, found 388.0752.

Dimethyl ((3,4-dichlorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91o).



The general procedure was followed to give 19.7 g (90 %) of **91o** as a white solid.

Mp: 199-201 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (broad s, 1H, NH), 7.44 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.22 (s, 1H, CH_{Ar}), 7.15 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H, CH_{Ar}), 7.05 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H, CH_{Ar}), 6.97 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.79 (dd, $^{2}J_{PH}$ = 24.7 Hz, $^{3}J_{HH}$ = 10.3 Hz, 1H, CHP), 3.98 (d, $^{3}J_{PH}$ = 10.9 Hz, 3H, CH_3O), 3.52 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.28 (s, 3H, CH_3) ppm.

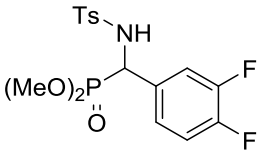
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.6 ($C_{quat}CH_3$ Ts), 137.7 (d, $^{4}J_{PC}$ = 1.9 Hz, C_{quat}S Ts), 133.5 (C_{quat}CH), 132.6 (d, $^{4}J_{PC}$ = 2.6 Hz, CCl), 132.3 (d, $^{5}J_{PC}$ = 3.5 Hz, CCl), 130.3 (d, $^{3}J_{PC}$ = 5.9 Hz, C_{Ar} *o*-3Cl), 130.2 (d, $^{4}J_{PC}$ = 2.3 Hz, C_{Ar} *o*-4Cl), 129.1 (2xC_{Ar} Ts), 127.8 (d, $^{3}J_{PC}$ = 5.8 Hz, C_{Ar} *p*-3Cl), 127.1 (2xC_{Ar} Ts), 55.4 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 54.4 (d, $^{1}J_{PC}$ = 159.2 Hz, CHP), 54.2 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 21.5 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.0 ppm.

IR ν 3442(N-H), 1324 (O=S=O), 1229 (P=O), 1168 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{19}Cl_2NO_5PS$ $[M+H]^+$ 438.0093, found 438.0104.

Dimethyl ((3,4-difluorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91p).



The general procedure was followed to give 18.2 g (90 %) of **91p** as a white solid.

Mp: 156-158 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (broad s, 1H, NH), 7.46 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.12 (m, 1H, CH_{Ar}), 6.96 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.92 – 6.82 (m, 2H, 2xCH_{Ar}), 4.80 (dd, $^{2}J_{PH}$ = 24.6 Hz, $^{3}J_{HH}$ = 10.2 Hz, 1H, CHP), 3.92 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.47 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.24 (s, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.0 (dt, $^{1}J_{FC}$ = 249.2 Hz, $^{3}J_{FC}$ = 12.4 Hz, CF), 149.9 (dt, $^{1}J_{FC}$ = 248.5 Hz, $^{3}J_{FC}$ = 12.4 Hz, CF), 143.2 ($C_{quat}CH_3$ Ts), 137.9 (C_{quat}S Ts), 130.6 (dd, $^{3}J_{FC}$ = 5.5 Hz, $^{2}J_{PC}$ = 3.8 Hz, C_{quat}CH), 129.0 (2xC_{Ar} Ts), 127.0 (2xC_{Ar} Ts), 124.7 (dt, $^{3}J_{PC}$ = 6.4 Hz, $^{3}J_{FC}$ = 3.5 Hz, C_{Ar} *m*-4F), 117.4 (dd, $^{2}J_{FC}$ = 18.6 Hz, $^{3}J_{PC}$ = 5.4 Hz, C_{Ar} *o*-3F), 116.9 (dd, $^{2}J_{FC}$ = 17.5 Hz, $^{4}J_{PC}$ = 2.1 Hz, C_{Ar} *o*-4F), 55.1 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.2 (d, $^{1}J_{PC}$ = 159.8 Hz, CHP), 54.0 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 21.3 (CH_3 Ts) ppm.

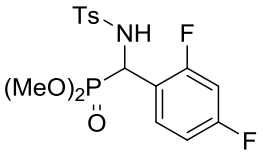
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.2 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -138.0, -138.9 ppm.

IR ν 3442(N-H), 1331 (O=S=O), 1236 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{19}F_2NO_5PS$ $[M+H]^+$ 406.0684, found 406.0690.

Dimethyl ((2,4-difluorophenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91q).



The general procedure was followed to give 18.0 g (89 %) of **91q** as a white solid.

Mp: 208-209 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, $^{3}J_{HH}$ = 10.5 Hz, $^{3}J_{PH}$ = 3.2 Hz, 1H, NH), 7.49 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.44 (m, 1H, CH_{Ar}), 6.96 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.60 – 6.48 (m, 2H, 2xCH_{Ar}), 5.18 (dd, $^{2}J_{PH}$ = 24.7 Hz, $^{3}J_{HH}$ = 10.5 Hz, 1H, CHP), 3.97 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.53 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.24 (s, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6 (ddd, $^{1}J_{FC}$ = 250.5 Hz, $^{3}J_{FC}$ = 12.0, $^{5}J_{PC}$ = 3.1 Hz, CF), 159.7 (ddd, $^{1}J_{FC}$ = 250.1 Hz, $^{3}J_{FC}$ = 12.0, $^{3}J_{PC}$ = 6.9 Hz CF), 143.2 ($C_{quat}CH_3$ Ts), 137.5 (d, $^{4}J_{PC}$ = 1.8 Hz, C_{quat}S Ts), 130.9 (dt, $^{3}J_{FC}$ = 9.8 Hz,$^{3}J_{PC}$ = 4.1 Hz, C_{Ar} *m*-4F), 129.1 (2xC_{Ar} Ts), 127.0 (2xC_{Ar} Ts), 117.3 (dd, $^{2}J_{FC}$ = 14.5 Hz, $^{2}J_{PC}$ = 3.8 Hz, C_{quat}CH), 111.5 (ddd, $^{2}J_{FC}$ = 21.3 Hz, $^{4}J_{FC}$ = 3.1 Hz, $^{4}J_{PC}$ = 2.9 Hz, C_{Ar} *o*-4F), 103.3 (dt, $^{2}J_{FC}$ = 25.9 Hz, $^{4}J_{PC}$ = 1.9 Hz, C_{Ar} *o*-2F), 55.3 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.0 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 46.8 (dd, $^{1}J_{PC}$ = 163.6 Hz, $^{3}J_{FC}$ = 2.9 Hz, CHP), 21.4 (CH_3 Ts) ppm.

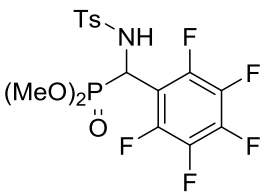
^{31}P NMR (120 MHz, $CDCl_3$) δ 20.9 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -110.1, -113.4 ppm.

IR ν 3439(N-H), 1333 (O=S=O), 1245 (P=O), 1157 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{19}F_2NO_5PS$ $[M+H]^+$ 406.0684, found 406.0690.

Dimethyl (((4-methylphenyl)sulfonamido)(perfluorophenyl)methyl)phosphonate (91r).



The general procedure was followed to give 20.7 g (90 %) of **91r** as a white solid.

Mp: 191-193 °C (Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 6.99 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 5.07 (d, $^2J_{PH}$ = 24.8 Hz, 1H, CHP), 4.05 (broad s, 1H, NH), 3.76 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.65 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 2.27 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ146.0 (m, 2xCF), 142.6 ($C_{quat}CH_3$ Ts), 139.4 (m, 2xCF), 138.8 (C_{quat}S Ts), 136.0 (m, CF), 129.0 (2xC_{Ar} Ts), 126.8 (2xC_{Ar} Ts), 110.3 (m, C_{quat}CH), 54.6 (d, $^2J_{PC}$ = 6.9 Hz, CH_3O), 53.9 (d, $^2J_{PC}$ = 7.3 Hz, CH_3O), 46.6 (d, $^1J_{PC}$ = 169.3 Hz, CHP), 21.2 (CH_3 Ts) ppm.

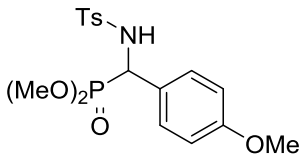
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.5 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -140.7, -155.5, -162.9 ppm.

IR ν 3439(N-H), 1338 (O=S=O), 1267 (P=O), 1170 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{16}F_5NO_5PS$ $[M+H]^+$ 460.0402, found 460.0420.

Dimethyl ((4-methoxyphenyl)((4-methylphenyl)sulfonamido)methyl)phosphonate (91s).[120]



The general procedure was followed to give 17.2 g (86 %) of **91s** as a white solid.

Mp: 163-164 °C (Toluene). Lit.[120] 166-168 (AcOEt-hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 3H, 2xCH_{Ar} *o*-Ts + NH), 7.12 (dd, $^{3}J_{HH}$ = 8.6 Hz, $^{4}J_{PH}$ = 1.8 Hz, 2H, 2xCH_{Ar}), 6.95 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.58 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H, 2xCH_{Ar}), 4.77 (dd, $^{2}J_{PH}$ = 24.0 Hz, $^{3}J_{HH}$ = 9.7 Hz, 1H, CHP), 3.84 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3OP), 3.69 (s, 3H, CH_3OAr), 3.40 (d, $^{3}J_{PH}$ -= 10.5 Hz, 3H, CH_3OP), 2.25 (s, 3H, CH_3) ppm.

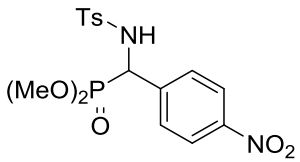
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5 (d, $^{5}J_{PC}$ = 2.7 Hz, $C_{quat}OCH_3$), 142.8 ($C_{quat}CH_3$ Ts), 138.2 (d, $^{4}J_{PC}$ = 1.9 Hz, C_{quat}S Ts), 129.7 (d, $^{3}J_{PC}$ = 6.0 Hz 2xC_{Ar} *m*-OCH_3), 129.1 (2xC_{Ar} Ts), 127.2 (2xC_{Ar} Ts), 125.5 (C_{quat}CH), 113.8 (d, $^{4}J_{PC}$ = 2.0 Hz, 2xC_{Ar} *o*-OCH_3), 55.4 (CH_3OAr), 54.7 (d, $^{2}J_{PC}$ = 7.2 Hz, CH_3OP), 54.5 (d, $^{1}J_{PC}$ = 159.3 Hz, CHP), 54.1 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_3OP), 21.5 (CH_3Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.2 ppm.

IR ν 3426(N-H), 1345 (O=S=O), 1241 (P=O), 1152 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{23}NO_6PS$ $[M+H]^+$ 400.0978, found 400.0978.

Dimethyl (((4-methylphenyl)sulfonamido)(4-nitrophenyl)methyl)phosphonate (91t).[119]



The general procedure was followed to give 19.1 g (92 %) of **91t** as a white solid.

Mp: 209-210 °C (Toluene). Lit.[119] 207-208 (AcOEt-hexanes).

^{1}H NMR (400 MHz, DMSO) δ 9.00 (dd, $^{3}J_{HH}$ = 10.4 Hz, $^{3}J_{PH}$ = 2.5 Hz, 1H, NH), 7.94 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, 2xCH_{Ar}), 7.51 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{PH}$ = 2.1 Hz, 2H, 2xCH_{Ar}), 7.45 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.07 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 5.09 (dd, $^{2}J_{PH}$ = 25.2 Hz, $^{3}J_{HH}$ =10.4 Hz, 1H, CHP), 3.69 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.50 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 2.19 (s, 3H, CH_3) ppm.

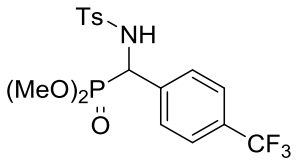
^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 146.6 (d, $^{5}J_{PC}$ = 3.2 Hz, $C_{quat}NO_2$), 142.6 ($C_{quat}CH$), 142.0 ($C_{quat}CH_3$ Ts), 137.8 (d, $^{4}J_{PC}$ = 1.8 Hz, C_{quat}S Ts), 129.5 (d, $^{3}J_{PC}$ = 5.3 Hz, 2xC_{Ar} *m*-NO_2), 129.0 (2xC_{Ar} Ts), 126.6 (2xC_{Ar} Ts), 122.7 (d, $^{4}J_{PC}$ = 2.2 Hz, 2xC_{Ar} *o*-NO_2), 54.0 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 53.4 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 53.3 (d, $^{1}J_{PC}$ = 154.3 Hz, CHP), 20.7 (CH_3 Ts) ppm.

^{31}P NMR (121 MHz, DMSO) δ 21.9 ppm.

IR ν 3433 (N-H), 1333 (O=S=O), 1237 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{20}N_2O_7PS$ $[M+H]^+$ 415.0724, found 415.0731.

Dimethyl (((4-methylphenyl)sulfonamido)(4-(trifluoromethyl)phenyl)methyl)phosphonate (91u).[119]



The general procedure was followed to give 20.3 g (93 %) of **91u** as a white solid.

Mp: 228-230 °C (Toluene). Lit.[119] 228-230 (AcOEt-hexanes).

^{1}H NMR (300 MHz, DMSO) δ 8.91 (dd, $^{3}J_{HH}$ = 10.4 Hz, $^{3}J_{PH}$ = 1.8 Hz, 1H, NH), 7.57 – 7.26 (m, 6H, 6xCH_{Ar}), 7.01 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.98 (dd, $^{2}J_{PH}$ = 25.0 Hz, $^{3}J_{HH}$ = 10.5 Hz, 1H, CHP), 3.70 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.49 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.19 (s, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, DMSO) δ 142.4 ($C_{quat}CH_3$ Ts), 138.7 (C_{quat}S Ts), 137.8(C_{quat}CH), 129.0 (d, $^{3}J_{PC}$ = 5.6 Hz, C_{Ar} *m*-CF_3), 128.9 (2xC_{Ar} Ts), 127.8 (qd, $^{2}J_{FC}$ = 31.6 Hz, $^{5}J_{PC}$ = 2.4 Hz, $C_{quat}CF_3$), 126.6 (2xC_{Ar} Ts), 124.5 (C_{Ar} *o*-CF_3), 124.1 (q, $^{1}J_{FC}$ = 272.1 Hz, CF_3), 54.0 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 53.4 (d, $^{1}J_{PC}$ = 155.4 Hz, CHP), 53.4 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_3O), 20.6 (CH_3 Ts) ppm.

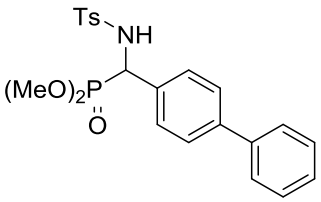
^{31}P NMR (120 MHz, DMSO) δ 22.3 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ-61.6 ppm.

IR ν 3436(N-H), 1321 (O=S=O), 1240 (P=O), 1159 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{20}F_3NO_5PS$ $[M+H]^+$ 438.0747, found 438.0750.

Dimethyl ([1,1'-biphenyl]-4-yl((4-methylphenyl)sulfonamido)methyl)phosphonate (91v).



The general procedure was followed to give 19.6 g (88 %) of **91v** as a white solid.

Mp: 195-196 °C (Toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, $^{3}J_{HH}$ = 10.1 Hz, $^{3}J_{PH}$ =3.7 Hz, 1H, NH), 7.52 – 7.27 (m, 11H¸ 11xCH_{Ar}), 6.92 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.94 (dd, $^{2}J_{PH}$ = 24.5 Hz, $^{3}J_{HH}$ = 10.1 Hz, 1H, CHP), 3.97 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.49 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.17 (s, 3H, CH_3 Ts) ppm.

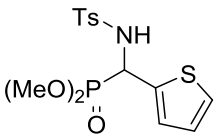
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.8 ($C_{quat}CH_3$ Ts), 140.8 (d, $^{5}J_{PC}$ = 3.0 Hz, C_{quat}Ph), 140.4 (d, $^{6}J_{PC}$ = 0.9 Hz, C_{quat}Ar), 138.1 (d, $^{4}J_{PC}$ = 1.5 Hz, C_{quat}S Ts), 132.3 (C_{quat}CH), 129.0 – 128.8 (m, 6xC_{Ar}), 127.6 (C_{Ar}), 127.2 (2xC_{Ar}), 126.9 (4xC_{Ar}), 54.9 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.9 (d, $^{1}J_{PC}$ = 158.2 Hz, CHP), 54.0 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 21.4 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3424(N-H), 1340 (O=S=O), 1269 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{22}H_{25}NO_5PS$ $[M+H]^+$ 446.1186, found 446.1192.

Dimethyl (((4-methylphenyl)sulfonamido)(thiophen-2-yl)methyl)phosphonate (91w).[119]



The general procedure was followed to give 16.5 g (88 %) of **91w** as a grey solid.

Mp: 145-147 °C (Toluene). Lit.[119] 150-152 (AcOEt-hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (broad d, $^{3}J_{HH}$ = 8.5 Hz, 1H, NH), 7.55 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.09 – 6.96 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 6.69 (m, 1H, CH_{Ar}), 5.08 (dd, $^{2}J_{PH}$ = 24.1 Hz, $^{3}J_{HH}$ = 9.7 Hz, 1H, CHP), 3.87 (d, $^{3}J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.49 (d, $^{3}J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.28 (s, 3H, CH_3) ppm.

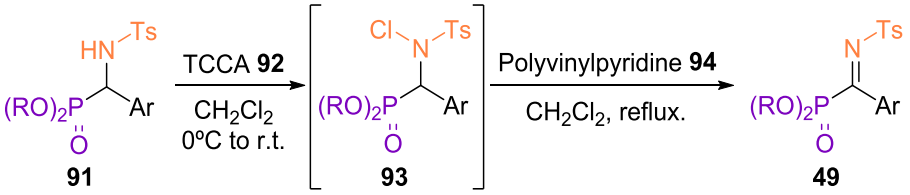
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.9 ($C_{quat}CH_3$ Ts), 138.0 (d, $^{4}J_{PC}$ = 1.7 Hz, C_{quat}S Ts), 135.5 (C_{quat}2-thienyl), 129.0 (2xC_{Ar} Ts), 128.0 (d, $^{3}J_{PC}$ = 7.1 Hz, C_{Ar} 3-thienyl), 127.0 (2xC_{Ar} Ts), 126.8 (d, $^{4}J_{PC}$ = 2.3 Hz, C_{Ar} 4-thienyl), 125.9 (d, $^{5}J_{PC}$ = 3.3 Hz, C_{Ar} 5-thienyl), 54.9 (d, $^{2}J_{PC}$ = 7.1 Hz, CH_3O), 54.1 (d, $^{2}J_{PC}$ = 7.0 Hz, CH_3O), 50.2 (d, $^{1}J_{PC}$ = 165.8 Hz, CHP), 21.4 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 20.3 ppm.

IR ν 3439(N-H), 1322 (O=S=O), 1235 (P=O), 1160 (O=S=O) cm^{-1}.

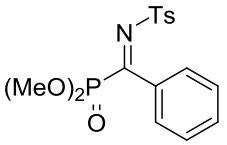
ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{14}H_{19}NO_5PS_2$ $[M+H]^+$ 376.0437, found 376.0445.

General procedure for the synthesis of ketimines 49.



To a solution of *N*-tosyl α-aminophosphonate **91** (10 mmol) in CH_2Cl_2 (30 mL) was added trichloroisocyanuric acid (7.0 g, 30 mmol). The resulting suspension was stirred at 0 °C until disappearance of the starting *N*-tosyl α-aminophosphonate, as monitored by ^{31}P NMR. The solid residue was eliminated by filtration to afford a clear solution of intermediate **93** and then, poly(4-vinylpyridine) (3.0 g), previously dried at 100 °C overnight, was added. The resulting suspension was stirred under reflux overnight and the reaction was then filtered and concentrated under reduced pressure. The resulting yellow oily crude was purified by crystallization from diethyl ether to afford pure α-ketiminophosphonate **49**.

Dimethyl (*E*)-(phenyl(tosylimino)methyl)phosphonate (49a).[54]



The general procedure was followed using **91a** (3.7 g, 10 mmol) as starting material, affording 3.2 g (86 %) of **49a** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93a** was ensured by ^{31}P NMR (δ = 19.4 ppm).

The *E* configuration of the imine double bond was stablished on the basis of COSY, NOE and HOESY experiments. Both doublets assigned to aromatic ortho CH of tosyls and phenyl groups at δ = 7.79 and 7.76 ppm showed NOE effect. The two doublets assigned to the aromatic protons of *N*-tosyl substituent at δ = 7.79 and 7.31 ppm did not show NOE effect with the doublet at δ = 3.72 ppm, corresponding to the methoxy hydrogens of the phosphonate group, and neither showed HOE effect with phosphorus signal at δ = 5.7 ppm

Mp: 103-104 °C (Et_2O). Lit.[54] 104-105 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.70 (m, 4H, 2xCH_{Ar} + 2xCH_{Ar} *o*-Ts), 7.52 (m, 1H, CH_{Ar}) 7.56 (m, 2H, 2xCH_{Ar}), 7.28 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.72 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.41 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.5 (d, $^1J_{PC}$ = 197.8 Hz, CN), 144.6 ($C_{quat}CH_3$ Ts), 136.9 (d, $^4J_{PC}$ = 2.2 Hz, C_{quat}S Ts), 133.8 (d, $^2J_{PC}$ = 24.9 Hz, C_{quat}CN), 131.9 (d, $^5J_{PC}$ = 1.7 Hz, C_{Ar}), 129.7 (2xC_{Ar} Ts), 128.4 (2xC_{Ar}),

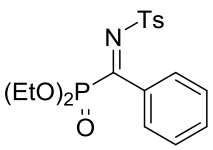
128.3 (d, $^{3}J_{PC}$ = 4.4 Hz, 2xC_{Ar}), 127.8 (2xC_{Ar} Ts), 54.9 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.7 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.7 ppm.

IR ν 1617 (C=N), 1336 (O=S=O), 1262 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{19}NO_5PS$ $[M+H]^+$ 368.0716, found 368.0716.

Diethyl (*E*)-(phenyl(tosylimino)methyl)phosphonate (49b).[54]



The general procedure was followed using **91b** (4.0 g, 10 mmol) as starting material, affording 3.1 g (79 %) of **49b** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93b** was ensured by ^{31}P NMR (δ = 18.1 ppm).

Mp: 112-113 °C (Et_2O). Lit.[54] 112-113 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.73 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, 2×CH_{Ar}), 7.51 - 7.41 (m, 3H, 3×CH_{Ar}), 7.27 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.12 (m, 4H, 2×CH_2), 2.41 (s, 3H, CH_3 Ts), 1.12 (t, $^{3}J_{PH}$ = 7.0 Hz, 6H, 2×$CH_2C\underline{H}_3$) ppm.

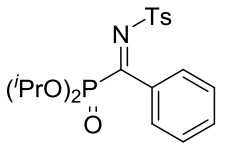
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 176.8 (d, $^{1}J_{PC}$ = 176.9 Hz, CN), 144.7 ($C_{quat}CH_3$ Ts), 137.1 (d, $^{4}J_{PC}$ = 2.2 Hz, C_{quat}S Ts), 133.8 (d, $^{2}J_{PC}$ = 24.8 Hz, C_{quat}CN), 131.9 (CH_{Ar}), 129.9 (2xC_{Ar} Ts), 128.6 (2×CH_{Ar}), 128.4 (d, $^{3}J_{PC}$ = 4.0 Hz, 2xC_{Ar}), 127.9 (2xC_{Ar} Ts), 64.3 (d, $^{2}J_{PC}$= 7.0 Hz, 2×CH_2), 21.8 (CH_3 Ts), 15.8 (d, $^{3}J_{PC}$= 6.8 Hz, 2× $CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 4.1 ppm.

IR ν 1605 (C=N), 1334 (O=S=O), 1261 (P=O), 1168 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{23}NO_5PS$ $[MH]^+$ 396.1035, found 396.1031.

Diisopropyl (*E*)-(phenyl(tosylimino)methyl)phosphonate (49c).[54]



The general procedure was followed using **91c** (4.3 g, 10 mmol) as starting material, affording 3.3 g (77 %) of **49c** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93c** was ensured by ^{31}P NMR (δ = 16.1 ppm).

Mp: 114-115 °C (Et_2O). Lit.[54] 114-115 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.75 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2×CH_{Ar}), 7.53 - 7.43 (m, 3H, 3×CH_{Ar}), 7.28 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.66 (m, 2H, 2×CH), 2.43 (s, 3H, CH_3 Ts), 1.27 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2×CH_3), 1.09 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2×CH_3) ppm.

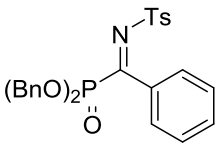
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 178.5 (d, $^1J_{PC}$ = 198.1 Hz, CN), 144.0 ($C_{quat}CH_3$ Ts), 136.7 (d, $^4J_{PC}$ = 2.3 Hz, C_{quat}S Ts), 133.8 (d, $^2J_{PC}$ = 24.6 Hz, C_{quat}CN), 131.1(d, $^5J_{PC}$ = 1.0 Hz, C_{Ar}), 129.1 (2xC_{Ar} Ts), 127.8 (d, $^3J_{PC}$ = 4.1 Hz, 2xC_{Ar}), 127.6 (2xC_{Ar} Ts), 127.3 (2xC_{Ar}), 73.5 (d, $^2J_{PC}$= 7.2 Hz, 2×CH), 23.7 (d, $^3J_{PC}$= 3.4 Hz, 2×CH<u>C</u>H_3), 22.9 (d, $^3J_{PC}$= 5.8 Hz, 2×CH<u>C</u>H_3), 21.3 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 3.2 ppm.

IR ν 1611 (C=N), 1331 (O=S=O), 1258 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{27}NO_5PS$ $[MH]^+$ 424.1348, found 424.1353.

Dibenzyl (*E*)-(phenyl(tosylimino)methyl)phosphonate (49d).[54]



The general procedure was followed using **91d** (5.2 g, 10 mmol) as starting material, affording 3.3 g (79 %) of **49d** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93d** was ensured by ^{31}P NMR (δ = 18.9 ppm).

Mp: 130-131 °C (Et_2O). Lit.[54] 130-131 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.63 (d, $^3J_{HH}$ = 7.3 Hz, 2H, 2×CH_{Ar}), 7.34 (d, $^3J_{HH}$ = 7.3 Hz, 2H, 2×CH_{Ar}), 7.24 - 7.02 (m, 13H, 11×CH_{Ar} + 2xCH_{Ar} *m*-Ts), 4.95 (d, $^3J_{PH}$ = 7.1 Hz, 4H, CH_2), 4.89 (d, $^3J_{PH}$ = 8.0 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3 Ts) ppm.

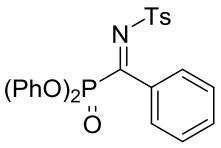
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 177.9 (d, $^1J_{PC}$ = 197.7 Hz, CN), 144.8 ($C_{quat}CH_3$ Ts), 136.3 (d, $^4J_{PC}$ = 1.6 Hz, C_{quat}S Ts), 135.9 (d, $^3J_{PC}$ = 6.2 Hz, $C_{quat}CH_2$), 135.4 (d, $^3J_{PC}$ = 6.5 Hz, $C_{quat}CH_2$), 134.0 (d, $^2J_{PC}$ = 25.3 Hz, C_{quat}CN), 132.1 (C_{Ar}), 129.9 (2×C_{Ar}), 129.0 - 128.0 (m, 16×C_{Ar}), 60.1 (d, $^2J_{PC}$= 6.9 Hz, 2×CH_2), 21.9 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 4.6 ppm.

IR ν 1616 (C=N), 1330 (O=S=O), 1260 (P=O), 1167 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) m/z calcd. for $C_{28}H_{27}NO_5PS$ $[M+H]^+$ 520.1348, found 520.1350.

Diphenyl (*E*)-(phenyl(tosylimino)methyl)phosphonate (49e).[54]



The general procedure was followed using **91e** (4.9 g, 10 mmol) as starting material, affording 4.2 g (84 %) of **49e** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93e** was ensured by ^{31}P NMR (δ = 10.8 ppm).

Mp: 99-100 °C (Et_2O). Lit.[54] 99-100 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.73 - 7.46 (m, 5H, 5×CH_{Ar}), 7.30 – 6.98 (m, 12H, 10×CH_{Ar} + 2xCH_{Ar} *m*-Ts), 2.48 (s, 3H, CH_3 Ts) ppm

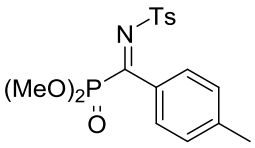
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.5 (d, $^1J_{PC}$ = 202.8 Hz, CN), 150.1 (d, $^2J_{PC}$ = 8.6 Hz $C_{quat}O$), 149.1 (d, $^2J_{PC}$ = 8.6 Hz $C_{quat}O$), 145.0 ($C_{quat}CH_3$ Ts), 136.7 (d, $^4J_{PC}$ = 2.3 Hz, $C_{quat}S$ Ts), 133.3 (d, $^2J_{PC}$ = 27.6 Hz, $C_{quat}CN$), 132.8 (C_{Ar}), 131.1 (d, $^5J_{PC}$ = 1.0 Hz C_{Ar}), 130.1 (2×C_{Ar}), 129.9 (2×C_{Ar}), 129.8 (2×C_{Ar}), 129.0 (d, $^3J_{PC}$ = 4.7 Hz 2×C_{Ar}), 128.7 (2×C_{Ar}), 128.0 (2×C_{Ar}), 126.1 (C_{Ar}), 121.8 (d, $^3J_{PC}$ = 4.6 Hz 2×C_{Ar}), 120.5 (d, $^3J_{PC}$ = 4.6 Hz 2×C_{Ar}), 22.0 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ -4.5 ppm.

IR ν 1612 (C=N), 1333 (O=S=O), 1260 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) m/z calcd. for $C_{26}H_{23}NO_5PS$ $[M+H]^+$ 492.1035, found 492.1038.

Dimethyl (*E*)-(p-tolyl(tosylimino)methyl)phosphonate (49f).



The general procedure was followed using **91f** (3.8 g, 10 mmol) as starting material, affording 3.5 g (91 %) of **49f** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93f** was ensured by ^{31}P NMR (δ = 19.7 ppm).

Mp: 88-90 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.74 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 7.35 – 7.13 (m, 4H, 2xCH_{Ar} + 2xCH_{Ar} *m*-Ts), 3.72 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

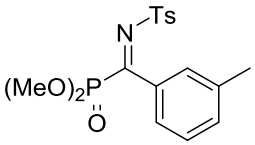
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.12 (d, $^1J_{PC}$ = 197.8 Hz, CN), 144.4 ($C_{quat}CH_3$ Ts), 143.2 (d, $^5J_{PC}$ = 1.5 Hz, $C_{quat}CH_3$), 137.3 (d, $^4J_{PC}$ = 2.1 Hz, C_{quat}S Ts), 131.0 (d, $^2J_{PC}$ = 22.0 Hz, C_{quat}CN), 129.7 (2xC_{Ar} Ts), 129.1 (2xC_{Ar}), 128.9 (d, $^3J_{PC}$ = 4.5 Hz, 2xC_{Ar}), 127.7 (2xC_{Ar} Ts), 54.9 (d, $^2J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.9 (CH_3 Ts), 21.7 (CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.9 ppm.

IR ν 1603 (C=N), 1334 (O=S=O), 1265 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{20}NO_5PS$ $[M+H]^+$ 382.0873, found 382.0879.

Dimethyl (*E*)-(m-tolyl(tosylimino)methyl)phosphonate (49g).



The general procedure was followed using **91g** (3.8 g, 10 mmol) as starting material, affording 3.4 g (88 %) of **49g** as a pale yellow oil. Formation of intermediate *N*-chloro α-aminophosphonate **93g** was ensured by ^{31}P NMR (δ = 19.5 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.54 – 7.48 (m, 2H, 2xCH_{Ar}), 7.34 – 7.30 (m, 2H, 2xCH_{Ar}), 7.26 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.71 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.40 (s, 3H, CH_3 Ts), 2.37 (s, 3H, CH_3) ppm.

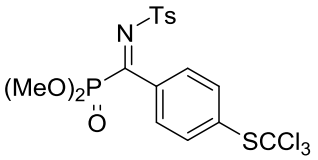
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.6 (d, $^{1}J_{PC}$ = 197.5 Hz, CN), 144.5 ($C_{quat}CH_3$ Ts), 138.2 (d, $^{4}J_{PC}$ = 0.7 Hz, $C_{quat}CH_3$), 136.9 (d, $^{4}J_{PC}$ = 2.3 Hz, C_{quat}S Ts), 133.7 (d, $^{2}J_{PC}$ = 24.9 Hz, C_{quat}CN), 132.8 (d, $^{5}J_{PC}$ = 1.5 Hz, C_{Ar} *o*-CH_3), 129.6 (2xC_{Ar} Ts), 128.4 (d, $^{3}J_{PC}$ = 4.0 Hz, C_{Ar} *o*-CH_3), 128.2 (C_{Ar} *m*-CH_3), 127.7 (2xC_{Ar} Ts), 125.4 (d, $^{3}J_{PC}$ = 4.5 Hz, C_{Ar} *p*-CH_3), 54.9 (d, $^{2}J_{PC}$ = 7.1 Hz, 2xCH_3O), 21.7 (CH_3 Ts), 21.5 (CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.7 ppm.

IR ν 1605 (C=N), 1334 (O=S=O), 1260 (P=O), 1169 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{21}NO_5PS$ $[M+H]^+$ 382.0873, found 382.0868.

Dimethyl (*E*)-((tosylimino)(4-((trichloromethyl)thio)phenyl)methyl)phosphonate (49h).



The general procedure was followed using **91h** (4.2 g, 10 mmol) as starting material, affording 4.7 g (91 %) of **49h** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93h** was ensured by ^{31}P NMR (δ = 18.7 ppm).

Mp: 102-104 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar}), 7.82 – 7.70 (m, 4H, 2xCH_{Ar} + 2xCH_{Ar} *o*-Ts), 7.30 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.75 (d, $^{3}J_{PH}$ = 11.0 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

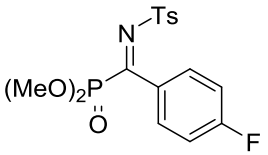
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.4 (d, $^{1}J_{PC}$ = 200.0 Hz, CN), 145.0 ($C_{quat}CH_3$ Ts), 136.9 (d, $^{2}J_{PC}$ = 24.6 Hz, C_{quat}CN), 136.7 (2xC_{Ar} *o*-$SCCl_3$), 136.4 (d, $^{4}J_{PC}$ = 2.2 Hz, C_{quat}S Ts), 134.2 (d, $^{5}J_{PC}$ = 1.8 Hz, $C_{quat}SCCl_3$), 129.9 (2xC_{Ar} Ts), 128.7 (d, $^{3}J_{PC}$ = 4.0 Hz, C_{Ar} *m*-$SCCl_3$), 127.9 (2xC_{Ar} Ts), 98.0 (CCl_3), 55.1 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.1 ppm.

IR ν 1608 (C=N), 1336 (O=S=O), 1264 (P=O), 1162 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{18}Cl_3NO_5PS_2$ $[M+H]^+$ 515.9424, found 515.9434.

Dimethyl (*E*)-((4-fluorophenyl)(tosylimino)methyl)phosphonate (49i).



The general procedure was followed using **91i** (3.9 g, 10 mmol) as starting material, affording 3.6 g (92 %) of **49i** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93i** was ensured by ^{31}P NMR (δ = 19.2 ppm).

Mp: 101-102 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H, 2xCH_{Ar}), 7.79 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.30 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.14 (m, 2H, 2xCH_{Ar}), 3.73 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.9 (d, $^{1}J_{PC}$ = 199.3 Hz, CN), 164.9 (d, $^{1}J_{FC}$ = 254.9 Hz, CF), 144.7 ($C_{quat}CH_3$ Ts), 136.9 (d, $^{4}J_{PC}$ = 2.5 Hz C_{quat}S Ts), 131.3 (dd, $^{3}J_{FC}$ = 9.1 Hz, $^{3}J_{PC}$ = 4.4 Hz, 2xC_{Ar} *m*-F), 130.0 (d, $^{2}J_{PC}$ = 3.1 Hz, C_{quat}CN), 129.7 (2xC_{Ar} Ts), 127.7 (2xC_{Ar} Ts), 115.8 (d, $^{2}J_{FC}$ = 22.1 Hz, 2xC_{Ar} *o*-F), 54.9 (d, $^{2}J_{PC}$ = 7.2 Hz, 2xCH_3O), 21.7 (CH_3 Ts) ppm.

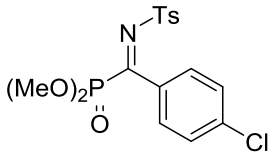
^{31}P NMR (120 MHz, $CDCl_3$) δ 5.6 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -106.1 ppm.

IR ν 1612 (C=N), 1330 (O=S=O), 1261 (P=O), 1164 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{18}FNO_5PS$ $[M+H]^+$ 386.0622, found 386.0628.

Dimethyl (*E*)-((4-chlorophenyl)(tosylimino)methyl)phosphonate (49j).



The general procedure was followed using **91j** (4.0 g, 10 mmol) as starting material, affording 3.7 g (92 %) of **49j** as a pale yellow solid. Formation of intermediate *N*-chloro α-aminophosphonate **93j** was ensured by ^{31}P NMR (δ = 18.9 ppm).

Mp: 101-102 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 7.73 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.43 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 7.30 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.73 (d, $^{3}J_{PH}$ = 10.8 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

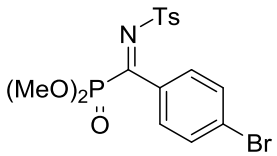
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.9 (d, $^{1}J_{PC}$ = 199.6 Hz, CN), 144.8 ($C_{quat}CH_3$ Ts), 138.6 (d, $^{5}J_{PC}$ = 1.7 Hz, CCl), 136.7 (d, $^{4}J_{PC}$ = 2.2 Hz, C_{quat}S Ts), 132.0 (d, $^{2}J_{PC}$ = 25.7 Hz, C_{quat}CN), 129.9 (d, $^{3}J_{PC}$ = 4.4 Hz, 2xC_{Ar} *m*-Cl), 129.7 (2xC_{Ar} Ts), 128.7 (2xC_{Ar} *o*-Cl), 127.7 (2xC_{Ar} Ts), 54.9 (d, $^{2}J_{PC}$ = 7.1 Hz, 2xCH_3O), 21.7 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.5 ppm.

IR ν 1608 (C=N), 1329 (O=S=O), 1261 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{16}H_{18}ClNO_5PS$ $[M+H]^+$ 402.0327, found 402.0332.

Dimethyl (*E*)-((4-bromophenyl)(tosylimino)methyl)phosphonate (49k).



The general procedure was followed using **91k** (4.5 g, 10 mmol) as starting material, affording 3.8 g (86 %) of **49k** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93k** was ensured by ^{31}P NMR (δ = 18.8 ppm).

Mp: 99-100 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.63 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar}), 7.58 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar}), 7.29 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.73 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

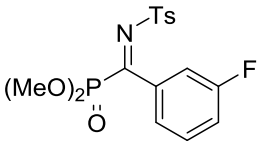
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.1 (d, $^{1}J_{PC}$ = 200.1 Hz, CN), 144.9 ($C_{quat}CH_3$ Ts), 136.7 (d, $^{4}J_{PC}$ = 2.1 Hz, C_{quat}S Ts), 132.5 (d, $^{2}J_{PC}$ = 25.7 Hz, C_{quat}CN), 131.7 (2xC_{Ar} *o*-Br), 129.9 (d, $^{3}J_{PC}$ = 4.3 Hz, 2xC_{Ar} *m*-Br), 129.8 (2xC_{Ar} Ts), 127.8 (2xC_{Ar} Ts), 127.1 (d, $^{5}J_{PC}$ = 1.8 Hz, CBr), 55.0 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.3 ppm.

IR ν 1606 (C=N), 1333 (O=S=O), 1266 (P=O), 1162 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{16}H_{18}BrNO_5PS$ $[M+H]^+$ 447.9762, found 447.9777.

Dimethyl (*E*)-((3-fluorophenyl)(tosylimino)methyl)phosphonate (49l).



The general procedure was followed using **91l** (3.9 g, 10 mmol) as starting material, affording 3.4 g (89 %) of **49l** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93l** was ensured by ^{31}P NMR (δ = 18.8 ppm).

Mp: 103-105 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.53 – 7.39 (m, 3H, 3xCH_{Ar}), 7.30 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.21 (m, 1H, CH_{Ar}), 3.75 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.43 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.8 (d, $^{1}J_{PC}$ = 199.8 Hz, CN), 162.1 (d, $^{1}J_{FC}$ = 249.3 Hz, CF), 144.9 ($C_{quat}CH_3$ Ts), 136.6 (C_{quat}S Ts), 135.4 (dd, $^{2}J_{PC}$ = 25.7 Hz, $^{3}J_{FC}$ = 7.5 Hz, C_{quat}CN), 130.2 (d, $^{3}J_{FC}$ = 8.0 Hz, C_{Ar} *m*-F), 129.8 (2xC_{Ar} Ts), 127.9 (2xC_{Ar} Ts), 124.6 – 123.3 (m, C_{Ar} *p*-F), 118.9 (d, $^{2}J_{FC}$ = 21.1 Hz, C_{Ar} *o*-F), 115.3 (dd, $^{2}J_{FC}$ = 24.1 Hz, $^{3}J_{PC}$ = 3.8 Hz, C_{Ar} *o*-F), 55.1 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

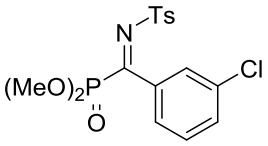
^{31}P NMR (120 MHz, $CDCl_3$) δ 5.3 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -111.4 ppm.

IR ν 1602 (C=N), 1333 (O=S=O), 1264 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{18}FNO_5PS$ $[M+H]^+$ 386.0622, found 386.0628.

Dimethyl (*E*)-((3-chlorophenyl)(tosylimino)methyl)phosphonate (49m).



The general procedure was followed using **91m** (4.0 g, 10 mmol) as starting material, affording 3.6 g (90 %) of **49m** as a colorless oil. Formation of intermediate *N*-chloro α-aminophosphonate **93m** was ensured by ^{31}P NMR (δ = 18.7 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.61 (m, 1H, CH_{Ar}), 7.57 (m, 1H, CH_{Ar}), 7.46 (m, 1H, CH_{Ar}), 7.38 (t, $^{3}J_{HH}$ = 7.9 Hz, 1H, CH_{Ar}), 7.28 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.74 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.41 (s, 3H, CH_3 Ts) ppm.

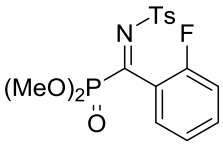
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.7 (d, $^{1}J_{PC}$ = 200.1 Hz, CN), 144.9 ($C_{quat}CH_3$ Ts), 136.4 (d, $^{4}J_{PC}$ = 2.4 Hz, C_{quat}S Ts), 135.1 (d, $^{2}J_{PC}$ = 25.2 Hz, C_{quat}CN), 134.5 (CCl), 131.7 (d, $^{5}J_{PC}$ = 1.5 Hz, C_{Ar} *o*-Cl), 129.8 (2xC_{Ar} Ts), 129.7 (C_{Ar} *m*-Cl), 127.8 (2xC_{Ar} Ts), 127.7 (d, $^{3}J_{PC}$ = 3.9 Hz, C_{Ar} *o*-Cl), 126.3 (d, $^{3}J_{PC}$ = 4.4 Hz, C_{Ar} *p*-Cl), 55.0 (d, $^{2}J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.7 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.2 ppm.

IR ν 1615 (C=N), 1336 (O=S=O), 1266 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{16}H_{18}ClNO_5PS$ $[M+H]^+$ 402.0327, found 402.0330.

Dimethyl (*E*)-((2-fluorophenyl)(tosylimino)methyl)phosphonate (49n).



The general procedure was followed using **91n** (3.9 g, 10 mmol) as starting material, affording 3.4 g (89 %) of **49n** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93n** was ensured by ^{31}P NMR (δ = 18.8 ppm).

Mp: 103-105 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.49 – 7.38 (m, 2H, 2xCH_{Ar}), 7.29 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.22 (m, 1H, CH_{Ar}), 7.10 (m, 1H, CH_{Ar}), 3.77 (d, $^{3}J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1 (d, $^{1}J_{PC}$ = 205.0 Hz, CN), 157.9 (dd, $^{1}J_{FC}$ = 250.2 Hz, $^{3}J_{FC}$ = 3.8 Hz, CF), 145.1 ($C_{quat}CH_3$ Ts), 135.8 (d, $^{4}J_{PC}$ = 2.8 Hz, C_{quat}S Ts), 132.9 (dd, $^{3}J_{FC}$ = 8.1 Hz, $^{5}J_{PC}$ = 1.8 Hz, C_{Ar} *m*-F), 129.8 (2xC_{Ar} Ts), 128.7 (dd, $^{3}J_{PC}$ = 3.2 Hz, $^{3}J_{FC}$ = 2.7 Hz, C_{Ar} *m*-F), 128.2 (2xC_{Ar} Ts), 124.2 (dd, $^{4}J_{FC}$ = 3.5 Hz, $^{4}J_{PC}$ = 0.9 Hz, C_{Ar} *p*-F), 121.8 (dd, $^{2}J_{PC}$ = 23.0 Hz, $^{2}J_{FC}$ = 17.5 Hz, C_{quat}CN), 115.8 (dd, $^{2}J_{FC}$ = 20.5 Hz, $^{4}J_{PC}$ = 1.1 Hz, C_{Ar} *o*-F), 55.0 (d, $^{2}J_{PC}$ = 6.9 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

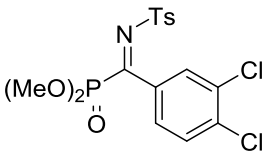
^{31}P NMR (120 MHz, $CDCl_3$) δ 4.44 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -110.46 ppm.

IR ν 1609 (C=N st), 1335 (O=S=O), 1265 (P=O), 1161 (O=S=O) cm^{-1}

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{18}FNO_5PS$ $[M+H]^+$ 386.0622, found 386.0622.

Dimethyl (*E*)-((3,4-dichlorophenyl)(tosylimino)methyl)phosphonate (49o).



The general procedure was followed using **91o** (4.4 g, 10 mmol) as starting material, affording 4.1 g (93 %) of **49o** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93o** was ensured by ^{31}P NMR (δ = 18.3 ppm).

Mp: 95-97 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.70 (m, 3H, CH_{Ar} + 2xCH_{Ar} *o*-Ts), 7.60 – 7.47 (m, 2H, 2xCH_{Ar}), 7.31 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.76 (d, $^3J_{PH}$ = 11.0 Hz, 6H, 2xCH_3O), 2.43 (s, 3H, CH_3 Ts) ppm.

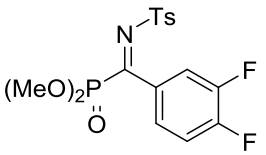
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5 (d, $^1J_{PC}$ = 197.5 Hz, CN), 145.1 ($C_{quat}CH_3$ Ts), 136.6 (d, $^5J_{PC}$ = 1.8 Hz, CCl), 136.4 (d, $^4J_{PC}$ = 2.1 Hz, $C_{quat}S$ Ts), 133.1 (d, $^2J_{PC}$ = 25.7 Hz, $C_{quat}CN$), 133.1 (CCl), 130.5 (C_{Ar} *m*-3Cl), 129.9 (d, $^3J_{PC}$ = 3.9 Hz, C_{Ar} *o*-3Cl), 129.8 (2xC_{Ar} Ts), 127.9 (2xC_{Ar} Ts), 127.6 (d, $^3J_{PC}$ = 4.4 Hz, C_{Ar} *p*-3Cl), 55.1 (d, $^2J_{PC}$ = 7.1 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 4.9 ppm.

IR ν 1612 (C=N st), 1339 (O=S=O), 1268 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{17}Cl_2NO_5PS$ $[M+H]^+$ 435.9937, found 435.9941.

Dimethyl (*E*)-((3,4-difluorophenyl)(tosylimino)methyl)phosphonate (49p).



The general procedure was followed using **91p** (4.1 g, 10 mmol) as starting material, affording 3.6 g (90 %) of **49p** as a colorless oil. Formation of intermediate *N*-chloro α-aminophosphonate **93p** was ensured by ^{31}P NMR (δ = 18.6 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.66 (m, 1H, CH_{Ar}), 7.57 (m, 1H, CH_{Ar}), 7.31 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.25 (m, 1H, CH_{Ar}), 3.74 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5 (d, $^1J_{PC}$ = 200.7 Hz, CN), 152.7 (ddd, $^1J_{FC}$ = 256.4 Hz, $^2J_{FC}$ = 12.5 Hz, $^5J_{PC}$ = 1.3 Hz, CF), 149.9 (dd, $^1J_{FC}$ = 251.8 Hz, $^2J_{FC}$ = 13.0 Hz, CF), 145.0 ($C_{quat}CH_3$ Ts), 136.6 (d, $^4J_{PC}$ = 2.3 Hz, C_{quat}S Ts), 130.6 – 130.0 (m, C_{quat}CN), 129.9 (2xC_{Ar} Ts), 127.8 (2xC_{Ar} Ts), 126.1 – 125.7 (m, C_{Ar} *p*-3F), 118.3 (ddd, $^2J_{FC}$ = 19.6 Hz, $^3J_{PC}$ = 4.1 Hz, $^3J_{FC}$ = 1.5 Hz, C_{Ar} *o*-3F), 117.8 (d, $^2J_{FC}$ = 18.0 Hz, C_{Ar} *m*-3F), 55.1 (d, $^2J_{PC}$ = 7.3 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

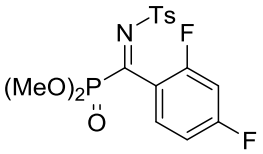
^{31}P NMR (120 MHz, $CDCl_3$) δ 5.2 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -131.1, -135.8 ppm.

IR ν 1607 (C=N st), 1333 (O=S=O), 1262 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{17}F_2NO_5PS$ $[M+H]^+$ 404.0528, found 404.0530.

Dimethyl (*E*)-((2,4-difluorophenyl)(tosylimino)methyl)phosphonate (49q).



The general procedure was followed using **91q** (4.1 g, 10 mmol) as starting material, affording 3.8 g (94 %) of **49q** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93q** was ensured by ^{31}P NMR (δ = 18.5 ppm).

Mp: 97-98 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.47 (m, 1H, CH_{Ar}), 7.31 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.99 (m, 1H, CH_{Ar}), 6.82 (m, 1H, CH_{Ar}), 3.78 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.43 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.8 (d, $^1J_{PC}$ = 206.7 Hz, CN), 164.7 (ddd, $^1J_{FC}$ = 254.5 Hz, $^3J_{FC}$ = 11.5 Hz, $^5J_{PC}$ = 1.7 Hz, CF), 158.7 (ddd, $^1J_{FC}$ = 253.1 Hz, $^3J_{FC}$ = 12.4 Hz, $^3J_{PC}$ = 3.7 Hz, CF), 145.3 ($C_{quat}CH_3$ Ts), 135.7 (d, $^4J_{PC}$ = 2.6 Hz, C_{quat}S Ts), 130.4 – 129.9 (m, C_{Ar} *m*-4F), 129.9 (2xC_{Ar} Ts), 128.2 (2xC_{Ar} Ts), 118.4 – 117.5 (m, C_{quat}CN), 111.9 (dd, $^2J_{FC}$ = 22.0 Hz, $^4J_{FC}$ = 3.5 Hz, C_{Ar} *p*-2F), 104.5 (dd, $^2J_{FC}$ = 25.1 Hz, $^2J_{FC}$ = 25.3 Hz, C_{Ar} *o*-2F), 55.0 (d, $^2J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

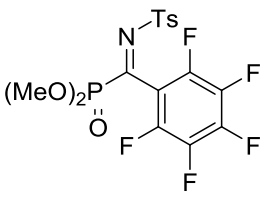
^{31}P NMR (120 MHz, $CDCl_3$) δ 4.3 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -104.6, -105.8 ppm.

IR ν 1615 (C=N st), 1335 (O=S=O), 1260 (P=O), 1168 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{17}F_2NO_5PS$ $[M+H]^+$ 404.0528, found 404.0532.

Dimethyl (*E*)-((perfluorophenyl)(tosylimino)methyl)phosphonate (49r).



The general procedure was followed using **91r** (4.6 g, 10 mmol) as starting material, affording 4.4 g (95 %) of **49r** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93r** was ensured by ^{31}P NMR (δ = 16.6 ppm).

Mp: 122-123 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.38 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.84 (d, $^3J_{PH}$ = 11.1 Hz, 6H, 2xCH_3O), 2.47 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.6 – 162.3 (m, CN), 146.2 ($C_{quat}CH_3$ Ts), 144.9 – 140.9 (m, CF), 144.3 – 140.2 (m, 2xCF), 139.9 – 135.7 (m, 2xCF), 134.6 (C_{quat}S Ts), 130.2 (2xC_{Ar} Ts), 128.5 (2xC_{Ar} Ts), 109.4 – 107.6 (m, CF), 55.2 (d, $^2J_{PC}$ = 6.7 Hz, 2xCH_3O), 21.9 (CH_3 Ts) ppm.

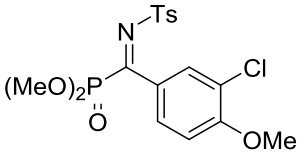
^{31}P NMR (120 MHz, $CDCl_3$) δ 2.9 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -137.6, -149.8, -160.5 ppm.

IR ν 1616 (C=N st), 1335 (O=S=O), 1258 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{14}F_5NO_5PS$ $[M+H]^+$ 458.0245, found 458.0248.

Dimethyl (E)-((3-chloro-4-methoxyphenyl)(tosylimino)methyl)phosphonate (49s).



The general procedure was followed using **91s** (4.0 g, 10 mmol) as starting material, affording 3.7 g (86 %) of **49s** as a pale yellow solid. Formation of *N*-chloro α-aminophosphonate **93s** was evidenced by ^{31}P NMR (δ = 19.0 ppm).

Mp: 107-109 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, CH_{Ar}), 7.80 (d, $^3J_{HH}$ = 8.6 Hz, 1H, CH_{Ar}), 7.74 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.25 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.95 (d, $^3J_{HH}$ = 8.6 Hz, 1H, CH_{Ar}), 3.89 (s, 3H, CH_3OAr), 3.69 (d, $^3J_{PH}$ = 10.8 Hz, 6H, 2xCH_3OP), 2.36 (s, 3H, CH_3 Ts) ppm.

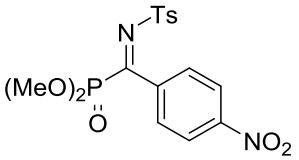
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.4 (d, $^1J_{PC}$ = 199.2 Hz, CN), 158.2 (d, $^5J_{PC}$ = 1.0 Hz, $C_{quat}OCH_3$), 144.5 ($C_{quat}CH_3$ Ts), 136.9 (d, $^4J_{PC}$ = 2.0 Hz, C_{quat}S Ts), 130.8 (d, $^3J_{PC}$ = 4.2 Hz, C_{Ar} *m*-OCH_3), 129.9 (d, $^3J_{PC}$ = 5.4 Hz, C_{Ar} *m*-OCH_3), 129.6 (2xC_{Ar} Ts), 127.4 (2xC_{Ar} Ts), 126.3 (d, $^2J_{PC}$ = 27.2 Hz, C_{quat}CN), 122.5 (CCl), 111.3 (C_{Ar} *o*-OCH_3), 56.3 (CH_3OAr), 54.8 (d, $^2J_{PC}$ = 7.2 Hz, 2xCH_3OP), 21.5 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.8 ppm.

IR ν 1609 (C=N st), 1332 (O=S=O), 1267 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{20}ClNO_6PS$ $[M+H]^+$ 432.0432, found 432.0421.

Dimethyl (*E*)-((4-nitrophenyl)(tosylimino)methyl)phosphonate (49t).



The general procedure was followed using **91t** (4.1 g, 10 mmol) as starting material, affording 3.5 g (85 %) of **49t** as a pale yellow solid. Formation of intermediate *N*-chloro α-aminophosphonate **93t** was ensured by ^{31}P NMR (δ = 18.2 ppm).

Mp: 110-112 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 7.85 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.79 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 7.33 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.78 (d, $^3J_{PH}$ = 11.0 Hz, 6H, 2xCH_3O), 2.45 (s, 3H, CH_3 Ts) ppm.

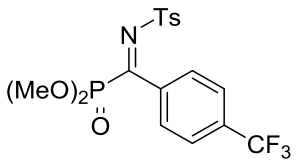
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.4 (d, $^1J_{PC}$ = 201.6 Hz, CN), 149.3 (d, $^5J_{PC}$ = 1.8 Hz, $C_{quat}NO_2$), 145.4 ($C_{quat}CH_3$ Ts), 139.8 (d, $^2J_{PC}$ = 24.6 Hz, $C_{quat}CN$), 136.1 ($C_{quat}S$ Ts), 129.96 (2xC_{Ar} Ts), 129.1 (d, $^3J_{PC}$ = 3.8 Hz, 2xC_{Ar} *m*-NO_2), 127.9 (2xC_{Ar} Ts), 123.5 (2xC_{Ar} *o*-NO_2), 55.2 (d, $^2J_{PC}$ = 7.3 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 4.7 ppm.

IR ν 1610 (C=N st), 1336 (O=S=O), 1263 (P=O), 1168 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{16}H_{18}N_2O_7PS$ $[M+H]^+$ 413.0567, found 413.0571.

Dimethyl (*E*)-((tosylimino)(4-(trifluoromethyl)phenyl)methyl)phosphonate (49u).



The general procedure was followed using **91u** (4.4 g, 10 mmol) as starting material, affording 3.8 g (87 %) of **49u** as a white solid. Formation of intermediate *N*-chloro α-aminophosphonate **93u** was ensured by ^{31}P NMR (δ = 18.6 ppm).

Mp: 92-93 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 4H, 4xCH_{Ar}), 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.30 (d, $^3J_{HH}$ = 8.2 Hz, 2xCH_{Ar} *m*-Ts), 3.76 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.43 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.1 (d, $^1J_{PC}$ = 200.5 Hz, CN), 145.1 ($C_{quat}CH_3$ Ts), 137.1 (d, $^2J_{PC}$ = 23.7 Hz, C_{quat}CN), 136.4 (d, $^4J_{PC}$ = 2.5 Hz C_{quat}S Ts), 133.1 (qd, $^2J_{FC}$ = 33.1 Hz, $^5J_{PC}$ = 1.6 Hz, $C_{quat}CF_3$), 129.8 (2xC_{Ar} Ts), 128.4 (d, $^3J_{PC}$ = 4.0 Hz, 2xC_{Ar} *m*-CF_3), 127.9 (2xC_{Ar} Ts), 125.4 (q, $^3J_{FC}$ = 3.8 Hz, 2xC_{Ar} *o*-CF_3), 123.6 (q, $^1J_{FC}$ = 272.6 Hz, CF_3), 55.1 (d, $^2J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

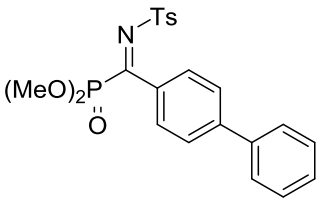
^{31}P NMR (120 MHz, $CDCl_3$) δ 5.1 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.6 ppm.

IR ν 1609 (C=N st), 1333 (O=S=O), 1266 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{18}F_3NO_5PS$ $[M+H]^+$ 436.0590, found 436.0598.

Dimethyl (*E*)-([1,1'-biphenyl]-4-yl(tosylimino)methyl)phosphonate (49v).



The general procedure was followed using **91v** (4.5 g, 10 mmol) as starting material, affording 4.0 g (89 %) of **49v** as a pale yellow oil. Formation of intermediate *N*-chloro α-aminophosphonate **93v** was ensured by ^{31}P NMR (δ = 19.4 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, $^3J_{HH}$ = 7.6 Hz, 2H, 2xCH_{Ar}), 7.82 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2xCH_{Ar}), 7.68 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.63 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2xCH_{Ar}), 7.47 (m, 2H, 2xCH_{Ar}), 7.40 (m, 1H, CH_{Ar}), 7.30 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.76 (d, $^3J_{PH}$ = 10.9 Hz, 6H, 2xCH_3O), 2.42 (s, 3H, CH_3 Ts) ppm.

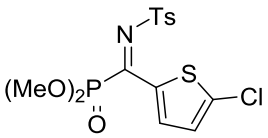
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.9 (d, $^1J_{PC}$ = 198.0 Hz, CN), 145.0 (d, $^5J_{PC}$ = 1.4 Hz, C_{quat}Ph), 144.6 ($C_{quat}CH_3$ Ts), 139.7 (C_{quat}Ar), 137.1 (d, $^4J_{PC}$ = 2.2 Hz, C_{quat}S Ts), 132.5 (d, $^2J_{PC}$ = 25.4 Hz, C_{quat}CN), 129.8 (2xC_{Ar} Ts), 129.4 (d, $^3J_{PC}$ = 4.4 Hz, 2xC_{Ar}), 129.1 (2xC_{Ar}), 128.4 (C_{Ar}), 127.8 (2xC_{Ar} Ts), 127.4 (2xC_{Ar}), 127.0 (2xC_{Ar}), 55.0 (d, $^2J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 5.9 ppm.

IR ν 1613 (C=N st), 1336 (O=S=O), 1263 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{22}H_{23}NO_5PS$ $[M+H]^+$ 444.1029, found 444.1028.

Dimethyl (E)-((5-chlorothiophen-2-yl)(tosylimino)methyl)phosphonate (49w).



The general procedure was followed using **91w** (3.8 g, 10 mmol) as starting material, affording 3.0 g (79 %) of **49w** as a yellow oil. Formation of intermediate *N*-chloro α-aminophosphonate **93w** was ensured by ^{31}P NMR (δ = 17.5 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, $^3J_{HH}$ = 5.0 Hz, 1H, CH thiophene), 7.87 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.34 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.03 (d, $^3J_{HH}$ = 4.3 Hz, 1H, CH thiophene), 3.83 (d, $^3J_{PH}$ = 11.2 Hz, 6H, 2xCH_3O), 2.44 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{PC}$ = 188.9 Hz, CN), 144.2 ($C_{quat}CH_3$ Ts), 140.1 (d, $^3J_{PC}$ = 3.8 Hz, C_{Ar} thiophene), 138.5 – 138.2 (m, $C_{quat}S$ Ts + CCl), 129.7 (2xC_{Ar} Ts), 128.4 (C_{Ar} thiophene), 127.8 (d, $^2J_{PC}$ = 13.2 Hz, $C_{quat}CN$), 127.1 (2xC_{Ar} Ts), 55.1 (d, $^2J_{PC}$ = 7.0 Hz, 2xCH_3O), 21.8 (CH_3 Ts) ppm.

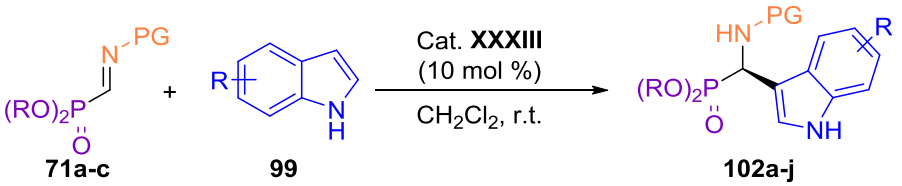
^{31}P NMR (120 MHz, $CDCl_3$) δ 4.7 ppm.

IR ν 1606 (C=N st), 1333 (O=S=O), 1260 (P=O), 1156 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{14}H_{16}ClNO_5PS_2$ $[M+H]^+$ 407.9902, found 407.9897.

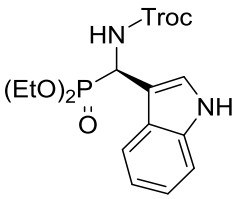
Chapter 2. Friedel-Crafts reactions of α-aldiminophosphonates with indole derivatives

General procedure for the asymmetric Friedel-Crafts reaction of α-aldiminophosphonates 71 and indole derivatives 99



To a solution of a freshly prepared aldimines **71** (0.1 mmol) and indole derivative **99** (0.1 mmol) in CH_2Cl_2 (2 mL), (*R*)-3,3'-Bis(9-phenantrenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (7.0 mg, 0.01 mmol) was added and the solution was stirred at room temperature for 12 h. The resulting solution was concentrated under vacuum and the crude residue was purified by column chromatography (hexanes/AcOEt).

(*R*)-2,2,2-Trichloroethyl ((diethoxyphosphoryl)(1*H*-indol-3-yl)methyl)carbamate (102a).



The general procedure was followed, using aldimine **71a** and indole, to afford 31.9 mg (70%) of **102a** as a white solid.

Mp: 105-106 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (broad s, 1H, NH indole), 7.71 (d, $^3J_{HH}$ = 7.7 Hz, 1H, CH_{Ar}), 7.40 – 7.29 (m, 2H, 2xCH_{Ar}), 7.21 – 7.06 (m, 2H, 2xCH_{Ar}), 6.25 (broad d, $^3J_{HH}$ = 10.0 Hz, 1H, NH), 5.57 (dd, $^2J_{PH}$ = 20.2 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, CHP), 4.85 (d, $^3J_{HH}$ = 12.1 Hz, 1H, CH_2CCl_3), 4.65 (d, $^3J_{HH}$ = 12.0 Hz, 1H, CH_2CCl_3), 4.34 – 4.17 (m, 2H, $C\underline{H}_2CH_3$), 3.99 (m, 1H, $C\underline{H}_aH_bCH_3$), 3.82 (m, 1H, $CH_a\underline{H}_bCH_3$), 1.35 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_2C\underline{H}_3$), 1.08 (t, $^3J_{HH}$ = 7.0 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$ δ 154.4 (d, $^3J_{PC}$ = 8.0 Hz, CO), 136.1 (C_{quat}), 126.2 (d, $^2J_{PC}$ = 8.8 Hz, C3 indole), 124.5 (d, $^3J_{PC}$ = 5.3 Hz, C2 indole), 122.4 (C_{Ar}), 119.9 (C_{Ar}), 118.9 (C_{Ar}), 111.6 (C_{Ar}), 108.7 (C_{quat}), 95.5 (CCl_3), 74.9 ($\underline{C}H_2CCl_3$), 63.4 (d, $^2J_{PC}$ = 6.2 Hz, $\underline{C}H_2CH_3$), 63.3 (d, $^2J_{PC}$ = 7.1 Hz, $\underline{C}H_2CH_3$), 44.9 (d, $^1J_{PC}$ = 162.9 Hz, CH), 16.6 (d, $^3J_{PC}$ = 5.9 Hz, CH_3), 16.3 (d, $^3J_{PC}$ = 5.7 Hz, CH_3) ppm.

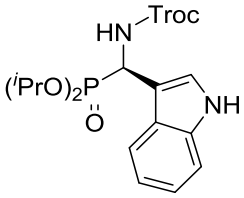
^{31}P NMR (120 MHz, $CDCl_3$) δ 23.1 ppm.

IR ν 3391 (N-H), 1727 (C=O), 1236 (P=O), 1220 (P-O-C), 1101 (P-O-C) cm^{-1}.

ESI-HRMS (Q-TOF) m/z: calcd. for $C_{16}H_{21}Cl_3N_2O_5P$ $[M+H]^+$ 457.0248, found 457.0250.

Ee (32 %) was determined by HPLC analysis (Chiracel-IC, Heptane/Ethanol 90:10, 1 mL/min). Retention time (min): 8.10 (minor) and 10.04 (major).

(*R*)-2,2,2-Trichloroethyl ((diisopropoxyphosphoryl)(1*H*-indol-3-yl)methyl)carbamate (102b).



The general procedure was followed, using aldimine **71b** and indole, to afford 35.3 mg (73%) of **102b** as a white solid.

Mp: 118-120 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (broad s, 1H, NH indole), 7.74 (d, $^3J_{HH}$ = 7.9 Hz, 1H, CH_{Ar}), 7.43 – 7.30 (m, 2H, 2xCH_{Ar}), 7.18 (ddd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH_{Ar}), 7.11 (ddd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, CH_{Ar}), 6.13 (broad d, $^3J_{HH}$ = 9.9 Hz, 1H, NH), 5.49 (dd, $^2J_{PH}$ = 21.1 Hz, $^3J_{HH}$ = 9.9 Hz, 1H, CHP), 4.82 (d, $^3J_{HH}$ = 12.0 Hz, 1H, CH_2CCl_3), 4.80 (m, 1H, C<u>H</u>CH_3), 4.64 (d, *J* = 12.0 Hz, 1H, CH_2CCl_3), 4.52 (m, 1H, C<u>H</u>CH_3), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.33 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.20 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CH_3), 0.88 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.3 (d, $^3J_{PC}$ = 9.0 Hz, CO), 136.1 (C_{quat}), 126.5 (d, $^2J_{PC}$ = 9.7 Hz, C3 indole), 124.4 (d, $^3J_{PC}$ = 5.5 Hz, C2 indole), 122.5 (C_{Ar}), 120.0 (C_{Ar}), 119.33 (C_{Ar}), 111.5 (C_{Ar}), 109.5 (C_{quat}),

95.5 (CCl_3), 74.9 (CH_2), 72.4 (d, $^2J_{PC}$ = 7.3 Hz, $\underline{C}HCH_3$), 72.1 (d, $^2J_{PC}$ = 7.6 Hz, $\underline{C}HCH_3$), 45.5 (d, $^1J_{PC}$ = 165.1 Hz, CH), 24.3 (d, $^3J_{PC}$ = 3.6 Hz, CH_3), 24.3 (d, $^3J_{PC}$ = 4.8 Hz, CH_3), 24.0 (d, $^3J_{PC}$ = 5.1 Hz, CH_3), 23.4 (d, $^3J_{PC}$ = 5.2 Hz, CH_3) ppm.

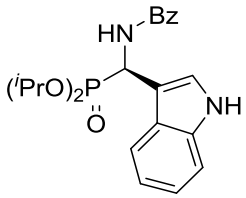
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.1 ppm.

IR ν 3389 (N-H), 1729 (C=O), 1239 (P=O), 1216 (P-O-C), 1103 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{18}H_{25}Cl_3N_2O_5P$ $[M+H]^+$ 485.0561, found 485.0563.

Ee (70 %) was determined by HPLC analysis (Chiracel-IC, Heptane/Ethanol 90:10, 1 mL/min). Retention time (min): 5.08 (minor) and 6.93 (major).

(*R*)-Diisopropyl (benzamido(1*H*-indol-3-yl)methyl)phosphonate (102c).



The general procedure was followed, using aldimine **71c** and indole, to afford 28.6 mg (69 %) of **102c** as a white solid

Mp: 76-78 °C (hexanes/AcOEt).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (broad s, 1H, NH indole), 7.84 (m, 1H, CH_{Ar}), 7.77 – 7.72 (m, 2H, 2xCH_{Ar}), 7.52 – 7.42 (m, 2H, 2xCH_{Ar}), 7.41 – 7.32 (m, 3H, 3xCH_{Ar}), 7.20 – 7.06 (m, 2H, 2xCH_{Ar}), 6.90 (broad d, $^3J_{HH}$ = 9.7 Hz, 1H, NH), 6.13 (dd, $^2J_{PH}$ = 20.5 Hz, $^3J_{HH}$ = 9.7 Hz, 1H, CHP), 4.84

(m, 1H, C<u>H</u>CH_3), 4.57 (m, 1H, C<u>H</u>CH_3), 1.36 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.27 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.20 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.93 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6 (d, $^3J_{PC}$ = 6.5 Hz, CO), 136.2 (C7a indole), 134.2 (C_{quat}CO), 131.8 (C_{Ar} Ph), 128.7 (2xC_{Ar} Ph), 127.2 (2xC_{Ar} Ph), 126.7 (d, $^3J_{PC}$ = 9.9 Hz, C3a indole), 124.6 (d, $^3J_{PC}$ = 5.3 Hz, C2 indole), 122.5 (C_{Ar} indole), 120.1 (C_{Ar} indole), 119.6 (C_{Ar} indole), 111.5 (C_{Ar} indole), 109.9 (C3 indole), 72.3 (d, $^2J_{PC}$ = 7.3 Hz, <u>C</u>HCH_3), 71.9 (d, $^2J_{PC}$ = 7.6 Hz, <u>C</u>HCH_3), 43.3 (d, $^1J_{PC}$ = 163.5 Hz, CHP), 24.4 (d, $^3J_{PC}$ = 3.5 Hz, CH_3), 24.3 (d, $^3J_{PC}$ = 3.2 Hz, CH_3), 24.0 (d, $^3J_{PC}$ = 5.0 Hz, CH_3), 23.5 (d, $^3J_{PC}$ = 5.2 Hz, CH_3) ppm.

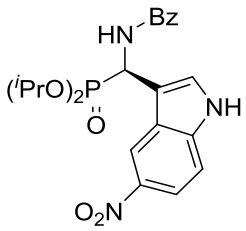
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3385 (N-H), 1714 (C=O), 1263 (P=O), 1220 (P-O-C), 1030 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{22}H_{28}N_2O_4P$ $[M+H]^+$ 415.1781, found 415.1781.

Ee (75 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:49:1, 1 mL/min). Retention time (min): 8.88 (minor) and 9.89 (major).

(*R*)-Diisopropyl (benzamido(5-nitro-1*H*-indol-3-yl)methyl)phosphonate (102d).



The general procedure was followed, using aldimine **71c** and 5-nitroindole, to afford 29.4 mg (64 %) of **102d** as a pale yellow solid.

Mp: 190-192 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (broad s, 1H, NH indole), 8.84 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H4 indole), 8.03 (dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.2 Hz, 1H, H6 indole), 7.80 (m, 2H, 2xCH_{Ar}), 7.51 (m, 1H, CH_{Ar}), 7.47 – 7.39 (m, 3H, 3xCH_{Ar}), 7.30 (d, $^3J_{HH}$ = 9.0 Hz, 1H, H7 indole), 7.10 (broad dd, $^3J_{HH}$ = 9.3 Hz, $^3J_{PH}$ = 3.8 Hz, 1H, NH), 6.04 (dd, $^2J_{PH}$ = 21.2 Hz, $^3J_{HH}$ = 9.3 Hz, 1H, CHP), 4.83 (m, 1H, C<u>H</u>CH_3), 4.63 (m, 1H, C<u>H</u>CH_3), 1.41 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.32 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.28 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.99 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ / Acetone-D6) δ 166.3 (d, $^3J_{PC}$ = 6.9 Hz, CO), 141.2 (C5 indole), 138.9 (C7a indole), 133.7 (C_{quat}CO), 131.1 (C_{Ar} Ph), 127.9 (2xC_{Ar} Ph), 127.7 (d, $^3J_{PC}$ = 7.9 Hz, C3a indole), 126.9 (2xC_{Ar} Ph), 125.5 (d, $^3J_{PC}$ = 8.1 Hz, C2 indole), 116.9 (C_{Ar} indole), 116.6 (C_{Ar} indole), 112.3 (C3 indole), 111.2 (C_{Ar} indole), 71.4 (d, $^2J_{PC}$ = 7.3 Hz, 2x<u>C</u>HCH_3), 42.8 (d, $^1J_{PC}$ = 163.5 Hz, CHP), 23.6 (d, $^3J_{PC}$ = 3.5 Hz, CH_3), 23.5 (d, $^3J_{PC}$ = 3.5 Hz, CH_3), 23.3 (d, $^3J_{PC}$ = 5.1 Hz, CH_3), 22.8 (d, $^3J_{PC}$ = 5.1 Hz, CH_3) ppm.

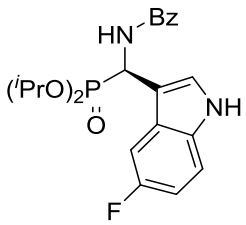
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.0 ppm.

IR ν 3233 (N-H), 1628 (C=O), 1230 (P=O), 1096 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{22}H_{27}N_3O_6P$ $[M+H]^+$ 460.1632, found 460.1631.

Ee (68 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 8.33 (major) and 10.95 (minor).

(*R*)-Diisopropyl (benzamido(5-fluoro-1*H*-indol-3-yl)methyl)phosphonate (102e).



The general procedure was followed, using aldimine **71c** and 5-fluoroindole, to afford 30.3 mg (70 %) of **102e** as a white solid.

Mp: 157-158 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (broad s, 1H, NH indole), 7.81 – 7.75 (m, 2H, 2xCH_{Ar}), 7.59 – 7.39 (m, 4H, 4xCH_{Ar}), 7.29 – 7.24 (m, 2H, 2xCH_{Ar}), 6.94 (dt, $^3J_{FH}$ = 9.0, $^4J_{HH}$ = 2.5 Hz, 1H, H4 indole), 6.81 (broad d, $^3J_{HH}$ = 9.7 Hz, 1H, NH), 6.01 (dd, $^2J_{PH}$ = 20.8 Hz, $^3J_{HH}$ = 9.7 Hz, 1H, CHP), 4.80 (m, 1H, C<u>H</u>CH_3), 4.59 (m, 1H, C<u>H</u>CH_3), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.29 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.23 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.96 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6 (d, $^3J_{PC}$ = 6.9 Hz, CO), 158.2 (d, $^1J_{FC}$ = 235.6 Hz, C5 indole), 134.1 (C7a indole), 132.6 (C_{quat}CO), 131.9 (C_{Ar} Ph), 128.8 (2xC_{Ar} Ph), 127.2 (2xC_{Ar} Ph), 127.1 (C3a indole), 126.10

(d, $^{3}J_{PC}$ = 6.1 Hz, C2 indole), 112.0 (d, $^{3}J_{FC}$ = 9.7 Hz, C7 indole), 111.2 (d, $^{2}J_{FC}$ = 26.5 Hz, C4 indole), 110.9 (d, $^{4}J_{FC}$ = 4.1 Hz, C3 indole), 104.9 (d, $^{2}J_{FC}$ = 24.2 Hz, C6 indole), 72.3 (d, $^{2}J_{PC}$ = 7.3 Hz, $\underline{C}HCH_3$), 72.1 (d, $^{2}J_{PC}$ = 7.6 Hz, $\underline{C}HCH_3$), 43.3 (d, $^{1}J_{PC}$ = 163.4 Hz, CHP), 24.4 (d, $^{3}J_{PC}$ = 3.3 Hz, CH_3), 24.3 (d, $^{3}J_{PC}$ = 3.3 Hz, CH_3), 24.0 (d, $^{3}J_{PC}$ = 5.0 Hz, CH_3), 23.5 (d, $^{3}J_{PC}$ = 5.0 Hz, CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.6 ppm.

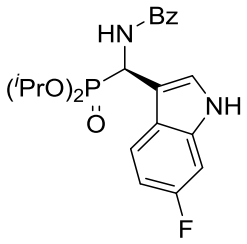
^{19}F NMR (282 MHz, $CDCl_3$) δ -123.8 ppm.

IR ν 3354 (N-H), 1634 (C=O), 1216 (P=O), 1093 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{22}H_{27}FN_2O_4P$ $[M+H]^+$ 433.1687, found 433.1689.

Ee (70 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 9.30 (major) and 12.09 (minor).

(*R*)-Diisopropyl (benzamido(6-fluoro-1*H*-indol-3-yl)methyl)phosphonate (102f).



The general procedure was followed, using aldimine **71c** and 6-fluoroindole, to afford 29.4 mg (68 %) of **102f** as a white solid.

Mp: 171-173 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (broad s, 1H, NH indole), 7.78 – 7.72 (m, 3H, 3xCH_{Ar}), 7.48 (m, 1H, CH_{Ar}), 7.44 – 7.36 (m, 3H, 3xCH_{Ar}), 7.02

(dd, $^{3}J_{FH}$ = 9.5, $^{4}J_{HH}$ = 2.3 Hz, 1H, H7 indole), 6.93 – 6.84 (m, 2H, NH + CH_{Ar}), 6.06 (dd, $^{2}J_{PH}$ = 20.7, $^{3}J_{HH}$ = 9.6 Hz, 1H, CHP), 4.80 (m, 1H, C<u>H</u>CH_3), 4.57 (m, 1H, C<u>H</u>CH_3), 1.36 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.28 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.22 (d, $^{3}J_{HH}$ = 6.1 Hz, 3H, CH_3), 0.94 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7 (d, $^{3}J_{PC}$ = 6.7 Hz, CO), 160.3 (d, $^{1}J_{FC}$ = 238.1 Hz, C6 indole), 136.1 (d, $^{3}J_{FC}$ = 12.5 Hz, C7a indole), 134.0 (C_{quat}CO), 131.9 (C_{Ar} Ph), 128.8 (2xC_{Ar} Ph), 127.2 (2xC_{Ar} Ph), 124.8 (dd, $^{3}J_{PC}$ = 6.0, $^{5}J_{FC}$ = 3.4 Hz, C2 indole), 123.2 (d, $^{3}J_{PC}$ = 9.6 Hz, C3a indole), 120.5 (d, $^{3}J_{FC}$ = 10.1 Hz, C4 indole), 110.3 (C3 indole), 108.9 (d, $^{2}J_{FC}$ = 24.5 Hz, C7 indole), 97.7 (d, $^{2}J_{FC}$ = 26.1 Hz, C5 indole), 72.4 (d, $^{2}J_{PC}$ = 7.3 Hz, <u>C</u>HCH_3), 72.1 (d, $^{2}J_{PC}$ = 7.7 Hz, <u>C</u>HCH_3), 43.3 (d, $^{1}J_{PC}$ = 163.3 Hz, CHP), 24.3 (d, $^{3}J_{PC}$ = 3.6 Hz, CH<u>C</u>H_3), 24.3 (d, $^{3}J_{PC}$ = 3.3 Hz, CH<u>C</u>H_3), 24.0 (d, $^{3}J_{PC}$ = 5.0 Hz, CH<u>C</u>H_3), 23.5 (d, $^{3}J_{PC}$ = 5.2 Hz, CH<u>C</u>H_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.7 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -121.1 ppm.

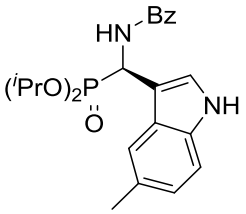
IR ν 3300 (N-H), 1641 (C=O), 1233 (P=O), 1097 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{22}H_{27}FN_2O_4P$ $[M+H]^+$ 433.1687, found 433.1692.

Ee (70 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 7.39 (major) and 12.20 (minor).

The structure of aminophosphonate **102f** was unequivocally determined by X-Ray diffraction.

(*R*)-Diisopropyl (benzamido(5-methyl-1*H*-indol-3-yl)methyl)phosphonate (102g).



The general procedure was followed, using aldimine **71c** and 5-methylindole, to afford 30.8 mg (72 %) of **102g** as a white solid.

Mp: 96-98 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (broad s, 1H, NH indole), 7.80 – 7.69 (m, 2H, 2xCH_{Ar}), 7.61 (s, 1H, CH_{Ar}), 7.51 – 7.32 (m, 4H, 4xCH_{Ar}), 7.24 (m, 1H, CH_{Ar}), 6.99 (m, 1H, CH_{Ar}), 6.77 (broad d, $^3J_{HH}$ = 9.7 Hz, 1H, NH), 6.09 (dd, $^2J_{PH}$ = 20.3 Hz, $^3J_{HH}$ = 9.7 Hz, 1H, CHP), 4.84 (m, 1H, C<u>H</u>CH_3), 4.53 (m, 1H, C<u>H</u>CH_3), 2.43 (s, 3H, CH_3 indole), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.28 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.21 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.94 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.57 (d, $^3J_{PC}$ = 6.3 Hz, CO), 134.46 (C_{quat}CO), 134.34 (C_{quat} indole), 131.73 (C_{Ar} Ph) , 129.41 (C5 indole), 128.69 (2xC_{Ar} Ph), 127.20 (2xC_{Ar} Ph), 126.94 (d, $^3J_{PC}$ = 10.3 Hz, C3a indole), 124.65 (d, $^3J_{PC}$ = 5.8 Hz, C2 indole), 124.23 (C_{Ar} indole), 119.14 (C_{Ar} indole), 111.05 (C_{Ar} indole), 109.55 (C3 indole), 72.23 (d, $^2J_{PC}$ = 7.2 Hz, <u>C</u>HCH_3), 71.92 (d, $^2J_{PC}$ = 7.6 Hz, <u>C</u>HCH_3), 43.23 (d, $^1J_{PC}$ = 163.5 Hz, CHP), 24.39 (d, $^3J_{PC}$ = 3.6 Hz, CH<u>C</u>H_3), 24.32 (d, $^3J_{PC}$ = 3.3 Hz, CH<u>C</u>H_3),

24.04 (d, $^{3}J_{PC}$ = 5.0 Hz, CH<u>C</u>H$_3$), 23.48 (d, $^{3}J_{PC}$ = 5.2 Hz, CH<u>C</u>H$_3$), 21.68 ($CH_{3\ indole}$) ppm.

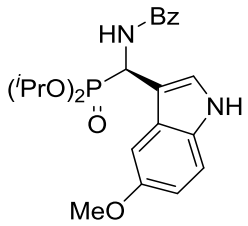
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3303 (N-H), 1638 (C=O), 1223 (P=O), 1099 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{23}H_{30}N_2O_4P$ $[M+H]^+$ 429.1938, found 429.1943.

Ee (75 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 9.49 (major) and 11.61 (minor).

(*R*)-Diisopropyl (benzamido(5-methoxy-1*H*-indol-3-yl)methyl)phosphonate (102h).



The general procedure was followed, using aldimine **71c** and 5-methoxylindole, to afford 32.4 mg (73 %) of **102h** as a white solid.

Mp: 126-127 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (broad s, 1H, NH indole), 7.82 – 7.66 (m, 2H, 2xCH_{Ar}), 7.57 – 7.35 (m, 4H, 4xCH_{Ar}), 7.30 (d, $^{4}J_{HH}$ = 2.4 Hz, 1H, H4$_{indol}$), 7.24 (d, $^{3}J_{HH}$ = 8.8 Hz, 1H, H7 indole), 6.84 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{HH}$ = 2.4 Hz, 1H, H6 indole), 6.77 (broad d, $^{3}J_{HH}$ = 9.7 Hz, 1H, NH), 6.08 (dd, $^{2}J_{PH}$ = 20.6 Hz, $^{3}J_{HH}$ = 9.7 Hz, 1H, CHP), 4.82 (m, 1H, C<u>H</u>CH$_3$), 4.60 (m, 1H, C<u>H</u>CH$_3$), 3.84 (s, 3H, CH_3O), 1.37 (d, $^{3}J_{HH}$ = 6.1 Hz, 3H, CH_3), 1.29

(d, $^3J_{HH}$ = 6.1 Hz, 3H, CH_3), 1.22 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CH_3), 0.96 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7 (d, $^3J_{PC}$ = 6.4 Hz, CO), 154.6 (C5 indole), 134.3 (C_{quat}CO), 131.8 (C_{Ar} Ph), 131.1 (C7a indole), 128.7 (2xC_{Ar} Ph), 127.3 (C3a indole), 127.2 (2xC_{Ar} Ph), 124.9 (d, $^3J_{PC}$ = 5.1 Hz, C2 indole), 113.4 (C_{Ar} indole), 112.1 (C_{Ar} indole), 110.2 (C3 indole), 100.9 (C6 indole), 72.2 (d, $^2J_{PC}$ = 7.1 Hz, $\underline{C}HCH_3$), 71.9 (d, $^2J_{PC}$ = 7.6 Hz, $\underline{C}HCH_3$), 55.9 (CH_3O), 43.2 (d, $^1J_{PC}$ = 163.5 Hz, CHP), 24.4 (d, $^3J_{PC}$ = 3.3 Hz, CH$\underline{C}H_3$), 24.3 (d, $^3J_{PC}$ = 3.0 Hz, CH$\underline{C}H_3$), 24.0 (d, $^3J_{PC}$ = 4.8 Hz, CH$\underline{C}H_3$), 23.5 (d, $^3J_{PC}$ = 5.0 Hz, CH$\underline{C}H_3$) ppm.

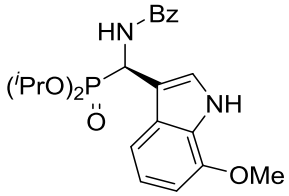
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3310 (N-H), 1638 (C=O), 1229 (P=O), 1005 (C-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{23}H_{30}N_2O_5P$ $[M+H]^+$ 445.1887, found 445.1890.

Ee (80 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 12.25 (major) and 14.91 (minor).

(*R*)-Diisopropyl (benzamido(7-methoxy-1*H*-indol-3-yl)methyl)phosphonate (102i).



The general procedure was followed, using aldimine **71c** and 7-methoxylindole, to afford 33.3 mg (75 %) of **102i** as a white solid.

Mp: 134-136 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (broad s, 1H, NH indole), 7.81 – 7.75 (m, 2H, 2xCH_{Ar}), 7.60 – 7.55 (m, 1H, CH_{Ar}), 7.46 – 7.40 (m, 2H, 2xCH_{Ar}), 7.40 – 7.29 (m, 2H, 2xCH_{Ar}), 7.17 (broad d, $^3J_{HH}$ = 9.8 Hz, 1H, NH), 7.05 (t, $^3J_{HH}$ = 7.9 Hz, 1H, CH_{Ar}), 6.63 (d, $^3J_{HH}$ = 7.7 Hz, 1H, CH_{Ar}), 6.14 (dd, $^2J_{PH}$ = 20.6, $^3J_{HH}$ = 9.8 Hz, 1H, CHP), 4.78 (m, 1H, C<u>H</u>CH_3), 4.55 (m, 1H, C<u>H</u>CH_3), 3.90 (s, 3H, CH_3O), 1.36 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.27 (d, $^3J_{HH}$ = 5.6 Hz, 5H, CH_3), 1.21 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.93 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5 (d, $^3J_{PC}$ = 6.6 Hz, CO), 146.2 (C7 indole), 134.3 (C_{quat}CO), 131.7 (C_{Ar} Ph), 128.7 (2xC_{Ar} Ph), 128.3 (d, $^3J_{PC}$ = 10.4 Hz, C3a indole), 127.4 (2xC_{Ar} Ph), 126.6 (C7a indole), 123.87 (d, $^3J_{PC}$ = 5.7 Hz, C2 indole), 120.8 (C_{Ar} indole), 112.4 (C_{Ar} indole), 110.9 (C3 indole), 102.4 (C_{Ar} indole), 72.2 (d, $^2J_{PC}$ = 7.5 Hz, <u>C</u>HCH_3), 71.9 (d, $^2J_{PC}$ = 7.4 Hz, <u>C</u>HCH_3), 55.4 (CH_3O), 43.2 (d, $^1J_{PC}$ = 163.3 Hz, CHP), 24.4 (d, $^3J_{PC}$ = 3.6 Hz, CH_3), 24.3 (d, $^3J_{PC}$ = 3.1 Hz, CH_3), 24.0 (d, $^3J_{PC}$ = 5.0 Hz, CH_3), 23.5 (d, $^3J_{PC}$ = 5.2 Hz, CH_3) ppm.

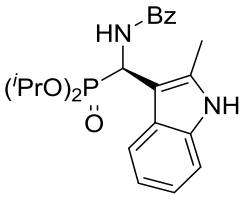
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3315 (N-H), 1637 (C=O), 1233 (P=O), 1004 (C-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{23}H_{30}N_2O_5P$ $[M+H]^+$ 445.1887, found 445.1893.

Ee (82 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 6.43 (minor) and 8.49 (major).

(*R*)-Diisopropyl (benzamido(2-methyl-1*H*-indol-3-yl)methyl)phosphonate (102j).



The general procedure was followed, using aldimine **71c** and 2-methylindole, to afford 30.0 mg (70 %) of **102j** as a purple solid.

Mp: 167-169 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (broad s, 1H, NH indole), 7.97 (m, 1H, CH_{Ar}), 7.88 – 7.65 (m, 2H, 2xCH_{Ar}), 7.50 (m, 1H, CH_{Ar}), 7.44 – 7.35 (m, 2H, 2xCH_{Ar}), 7.25 (m, 1H, CH_{Ar}), 7.18 (broad dd, $^3J_{HH}$ = 9.3 Hz, $^3J_{PH}$ = 3.9 Hz, 1H, NH), 7.13 – 7.02 (m, 2H, 2xCH_{Ar}), 5.87 (dd, $^2J_{PH}$ = 22.1 Hz, $^3J_{HH}$ = 9.3 Hz, 1H, CHP), 4.77 (m, 1H, C<u>H</u>CH_3), 4.37 (m, 1H, C<u>H</u>CH_3), 2.46 (d, $^4J_{HH}$ = 2.1 Hz, 3H, CH_3 indole), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.29 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.19 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 0.74 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8 (d, $^3J_{PC}$ = 8.1 Hz, CO), 135.4 (C_{quat}CO), 134.3 (d, $^3J_{PC}$ = 11.4 Hz, C2 indole), 134.3 (C7a indole), 131.8 (C_{Ar} Ph), 128.8 (2xC_{Ar} Ph), 127.1 (2xC_{Ar} Ph), 127.1 (C3a indole), 121.4 (C_{Ar} indole), 120.0 (C_{Ar} indole), 119.7 (C_{Ar} indole), 110.6 (C_{Ar} indole), 105.9 (C3 indole), 72.3 (d, $^2J_{PC}$ = 7.1 Hz, <u>C</u>HCH_3), 71.6 (d, $^2J_{PC}$ = 7.5 Hz, <u>C</u>HCH_3), 44.8 (d, $^1J_{PC}$ = 165.7 Hz, CHP), 24.5 (d, $^3J_{PC}$ = 2.7 Hz, CH<u>C</u>H_3),

24.3 (d, $^{3}J_{PC}$ = 3.5 Hz, CH<u>C</u>H$_3$), 24.1 (d, $^{3}J_{PC}$ = 5.0 Hz, CH<u>C</u>H$_3$), 23.0 (d, $^{3}J_{PC}$ = 6.0 Hz, CH<u>C</u>H$_3$), 12.1 (d, $^{4}J_{PC}$ = 1.6 Hz, $CH_{3\ indole}$) ppm.

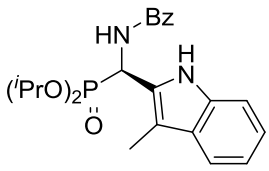
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.6 ppm.

IR ν 3294 (N-H), 1635 (C=O), 1245 (P=O), 1206 (P-O-C), 1106 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{30}N_2O_4P$ $[M+H]^+$ 429.1938, found 429.1944.

Ee (39 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 4.63 (major) and 6.33 (minor).

(*R*)-Diisopropyl (benzamido(3-methyl-1*H*-indol-2-yl)methyl)phosphonate (104).



The general procedure was followed, using aldimine **71c** and 3-methylindole, to afford 30.1 g (72%) of **104** as a white solid.

Mp: 144-145 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (broad s, 1H, NH indole), 8.52 (broad d, $^{3}J_{HH}$ = 9.9 Hz, 1H, NH), 7.82 (d, $^{3}J_{HH}$ = 8.4, 2H, 2xCH_{Ar}), 7.54 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, CH_{Ar}), 7.41 (m, 1H, CH_{Ar}), 7.33 – 7.23 (m, 2H, 2xCH_{Ar}), 7.04 (m, 1H, CH_{Ar}), 6.94 (t, $^{3}J_{HH}$ = 7.5 Hz, 1H, CH_{Ar}), 6.79 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, CH_{Ar}), 6.30 (dd, $^{2}J_{PH}$ = 21.2 Hz, $^{3}J_{HH}$ = 9.9 Hz, 1H, CHP), 4.72 (m, 1H, C<u>H</u>

CH_3), 4.46 (m, 1H, C<u>H</u>CH_3), 2.45 (s, 1H, $CH_{3\ indole}$), 1.33 – 1.18 (m, 9H, 3xCH_3), 0.95 (d, $^3J_{HH}$ = 6.1 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.9 (d, $^3J_{PC}$ = 6.9 Hz, CO), 136.2 (C7a indole), 134.2 (C_{quat}CO), 131.6 (C_{Ar} Ph), 128.4 (2xC_{Ar} Ph), 127.6 (2xC_{Ar} Ph), 127.4 (C2 indole), 127.4 (C3a indole), 122.2 (C_{Ar} indole), 119.1 (C_{Ar} indole), 118.8 (C_{Ar} indole), 111.4 (C_{Ar} indole), 110.6 (d, $^3J_{PC}$ = 10.0 Hz, C3 indole), 73.2 (d, $^2J_{PC}$ = 7.8 Hz, <u>C</u>HCH_3), 72.9 (d, $^2J_{PC}$ = 7.8 Hz, <u>C</u>HCH_3), 42.9 (d, $^1J_{PC}$ = 163.2 Hz, CHP), 24.4 (d, $^3J_{PC}$ = 3.3 Hz, CH_3), 24.1 (d, $^3J_{PC}$ = 5.0 Hz, CH_3), 24.0 (d, $^3J_{PC}$ = 3.9 Hz, CH_3), 23.4 (d, $^3J_{PC}$ = 5.5 Hz, CH_3), 8.9 (CH_3 indole) ppm.

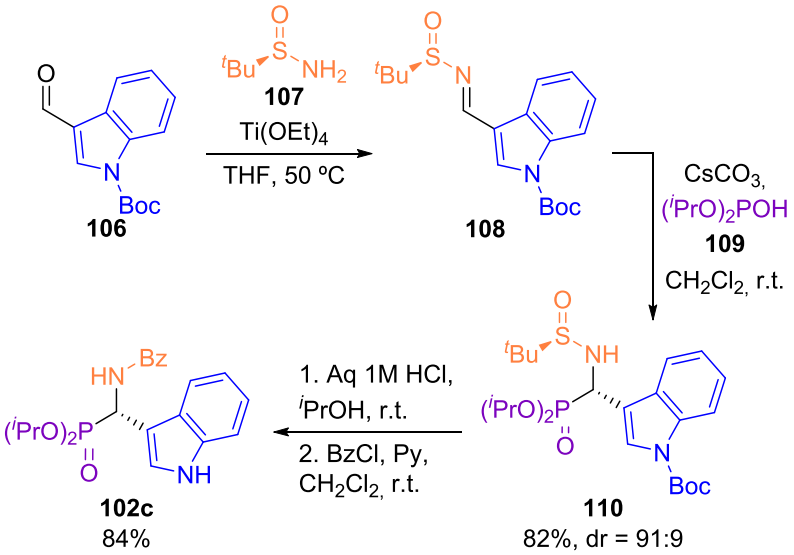
^{31}P NMR (120 MHz, $CDCl_3$) δ 20.7 ppm.

IR ν 3316 (N-H), 1667 (C=O), 1213 (P=O), 1123 (P-O-C) cm^{-1}.

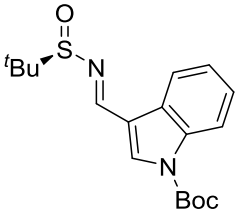
HRMS (ESI-TOF) m/z: Calcd. $C_{23}H_{30}N_2O_4P$ $[M+H]^+$ 429.1938, found 429.1943.

Ee (19 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:48:2, 1 mL/min). Retention time (min): 3.71 (minor) and 4.10 (major).

Determination of the absolute configuration of 102c

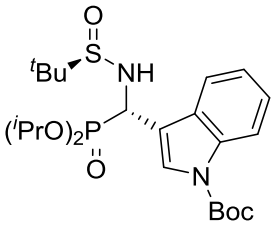


Synthesis of *tert*-butyl (*R*,*E*)-3-(((tert-*butyl*-sulfinyl)imino)methyl)-1*H*-indol-1-carboxylate (108).[121]



Following the reported methodology,[121] a mixture of aldehyde **106** (4.91 g, 20.0 mmol), (*R*)-*tert*-butanesulfinamide (**107**) (2.91 g, 24.0 mmol) and $Ti(OEt)_4$ (5.48 g, 24.0 mmol) was stirred in dry THF (50 mL) at 50 °C for 12 h. Then, 2 mL of water were added to quench the reaction and the suspended solid was filtered through celite. The filtrate was washed with Et_2O, dried over anhydrous $MgSO_4$ and the product was crystallized in Et_2O to afford the pure imine **108** as a white solid in quantitative yield. The spectroscopic data are in agreement with those of the literature.[121]

Synthesis of *tert*-butyl 3-((*S*)-(((*R*)-*tert*-butylsulfinyl)amino)(diisopropoxyphosphoryl)methyl)-1*H*-indol-1-carboxylate (110).



A mixture of imine **108** (1.1 g, 3.0 mmol), diisopropyl phosphite **109** (0.6 mL, 3.6 mmol) and $CsCO_3$ (5.9 g, 18.0 mmol) was stirred at room temperature for 5 days in CH_2Cl_2 (10 mL). Then, the reaction was washed with water (3×40 mL) and saturated solution of NH_4Cl (1×40 mL), the organic layer was dried over anhydrous $MgSO_4$ and the volatiles were distilled off under reduced pressure. The resulting crude crude product was purified by flash chromatography (hexanes/AcOEt) to give 1.3 g (82%) of α-aminophosphonate **110** as a white solid and a mixture of diastereomers (91:9). The major diastereomer was obtained after crystallization in hexanes/AcOEt.

Mp: 104-105 °C (hexanes/AcOEt).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CH_{Ar}), 7.77 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CH_{Ar}), 7.69 (d, $^4J_{HH}$ = 4.1 Hz, 1H, CH_{Ar}), 7.30 (m, 1H, CH_{Ar}), 7.20 (m, 1H, CH_{Ar}), 4.93 (dd, $^2J_{PH}$ = 17.7 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, CHP), 4.70 (m, 1H, C<u>H</u>CH_3), 4.59 (m, 1H, C<u>H</u>CH_3), 4.08 (dd, $^3J_{PH}$ = 5.6 Hz, $^3J_{HH}$ = 1.9 Hz, 1H, NH), 1.66 (s, 9H, ^{t}BuCO), 1.31 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.27 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.24 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 1.22 (s, 9H, ^{t}BuSO), 1.11 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.5 (CO), 135.8 (C7a indole), 129.1 (d, $^{3}J_{PC}$ = 2.9 Hz, C3a indole), 126.7 (d, $^{3}J_{PC}$ = 9.5 Hz, C2 indole), 124.76 (C_{Ar}), 122.48 (C_{Ar}), 121.7 (C_{Ar}), 115.2 (C_{Ar}), 113.3 (d, $^{2}J_{PC}$ = 8.5 Hz, C3 indole), 84.0 ($CO\underline{C}(CH_3)_3$), 72.5 (d, $^{2}J_{PC}$ = 7.2 Hz, $\underline{C}HCH_3$), 72.2 (d, $^{2}J_{PC}$ = 7.6 Hz, $\underline{C}HCH_3$), 55.9 ($SO\underline{C}(CH_3)_3$), 49.3 (d, $^{1}J_{PC}$ = 161.4 Hz, CHP), 28.3 ($COC(\underline{C}H_3)_3$), 24.3 (d, $^{3}J_{PC}$ = 3.5 Hz, $CH\underline{C}H_3$), 24.2 (d, $^{3}J_{PC}$ = 3.7 Hz, $CH\underline{C}H_3$), 24.1 (d, $^{3}J_{PC}$ = 5.2 Hz, $CH\underline{C}H_3$), 23.7 (d, $^{3}J_{PC}$ = 5.4 Hz, $CH\underline{C}H_3$), 22.7 ($SOC(\underline{C}H_3)_3$) ppm.

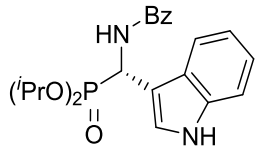
^{31}P RMN (120 MHz, $CDCl_3$) δ 19.34 ppm.

IR ν 3262 (N-H), 1736 (C=O), 1451 (CH_3), 1254 (P=O), 1066 (S=O) cm^{-1}.

HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{40}N_2O_6PS$ $[M+H]^+$ 515.2339, found 515.2345.

The absolute configuration of aminophosphonate **110** was determined by X-Ray diffraction.

(*S*)-Diisopropyl (benzamido(1*H*-indol-3-yl)methyl)phosphonate (102c).

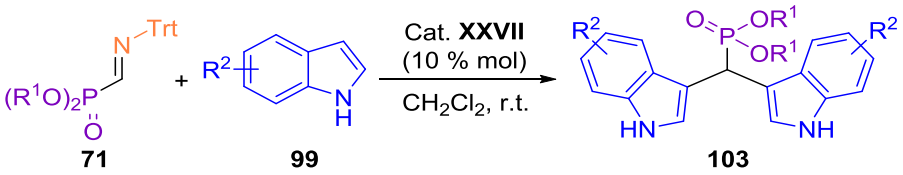


Following a modified literature procedure,[81] α-aminophosphonate **110** (257.1 mg, 0.5 mmol) was dissolved in ^{i}PrOH (2 mL) and 4N HCl (2 mL) was added. The reaction mixture was stirred at room temperature until the starting material was totally consumed (TLC). Then, the mixture was extracted with CH_2Cl_2 (2×15 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced

pressure. The crude product was again dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, and pyridine (44 µL, 0.55 mmol) and benzoyl chloride (64 µL, 0.55 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 2 h and then was quenched with 0.1 M HCl (5 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (hexanes/AcOEt) to give 174.1 mg of pure **102c** (84 %) as a white solid. Ee (90 %) was determined by HPLC analysis (Chiracel-IA, Heptane/CH_2Cl_2/Ethanol 50:49:1, 1 mL/min). Retention time (min): 8.14 (major) and 9.24 (minor). Comparison of the retention times with compound **102c** synthesized by the enantioselective Friedel−Crafts reaction from imine **71c** showed that both compounds have the opposite configuration.

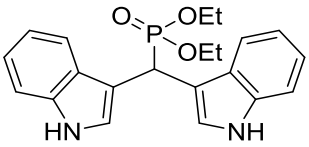
Chapter 3. Synthesis and antiproliferative evaluation of bis-(3-indolyl)methane phosphonates

General procedure for the synthesis of BIMPs 103



To a solution of the corresponding aldimine **71** (1.0 mmol) and the corresponding indole (2.0 mmol) in CH_2Cl_2 (10 mL), 1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (34.8 mg, 0.1 mmol) was added and the reaction mixture was stirred for 36 h at room temperature. After that, 20 mL of water were added and the organic phase was extracted with CH_2Cl_2 (2x10 mL) and dried of in $MgSO_4$. The volatiles were distilled off at reduced pressure to yield the crude product, which was purified by column chromatography (hexanes/AcOEt).

Diethyl (di(1*H*-indol-3-yl)methyl)phosphonate (103a).



The general procedure was followed using aldimine **71f** and indole, to afford 233.2 mg (61%) of **103a** as a white solid.

Mp: 144-146 °C (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 2H, 2xNH), 7.65 (d, $^3J_{HH}$ = 7.8 Hz, 2H, 2xCH_{Ar}), 7.39 – 7.20 (m, 4H, 4xCH_{Ar}), 7.20 – 6.93 (m, 4H, 4xCH_{Ar}), 5.07 (d, $^2J_{PH}$ = 24.9 Hz, 1H, CHP), 3.94 (m, 2H, CH_2), 3.72 (m, 2H, CH_2), 1.04 (t, $^3J_{HH}$ = 7.0 Hz, 6H, 2xCH_3) ppm.

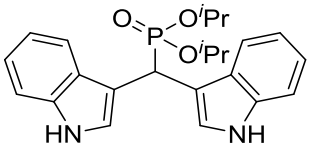
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.1 (2xC7a indole), 127.1 (d, $^2J_{PC}$ = 8.6 Hz, 2xC3 indole), 124.6 (d, $^3J_{PC}$ = 6.2 Hz, 2xC2 indole), 121.9 (2xC6 indole), 119.4 (2xC5 indole), 119.1 (2xC4 indole), 111.4 (2xC7 indole), 111.2 (d, $^3J_{PC}$ = 5.8 Hz, 2xC3a indole), 62.8 (d, $^2J_{PC}$ = 7.3 Hz, CH_2), 32.1 (d, $^1J_{PC}$ = 143.6 Hz, CHP), 16.4 (d, $^3J_{PC}$ = 5.7 Hz, CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 28.1 ppm.

IR ν 3406 (N-H), 3248 (C-H_{Ar}), 1206 (P=O), 1076 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{21}H_{23}N_2O_3PK$ $[M+K]^+$ 421.1078, found 421.1084.

Diisopropyl (di(1*H*-indol-3-yl)methyl)phosphonate (103b).



The general procedure was followed using aldimine **71g** and indole, to afford 246.1 mg (60%) of **103b** as a white solid.

Mp: 162-164 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 2H, 2xNH), 7.68 (d, $^3J_{HH}$ = 7.7 Hz, 2H, 2xCH_{Ar}), 7.31 – 7.21 (m, 4H, 4xCH_{Ar}), 7.15 – 7.04 (m, 4H, 4xCH_{Ar}), 5.04 (d, $^2J_{PH}$ = 25.2 Hz, 1H, CHP), 4.43 (m, 2H, 2xC<u>H</u>CH_3), 1.20 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3), 0.72 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3) ppm.

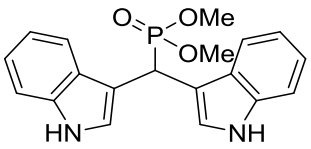
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.0 (2xC7a indole), 128.4 (2xC_{Ar}), 128.1 (2xC_{Ar}), 127.3 (d, $^2J_{PC}$ = 8.7 Hz, 2xC3 indole), 124.6 (d, $^3J_{PC}$ = 6.0 Hz, 2xC2 indole), 121.6 (2xC_{Ar}), 119.1 (2xC_{Ar}), 111.2 (d, $^3J_{PC}$ = 5.6 Hz, 2xC3a indole), 71.5 (d, $^2J_{PC}$ = 7.8 Hz, 2xC<u>H</u>CH_3), 32.4 (d, $^1J_{PC}$ = 145.5 Hz, CHP), 24.3 (d, $^3J_{PC}$ = 3.2 Hz, 2xCH_3), 23.2 (d, $^3J_{PC}$ = 5.3 Hz, 2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.3 ppm.

IR ν 3404 (N-H), 3180 (C-H_{Ar}), 1216 (P=O), 1099 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{23}H_{27}N_2O_3PNa$ $[M+Na]^+$ 433.1651, found 433.1666

Dimethyl (di(1*H*-indol-3-yl)methyl)phosphonate (103c).



The general procedure was followed using aldimine **71e** and indole, to afford 208.9 mg (59%) of **103c** as a white solid.

Mp: 239-240 °C (Et_2O).

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.61 (dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, 2H, 2xH4 indole), 7.39 (d, $^3J_{HH}$ = 2.7 Hz, 2H, 2xH2 indole), 7.34 (dt, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.0 Hz, 2H, 2xH7 indole), 7.08 (ddd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ =

7.0 Hz, $^{4}J_{HH}$ = 1.1 Hz, 2H, 2xH6 indole), 7.00 (ddd, $^{3}J_{HH}$ = 8.0 Hz, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, 2H, 2xH5 indole), 5.16 (d, $^{2}J_{PH}$ = 25.3 Hz, 1H, CHP), 3.52 (d, $^{3}J_{PH}$ = 10.6 Hz, 6H, 2xCH_3) ppm.

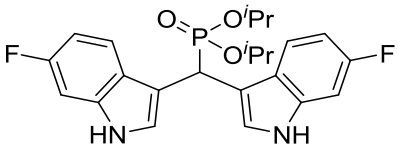
^{13}C {^{1}H} NMR (75 MHz, MeOH-d_4) δ 137.8 (2xC7a indole), 128.3 (d, $^{2}J_{PC}$ = 8.7 Hz, 2xC3 indole), 125.4 (d, $^{3}J_{PC}$ = 6.4 Hz, 2xC2 indole), 122.5 (2xC6 indole), 120.0 (2xC5 indole), 119.6 (2xC4 indole), 112.3 (2xC7 indole), 111.2 (d, $^{3}J_{PC}$ = 6.1 Hz, 2xC3a indole), 53.9 (d, $^{2}J_{PC}$ = 7.4 Hz, 2x CH_3), 32.8 (d, $^{1}J_{PC}$ = 143.7 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_{3:}$) δ 30.0 ppm.

IR ν 3378 (N-H), 3177 (C-H_{Ar}), 1209 (P=O), 1059 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{19}H_{19}N_2O_3PK$ $[M+K]^+$ 393.0776, found 393.0777.

Diisopropyl (bis(6-fluoro-1*H*-indol-3-yl)methyl)phosphonate (103d).



The general procedure was followed using aldimine **71g** and 6-fluoroindole, to afford 322.0 mg (69%) of **103d** as a pale brown solid.

Mp: 85-86 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 2H, 2xNH), 7.53 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{FH}$ = 5.3 Hz, 2H, 2xH4 indole), 7.28 (m, 2H, 2xH2 indole), 7.00 (dd, $^{3}J_{FH}$ = 9.7 Hz, $^{4}J_{HH}$ =2.3 Hz, 2H, 2xH7 indole), 6.81 (ddd, $^{3}J_{FH}$ = 9.6 Hz, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{HH}$ = 2.3 Hz, 2H, 2xH5 indole), 4.91 (d, $^{2}J_{PH}$ = 25.4 Hz, 1H, CHP),

4.49 (m, 2H, 2xC<u>H</u>CH$_3$), 1.22 (d, $^3J_{HH}$ = 6.1 Hz, 6H, 2xCH$_3$), 0.77 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH$_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0 (d, $^1J_{FC}$ = 237.3 Hz, 2xC6 indole), 136.08 (d, $^3J_{FC}$ = 12.7 Hz, 2xC7a indole), 124.56 (dd, $^3J_{PC}$ = 6.4 Hz, $^5J_{FC}$ = 3.57 Hz, 2xC2 indole), 124.00 (d, $^2J_{PC}$ = 8.5 Hz, 2xC3 indole), 120.0 (d, $^3J_{FC}$ = 10.2 Hz, 2xC4 indole), 111.6 (d, $^3J_{PC}$ = 5.5 Hz, 2xC3a indole), 108.1 (d, $^2J_{FC}$ = 24.6 Hz, 2xC7 indole), 97.6 (d, $^2J_{FC}$ = 26.0 Hz, 2xC5 indole), 71.6 (d, $^2J_{PC}$ = 7.8 Hz, 2x<u>C</u>HCH$_3$), 32.8 (d, $^1J_{PC}$ = 146.1 Hz, CHP), 24.4 (d, $^3J_{PC}$ = 3.3 Hz, 2xCH$_3$), 23.4 (d, $^3J_{PC}$ = 5.3 Hz, 2xCH$_3$) ppm.

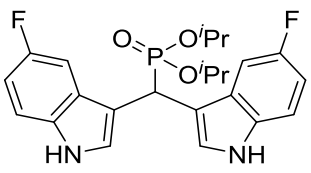
^{31}P NMR (120 MHz, $CDCl_3$) δ 24.9 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -121.9 ppm.

IR ν 3398 (N-H), 3216 (C-H$_{Ar}$), 1218 (P=O), 1100 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PK$ $[M+K]^+$ 485.1203, found 485.1204.

Diisopropyl (bis(5-fluoro-1*H*-indol-3-yl)methyl)phosphonate (103e).



The general procedure was followed using aldimine **71g** and 5-fluoroindole, to afford 298.7 mg (67%) of **103e** as a pale brown solid.

Mp: 88-89 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, $^3J_{HH}$ = 1.7 Hz, 2xNH), 7.30 – 7.24 (m, 4H, 4xCH$_{Ar}$), 7.15 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{FH}$ = 4.4 Hz, 2H, 2xH7 indole),

6.85 (td, $^{3}J_{FH}$ = $^{3}J_{HH}$ = 9.1 Hz, $^{4}J_{HH}$ = 2.5 Hz, 2H, 2xH6 indole), 4.82 (d, $^{2}J_{PH}$ = 25.3 Hz, 1H, CHP), 4.52 (m, 2H, 2xC<u>H</u>CH$_3$), 1.22 (d, $^{3}J_{HH}$ = 6.2 Hz, 6H, 2xCH$_3$), 0.79 (d, $^{3}J_{HH}$ = 6.2 Hz, 6H, 2xCH$_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9 (d, $^{1}J_{FC}$ = 234.3 Hz, 2xC5 indole), 132.7 (2xC7a indole), 127.7 (m, 2xC3 indole), 126.1 (d, $^{3}J_{PC}$ = 6.0 Hz, 2xC2 indole), 112.0 (d, $^{3}J_{FC}$ = 9.5 Hz, 2xC7 indole), 111.7 (m, 2xC3a indole), 110.5 (d, $^{2}J_{FC}$ = 26.3 Hz, 2xC4 indole), 104.3 (d, $^{2}J_{FC}$ = 23.8 Hz, 2xC6 indole), 71.7 (d, $^{2}J_{PC}$ = 7.7 Hz, 2x<u>C</u>HCH$_3$), 33.0 (d, $^{1}J_{PC}$ = 145.9 Hz, CHP), 24.3 (d, $^{3}J_{PC}$ = 3.3 Hz, 2xCH$_3$), 23.4 (d, $^{3}J_{PC}$ = 5.1 Hz, 2xCH$_3$) ppm.

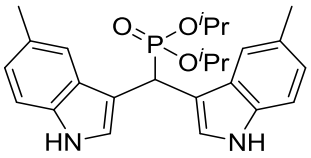
^{31}P NMR (120 MHz, $CDCl_3$) δ 24.8 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -125.1 ppm.

IR ν 3419 (N-H), 3213 (C-H$_{Ar}$), 1218 (P=O), 1101 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PK$ $[M+K]^+$ 485.1203, found 485.1201

Diisopropyl (bis(5-methyl-1*H*-indol-3-yl)methyl)phosphonate (103f).



The general procedure was followed using aldimine **71g** and 5-methylindole, to afford 272.3 mg (62%) of **103f** as a brown solid.

Mp: 92-94 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 2H, 2xNH), 7.48 (s, 2H, 2xH2 indole), 7.32 (m, 2H, 2xCH$_{Ar}$), 7.18 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xH7 indole), 6.96 (dd, $^{3}J_{HH}$ = 8.1, 1.1 Hz, 2H, 2xH6 indole), 4.94 (d, $^{2}J_{PH}$ = 25.2 Hz, 1H,

CHP), 4.49 (m, 2H, 2xC<u>H</u>CH_3), 2.42 (s, 6H, 2xC_{Ar} CH_3), 1.22 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3), 0.77 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3) ppm.

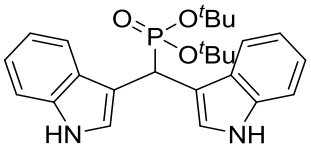
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.5 (2xC7a indole), 128.4 (2xC5 indole), 127.7 (d, $^2J_{PC}$ = 8.5 Hz, 2xC3 indole), 124.5 (d, $^3J_{PC}$ = 5.9 Hz, 2xC2 indole), 123.5 (2xC6 indole), 119.1 (2xC4 indole), 111.5 (d, $^3J_{PC}$ = 5.6 Hz, 2xC3 indole), 110.8 (2xC7 indole), 71.2 (d, $^2J_{PC}$ = 7.7 Hz, 2x<u>C</u>HCH_3), 32.6 (d, $^1J_{PC}$ = 145.3 Hz, CHP), 24.5 (d, $^3J_{PC}$ = 2.8 Hz, 2xCH<u>C</u>H_3), 23.4 (d, $^3J_{PC}$ = 5.3 Hz, 2xCH<u>C</u>H_3), 21.7 (2xCH_3 indol) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 25.5 ppm.

IR ν 3401 (N-H), 3245 (C-H_{Ar}), 1380 (C-H_{Me}), 1218 (P=O), 1097 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PNa$ $[M+Na]^+$ 461.1964, found 461.1960.

Di-*tert*-butyl (di(1*H*-indol-3-yl)methyl)phosphonate (103g).



The general procedure was followed using aldimine **71h** and indole, to afford 297.9 mg (68%) of **103g** as a white solid.

Mp: 162-164 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 2H, 2xNH), 7.66 (d, $^3J_{HH}$ = 7.8 Hz, 2H, 2xCH_{Ar}), 7.39 – 7.28 (m, 4H, 4xCH_{Ar}), 7.18 – 6.98 (m, 4H, 4xCH_{Ar}), 4.95 (d, $^2J_{PH}$ = 25.6 Hz, 1H, CHP), 1.20 (s, 18H, 6xCH_3) ppm.

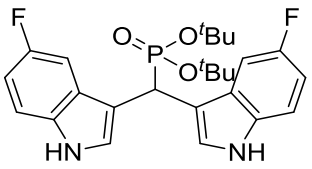
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.0 (2xC7a indole), 127.8 (d, $^{2}J_{PC}$ = 8.4 Hz, 2xC3 indole), 124.6 (d, $^{3}J_{PC}$ = 6.1 Hz, 2xC2 indole), 121.7 (2xC_{Ar}), 119.5 (2xC_{Ar}), 119.2 (2xC_{Ar}), 112.6 (d, $^{3}J_{PC}$ = 5.6 Hz, 2xC3a indole), 111.2 (2xC_{Ar}), 82.7 (d, $^{2}J_{PC}$ = 10.5 Hz, 2x$\underline{C}(CH_3)_3$), 35.1 (d, $^{1}J_{PC}$ = 149.4 Hz, CHP), 30.3 (d, $^{3}J_{PC}$ = 3.8 Hz, 6xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 18.7 ppm.

IR ν 3416 (N-H), 3219 (C-H_{Ar}), 1224 (P=O), 1168 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{25}H_{31}N_2O_3PK$ $[M+K]^+$ 477.1704, found 477.1715.

Di-*tert*-butyl (bis(5-fluoro-1*H*-indol-3-yl)methyl)phosphonate (103h).



The general procedure was followed using aldimine **71h** and 5-fluoroindole, to afford 327.2 mg (69%) of **103h** as a pale brown solid.

Mp: 145-147 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, Acetone-d_6) δ 10.39 (s, 2H, 2xNH), 7.60 (t, $^{3}J_{HH}$ = 2.4 Hz, 2H, 2xH2 indole), 7.42 (dd, $^{3}J_{FH}$ = 10.3, $^{4}J_{HH}$ = 2.5 Hz, 2H, 2xH4 indole), 7.34 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{FH}$ = 4.5 Hz, 2H, 2xH7 indole), 6.83 (td, $^{3}J_{FH}$ = $^{3}J_{HH}$ = 9.1 Hz, $^{4}J_{HH}$ = 2.5 Hz, 2H, 2xH6 indole), 4.88 (d, $^{2}J_{PH}$ = 25.7 Hz, 1H, CHP), 1.28 (s, 18H, 6xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, Acetone-d_6) δ 158.2 (d, $^{1}J_{FC}$ = 231.1 Hz, 2xC5 indole), 133.9 (2xC7a indole), 129.1 (d, $^{2}J_{PC}$ = 10.1 Hz, 2xC3 indole),

127.5 (dd, $^{3}J_{PC}$ = 6.3 Hz, $^{5}J_{FC}$ = 3.2 Hz 2xC2 indole), 113.2 (m, 2x 2xC3a indole), 112.9 (d, $^{3}J_{FC}$ = 9.6 Hz, 2xC7 indole), 110.0 (d, $^{2}J_{FC}$ = 26.4 Hz, 2xC4 indole), 105.1 (d, $^{2}J_{FC}$ = 23.9 Hz, 2xC6 indole), 82.5 (d, $^{2}J_{PC}$ = 9.9 Hz, 2x<u>C</u>$(CH_3)_3$), 36.9 (d, $^{1}J_{PC}$ = 149.7 Hz, CHP), 30.6 (d, $^{3}J_{PC}$ = 3.8 Hz, 6xCH_3) ppm.

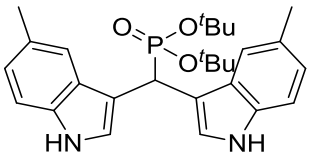
^{31}P NMR (120 MHz, Acetone-d_6) δ 18.9 ppm.

^{19}F NMR (282 MHz, Acetone-d_6) δ -127.5 ppm.

IR ν 3412 (N-H), 1217 (P=O), 1103 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{25}H_{29}F_2N_2O_3PNa$ $[M+Na]^+$ 497.1776, found 497.1779.

Di-*tert*-butyl (bis(5-methyl-1*H*-indol-3-yl)methyl)phosphonate (103i).



The general procedure was followed using aldimine **71h** and 5-methylindole, to afford 336.4 mg (72%) of **103i** as a white solid.

Mp: 194-195 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, Acetone-d_6) δ 10.25 (s, 2H, 2xNH), 7.59 – 7.52 (m, 2H, 2xCH_{Ar}), 7.47 (t, $^{3}J_{HH}$ = 2.7 Hz, 2H, 2xCH_{Ar}), 7.27 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar}), 6.92 (dd, $^{3}J_{HH}$ = 8.2 Hz, $^{3}J_{HH}$ = 1.5 Hz, 2H, 2xCH_{Ar}), 4.96 (d, $^{2}J_{PH}$ = 26.0 Hz, 1H, CHP), 2.41 (s, 6H, 2xCH_3-indol), 1.27 (s, 18H, 6xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, Acetone-d_6) δ 135.5 (2xC7a indole), 128.9 (d, $^{2}J_{PC}$ = 8.0 Hz, 2xC3 indole), 127.80 (2xC5 indole), 125.6 (d, $^{3}J_{PC}$ = 6.2 Hz,

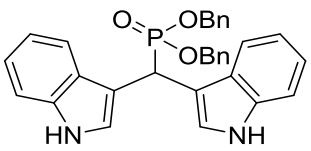
2xC2 indole), 123.4 (2xC6 indole), 119.7 (2xC4 indole), 112.4 (d, $^{3}J_{PC}$ = 5.7 Hz, 2xC3a indole), 111.7 (2xC7 indole), 82.4 (d, $^{2}J_{PC}$ = 10.3 Hz, 2x<u>C</u>$(CH_3)_3$), 36.1 (d, $^{1}J_{PC}$ = 149.7 Hz, CHP), 30.5 (d, $^{3}J_{PC}$ = 3.8 Hz, 6xCH_3), 21.8 (2xCH_3 indole) ppm.

^{31}P NMR (120 MHz, Acetone-d_6) δ 19.5 ppm.

IR ν 3407 (N-H), 1442 (C-H_{Me}), 1227 (P=O), 1106 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PK$ $[M+K]^+$ 505.2017, found 505.2024.

Dibenzyl (di(1*H*-indol-3-yl)methyl)phosphonate (103j)



The general procedure was followed using aldimine **71i** and indole, to afford 272.8 mg (55%) of **103j** as a white solid.

Mp: 131-132 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 2H, 2xNH), 7.64 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar}), 7.41 (t, $^{3}J_{HH}$ = 2.4 Hz, 2H, 2xCH_{Ar}), 7.34 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar}), 7.25 – 7.14 (m, 8H, 8xCH_{Ar}), 7.10 – 7.01 (m, 6H, 6xCH_{Ar}), 5.15 (d, $^{2}J_{PH}$ = 25.2 Hz, 1H, CHP), 4.88 (dd, $^{2}J_{HH}$ = 11.8 Hz, $^{3}J_{PH}$ = 7.3 Hz, 2H, C<u>H</u>$_a$H$_b$), 4.62 (dd, $^{2}J_{HH}$ = 11.8 Hz, $^{3}J_{PH}$ = 8.7 Hz, 2H, CH$_a$<u>H</u>$_b$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.6 (d, $^{3}J_{PC}$ = 5.8 Hz, 2x$C_{quat}CH_2$), 136.1 (2xC7a indole), 128.4 (4xC_{Ar} Ph), 128.2 (2xC_{Ar} Ph), 128.0 (4xC_{Ar} Ph), 127.1 (d, $^{2}J_{PC}$ = 8.9 Hz, 2xC3 indole), 124.4 (d, $^{3}J_{PC}$ = 6.4 Hz, 2xC2 indole), 122.2 (2xC_{Ar} indole), 119.7 (2xC_{Ar} indole), 119.3 (2xC_{Ar} indole),

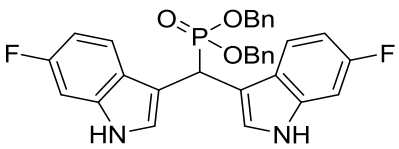
111.5 (d, $^{3}J_{PC}$ = 5.4 Hz, 2xC3a indole), 111.3 (2xC_{Ar} indole), 68.2 (d, $^{2}J_{PC}$ = 7.3 Hz, 2xCH_2), 32.6 (d, $^{1}J_{PC}$ = 143.5 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 28.9 ppm.

IR ν 3399 (N-H), 3172 (C-H_{Ar}), 1218 (P=O), 1092 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{27}N_2O_3PK$ $[M+K]^+$ 545.1391, found 545.1390.

Dibenzyl (bis(6-fluoro-1*H*-indol-3-yl)methyl)phosphonate (103k).



The general procedure was followed using aldimine **71i** and 6-fluoroindole, to afford 352.1 mg (65%) of **103k** as a pale orange solid.

Mp: 60-62 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 2H, 2xNH), 7.47 (dd, $^{3}J_{FH}$ = 8.6 Hz, $^{3}J_{HH}$ =5.3 Hz, 2H, 2xCH_{Ar}), 7.30 – 7.11 (m, 8H, 8xCH_{Ar}), 7.01 (d, $^{3}J_{HH}$ = 7.5 Hz, 4H, 4xCH_{Ar}), 6.94 (d, $^{3}J_{HH}$ = 9.6 Hz, 2H, 2xCH_{Ar}), 6.78 (m, 2H, 2xCH_{Ar}), 5.06 (d, $^{2}J_{PH}$ = 25.1 Hz, 1H, CHP), 4.84 (dd, $^{2}J_{HH}$ = 11.6 Hz, $^{3}J_{PH}$ = 7.4 Hz, 2H, C$\underline{H}_a$$H_b$), 4.63 (dd, $^{2}J_{HH}$ = 11.6 Hz, $^{3}J_{PH}$ = 9.1 Hz, 2H, $CH_a\underline{H}_b$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.0 (d, $^{1}J_{FC}$ = 237.4 Hz, 2xC6 indole), 136.1 (d, $^{3}J_{PC}$ = 8.5 Hz, 2x$C_{quat}CH_2$), 136.0 (d, $^{3}J_{FC}$ = 9.8 Hz, 2xC7a indole), 128.5 (m, 4xC_{Ar} Ph), 128.3 (m, 2xC_{Ar} Ph), 127.9 (m, 4xC_{Ar} Ph), 124.9 (dd, $^{3}J_{PC}$ = 6.5 Hz, $^{5}J_{FC}$ = 3.3 Hz, 2xC2 indole), 123.5 (d, $^{3}J_{PC}$ = 8.4 Hz, 2xC3 indole), 119.8 (d, $^{3}J_{PC}$ = 10.0 Hz, 2xC4 indole), 110.6 (d, $^{3}J_{PC}$ = 6.0 Hz,

2xC3a indole), 108.3 (d, $^{2}J_{FC}$ = 24.5 Hz, 2xC7 indole), 97.8 (d, $^{2}J_{FC}$ = 25.8 Hz, 2xC5 indole), 68.4 (d, $^{2}J_{PC}$ = 7.4 Hz, 2xCH_2), 32.7 (d, $^{1}J_{PC}$ = 143.3 Hz, CHP) ppm.

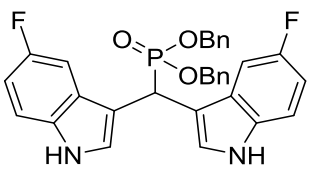
^{31}P NMR (120 MHz, $CDCl_3$) δ 27.6 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -121.6 ppm.

IR ν 3431 (N-H), 1224 (P=O), 1098 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PK$ $[M+K]^+$ 581.1203, found 581.1195.

Dibenzyl (bis(5-fluoro-1H-indol-3-yl)methyl)phosphonate (103l).



The general procedure was followed using aldimine **71i** and 5-fluoroindole, to afford 362.9 mg (67%) of **103l** as a pale orange solid.

Mp: 87-89 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 2H, 2xNH), 7.54 – 7.04 (m, 12H, 10xCH_{Ar}), 6.96 (d, $^{3}J_{HH}$ = 6.9 Hz, 4H, 4xCH_{Ar}), 6.84 (m, 2H, 2xCH_{Ar}), 4.91 (d, $^{2}J_{PH}$ = 25.0 Hz, 1H, CHP), 4.73 (dd, $^{2}J_{HH}$ = 11.3 Hz, $^{3}J_{PH}$ = 7.4 Hz, 2H, C$\underline{H}_a$$H_b$), 4.51 (m, 2H, $CH_a\underline{H}_b$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.9 (d, $^{1}J_{FC}$ = 234.6 Hz, 2xC5 indole), 143.8 (2xC3 indole), 135.9 (d, $^{3}J_{PC}$ = 5.9 Hz, 2x$C_{quat}CH_2$), 132.5 (2xC7a indole), 128.5 (4xC_{Ar} Ph), 128.4 (2xC_{Ar} Ph), 127.9 (4xC_{Ar} Ph), 127.2 (m, 2xC3a indole), 126.6 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC2 indole), 112.3 (d, $^{3}J_{FC}$ = 9.2

Hz, 2xC7 indole), 110.5 (d, $^{2}J_{FC}$ = 26.6 Hz, 2xC6/4 indole), 103.8 (d, $^{2}J_{FC}$ = 23.7 Hz, 2xC6/4 indole), 68.4 (d, $^{2}J_{PC}$ = 7.4 Hz, 2xCH_2), 32.4 (d, $^{1}J_{PC}$ = 143.3 Hz, CHP) ppm.

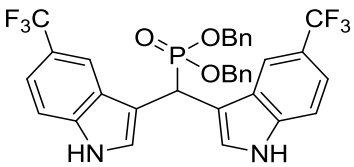
^{31}P NMR (120 MHz, $CDCl_3$) δ 27.0 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -124.8 ppm.

IR ν 3432 (N-H), 1212 (P=O), 1105 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PK$ $[M+K]^+$ 581.1203, found 581.1199.

Dibenzyl (bis(5-(trifluoromethyl)-1*H*-indol-3-yl)methyl)phosphonate (103m).



The general procedure was followed using aldimine **71i** and 5-trifluoromethylindole, to afford 347.1 mg (54%) of **103m** as a pale orange solid.

Mp: 107-108°C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 2H, 2xNH), 7.91 (s, 2H, 2xCH_{Ar}), 7.40 – 7.13 (m, 12H, 12xCH_{Ar}), 7.00 (d, $^{3}J_{HH}$ = 6.9 Hz, 4H, 4xCH_{Ar}), 5.07 (d, $^{2}J_{PH}$ = 24.9 Hz, 1H, CHP), 4.87 (dd, $^{2}J_{HH}$ = 11.4 Hz, $^{3}J_{PH}$ = 8.2 Hz, 2H, C$\underline{H}_a$$H_b$), 4.67 (m, 2H, $CH_a\underline{H}_b$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.5 (2xC7a indole), 135.7 (d, $^{3}J_{PC}$ = 5.4 Hz, $C_{quat}CH_2$), 128.3 (4xC_{Ar} Ph), 128.1 (4xC_{Ar} Ph), 128.0 (2xC_{Ar} Ph) , 126.3 (d, $^{3}J_{PC}$ = 6.4 Hz, 2xC2 indole), 126.1 (d, $^{2}J_{PC}$ = 8.0 Hz, 2xC3 indole),

125.4 (q, $^{1}J_{FC}$ = 271.5 Hz, 2xCF_3), 122.1 (q, $^{2}J_{FC}$ = 31.8 Hz, 2xC5 indole), 119.0 (q, $^{3}J_{FC}$ = 3.3 Hz, 2xC4 indole), 116.8 (q, $^{3}J_{FC}$ = 4.5 Hz, 2xC6 indole), 111.9 (2xC7 indole), 111.2 (d, $^{3}J_{PC}$ = 6.0 Hz, 2xC3a indole), 68.7 (d, $^{2}J_{PC}$ = 7.5 Hz, 2xCH_2), 32.6 (d, $^{1}J_{PC}$ = 142.4 Hz, CHP) ppm.

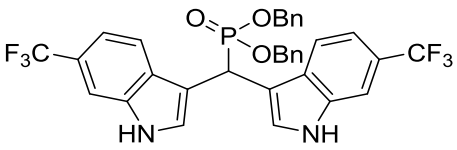
^{31}P NMR (120 MHz, $CDCl_3$) δ 26.5 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -60.6 ppm.

IR ν 3423 (N-H), 1256 (P=O), 1101 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{25}F_6N_2O_3PK$ $[M+K]^+$ 681.1139, found 681.1131.

Dibenzyl (bis(6-(trifluoromethyl)-1*H*-indol-3-yl)methyl)phosphonate (103n).



The general procedure was followed using aldimine **71i** and 6-trifluoromethylindole, to afford 340.3 mg (53%) of **103n** as a pale orange solid.

Mp: 96-97 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 2H, 2xNH), 7.63 – 7.59 (m, 4H, 4xCH_{Ar}), 7.35 – 7.22 (m, 4H, 4xCH_{Ar}), 7.21 – 7.13 (m, 6H, 6xCH_{Ar}), 7.03 – 6.97 (d, $^{3}J_{HH}$ = 6.7 Hz, 4H, 4xCH_{Ar}), 5.11 (d, $^{2}J_{PH}$ = 25.2 Hz, 1H, CHP), 4.87 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 7.7 Hz, 2H, C$\underline{H}_a$$H_b$), 4.71 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 9.3 Hz, 2H, $CH_a\underline{H}_b$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.8 (d, $^{3}J_{PC}$ = 5.7 Hz, $C_{quat}CH_2$), 135.0 (2xC7a indole), 129.0 (d, $^{2}J_{PC}$ = 9.3 Hz, 2xC3 indole), 128.3 (4xC_{Ar} Ph), 128.1 (4xC_{Ar} Ph), 128.0 (2xC_{Ar} Ph), 127.1 (d, $^{3}J_{PC}$ = 6.2 Hz, 2xC2 indole), 125.3 (q, $^{1}J_{FC}$ = 271.6 Hz, 2xCF_3), 124.3 (q, $^{2}J_{FC}$ = 31.9 Hz, 2xC6 indole), 119.5 (2xC7 indole), 116.4 (q, $^{3}J_{FC}$ = 3.5 Hz, 2xC5 indole), 110.9 (d, $^{3}J_{PC}$ = 5.8 Hz, 2xC3a indole), 109.2 (q, $^{3}J_{FC}$ = 4.4 Hz, 2xC4 indole), 68.6 (d, $^{2}J_{PC}$ = 7.5 Hz, 2xCH_2), 32.6 (d, $^{1}J_{PC}$ = 143.9 Hz, CHP) ppm.

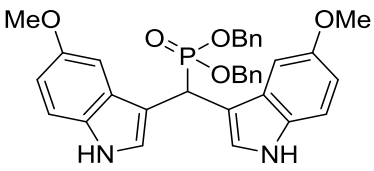
^{31}P NMR (120 MHz, $CDCl_3$) δ 26.9 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -61.0 ppm.

IR ν 3419 (N-H), 1260 (P=O), 1097 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{25}F_6N_2O_3PK$ $[M+K]^+$ 681.1139, found 681.1138.

Dibenzyl (bis(5-methoxy-1*H*-indol-3-yl)methyl)phosphonate (103o).



The general procedure was followed using aldimine **71i** and 5-methoxyindole, to afford 323.0 mg (57%) of **103o** as a brown solid.

Mp: 140-142 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H, 2xNH), 7.41 – 7.34 (m, 2H, 2xCH_{Ar}), 7.24 – 7.10 (m, 8H, 8xCH_{Ar}), 7.08 – 6.96 (m, 6H, 6xCH_{Ar}), 6.82 (dd, $^{3}J_{HH}$ = 8.7 Hz, $^{4}J_{HH}$ = 2.5 Hz, 2H, CH_{Ar}), 5.03 (d, $^{2}J_{PH}$ = 25.1 Hz, 1H,

CHP), 4.86 (dd, $^{2}J_{HH}$ = 11.6 Hz, $^{3}J_{PH}$ = 7.0 Hz, 2H, C$\underline{H}_a$H$_b$), 4.60 (dd, $^{2}J_{HH}$ = 11.6 Hz, $^{3}J_{PH}$ = 8.4 Hz, 2H, CH$_a\underline{H}_b$), 3.70 (s, 6H, 2xCH$_3$O) ppm.

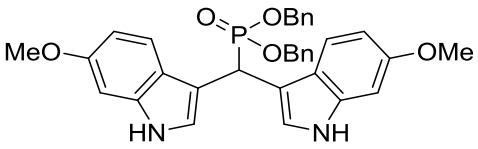
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.1 (2xC5 indole), 136.4 (d, $^{3}J_{PC}$ = 6.3 Hz, 2xC$_{quat}$CH$_2$), 131.3 (2xC7a indole), 128.4 (4xC$_{Ar}$ Ph), 128.2 (2xC$_{Ar}$ Ph), 128.0 (4xC$_{Ar}$ Ph), 127.5 (d, $^{2}J_{PC}$ = 8.4 Hz, 2xC3 indole), 125.4 (d, $^{3}J_{PC}$ = 6.1 Hz, 2xC2 indole), 112.4 (2xC$_{Ar}$ indole), 112.2 (2xC$_{Ar}$ indole), 110.7 (d, $^{3}J_{PC}$ = 5.8 Hz, 2xC3a indole), 101.0 (2xC$_{Ar}$ indole), 68.3 (d, $^{2}J_{PC}$ = 7.3 Hz, 2xCH$_2$), 55.9 (2xCH$_3$O), 32.1 (d, $^{1}J_{PC}$ = 142.7 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 27.7 ppm.

IR ν 3425 (N-H), 1452 (C-H$_{OMe}$), 1218 (P=O), 1053 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{31}N_2O_5PK$ [M+K]$^{+}$ 605.1603, found 605.1601.

Dibenzyl (bis(6-methoxy-1*H*-indol-3-yl)methyl)phosphonate (103p).



The general procedure was followed using aldimine **71i** and 6-methoxyindole, to afford 344.6 mg (61%) of **103p** as a brown solid.

Mp: 109-110 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2H, 2xNH), 7.47 (d, $^{3}J_{HH}$ = 9.28 Hz, 2H, 2xCH$_{Ar}$), 7.29 – 7.26 (m, 4H, 4xCH$_{Ar}$), 7.21 – 7.17 (m, 4H, 4xCH$_{Ar}$), 7.03 – 6.98 (m, 4H, 4xCH$_{Ar}$), 6.72 – 6.68 (m, 4H, 4xCH$_{Ar}$), 5.04 (d, $^{2}J_{PH}$ = 25.1 Hz, 1H, CHP), 4.82 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 7.1 Hz, 2H, C$\underline{H}_a$H$_b$),

4.56 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 8.6 Hz, 2H, CH_aH_b), 3.75 (s, 6H, 2xCH_3O) ppm.

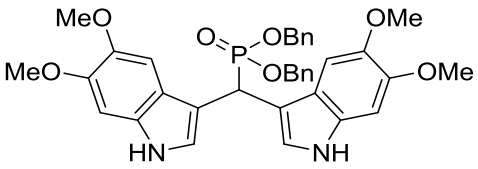
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.5 (2xC6 indole), 136.8 (2xC7a indole), 136.4 (d, $^{3}J_{PC}$ = 6.0 Hz, 2x$C_{quat}CH_2$), 128.4 (4xC_{Ar} Ph), 128.1 (2xC_{Ar} Ph), 128.0 (4xC_{Ar} Ph), 123.5 (d, $^{3}J_{PC}$ = 6.6 Hz, 2xC2 indole), 121.5 (d, $^{2}J_{PC}$ = 8.7 Hz, 2xC3 indole), 119.7 (2xC4 indole), 110.8 (d, $^{3}J_{PC}$ = 6.1 Hz, 2xC3a indole), 109.7 (2xC5 indole), 94.7 (2xC7 indole), 68.2 (d, $^{2}J_{PC}$ = 7.3 Hz, 2xCH_2), 55.7 (2xCH_3O), 32.7 (d, $^{1}J_{PC}$ = 142.7 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 27.9 ppm.

IR ν 3422 (N-H), 1448 (C-H_{OMe}), 1194 (P=O), 1059 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{31}N_2O_5PK$ $[M+K]^+$ 605.1603, found 605.1600.

Dibenzyl (bis(5,6-dimethoxy-1*H*-indol-3-yl)methyl)phosphonate (103q).



The general procedure was followed using aldimine **71i** and 5, 6-dimethoxyindole, to afford 363.5 mg (58%) of **103q** as a brown solid.

Mp: 134-136 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 2H, 2xNH), 7.37 – 7.29 (m, 2H, 2xCH_{Ar}), 7.27 – 7.20 (m, 4H, 4xCH_{Ar}), 7.14 – 7.04 (m, 8H, 8xCH_{Ar}), 6.86

(s, 2H, 2xCH_{Ar}), 5.19 (d, $^2J_{PH}$ = 25.3 Hz, 1H, CHP), 4.87 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{PH}$ = 6.5 Hz, 2H, CH_aH_b), 4.70 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{PH}$ = 7.8 Hz, 2H, CH_aH_b), 3.73 (s, 6H, 2xCH_3O), 3.65 (s, 6H, 2xCH_3O) ppm.

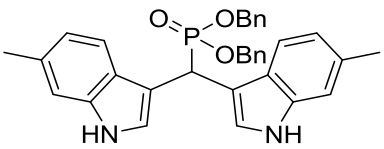
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.1 (2xC6 indole), 145.0 (2xC5 indole), 136.2 (d, $^3J_{PC}$ = 6.4 Hz, 2x$C_{quat}CH_2$), 130.2 (2xC7a indole), 128.6 (4xC_{Ar} Ph), 128.4 (4xC_{Ar} Ph), 127.9 (2xC_{Ar} Ph), 123.7 (d, $^3J_{PC}$ = 5.9 Hz, 2xC2 indole), 119.7 (d, $^2J_{PC}$ = 7.9 Hz, 2xC3 indole), 110.0 (d, $^3J_{PC}$ = 6.0 Hz, 2xC3a indole), 100.6 (2xC4 indole), 94.7 (2xC7 indole), 68.3 (d, $^2J_{PC}$ = 7.3 Hz, 2xCH_2), 56.3 (2xCH_3O), 56.1 (2xCH_3O), 32.6 (d, $^1J_{PC}$ = 142.2 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 27.4 ppm.

IR ν 3401 (N-H), 1445(C-H_{OMe}), 1203 (P=O), 1150 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{35}H_{35}N_2O_7PK$ $[M+K]^+$ 665.1814, found 665.1813.

Dibenzyl (bis(6-methyl-1*H*-indol-3-yl)methyl)phosphonate (103r).



The general procedure was followed using aldimine **71i** and 6-methylindole, to afford 342.0 mg (64%) of **103r** as a pale brown solid.

Mp: 81-83 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 2H, 2xNH), 7.49 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar}), 7.29 – 7.13 (m, 8H, 8xCH_{Ar}), 7.10 – 6.98 (m, 6H, 6xCH_{Ar}),

6.87 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar}), 5.09 (d, $^{2}J_{PH}$ = 25.1 Hz, 1H, CHP), 4.86 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 7.1 Hz, 2H, C$\underline{H}_a H_b$), 4.60 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 8.6 Hz, 2H, $CH_a\underline{H}_b$), 2.42 (s, 6H, 2xCH_3) ppm.

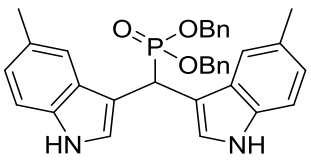
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.6 (2x$C_{quat}CH_2$), 131.8 (2xC7a indole), 128.4 (4xC_{Ar} Ph), 128.1 (2xC_{Ar} Ph), 128.0 (4xC_{Ar} Ph), 125.0 (d, $^{2}J_{PC}$ = 8.8 Hz, 2xC3 indole), 123.9 (d, $^{3}J_{PC}$ = 6.3 Hz, 2xC2 indole), 121.4 (2xC5 indole), 118.9 (2xC4 indole), 111.3 (2xC7 indole), 111.0 (d, $^{3}J_{PC}$ = 5.8 Hz, 2xC3a indole), 68.2 (d, $^{2}J_{PC}$ = 6.9 Hz, 2xCH_2), 32.7 (d, $^{1}J_{PC}$ = 142.8 Hz, CHP), 21.8 (2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 27.9 ppm.

IR ν 3430 (N-H), 1454 (C-H_{Me}), 1222 (P=O) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{31}N_2O_3PK$ $[M+K]^+$ 573.1704, found 573.1701.

Dibenzyl (bis(5-methyl-1*H*-indol-3-yl)methyl)phosphonate (103s).



The general procedure was followed using aldimine **71i** and 5-methylindole, to afford 347.2 mg (65%) of **103s** as a white solid.

Mp: 185-187 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 2H, 2xNH), 7.43 (s, 2H, 2xH2 indole), 7.32 – 7.27 (m, 2H, 2xCH_{Ar}), 7.25 – 7.13 (m, 8H, 8xCH_{Ar}), 7.06 – 6.94 (m, 6H, 6xCH_{Ar}), 5.11 (d, $^{2}J_{PH}$ = 25.1 Hz, 1H, CHP), 4.89 (dd, $^{2}J_{HH}$

= 11.7 Hz, $^{3}J_{PH}$ = 7.0 Hz, 2H, C$\underline{H}_a$H$_b$), 4.59 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{PH}$ = 8.1 Hz, 2H, CH$_a$$\underline{H}_b$), 2.38 (s, 6H, 2xCH$_3$) ppm.

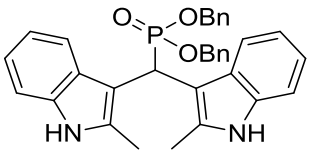
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.6 (d, $^{3}J_{PC}$ = 6.3 Hz, 2xC$_{quat}$CH$_2$), 134.5 (2xC7a indole), 128.7 (2xC5 indole), 128.4 (4xC$_{Ar}$ Ph), 128.1 (2xC$_{Ar}$ Ph), 127.97 (4xC$_{Ar}$ Ph), 127.30 (d, $^{2}J_{PC}$ = 8.4 Hz, 2xC3 indole), 124.81 (d, $^{3}J_{PC}$ = 6.2 Hz, 2xC2 indole), 123.72 (2xC6 indole), 118.84 (2xC4 indole), 111.05 (2xC7 indole), 110.52 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC3a indole), 68.20 (d, $^{2}J_{PC}$ = 7.2 Hz, 2xCH$_2$), 32.47 (d, $^{1}J_{PC}$ = 142.7 Hz, CHP), 21.65 (2xCH$_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 28.0 ppm.

IR ν 3431 (N-H), 1451 (C-H$_{Me}$), 1221 (P=O) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{31}N_2O_3PK$ [M+K]$^{+}$ 573.1704, found 573.1703

Dibenzyl (bis(2-methyl-1*H*-indol-3-yl)methyl)phosphonate (103t).



The general procedure was followed using aldimine **71i** and 2-methylindole, to afford 336.9 mg (63%) of **103t** as a pale brown solid.

Mp: 212-213 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 4H, 2xNH+2xCH$_{Ar}$), 7.32 – 7.13 (m, 8H, 4xCH$_{Ar}$), 7.12 – 6.97 (m, 8H, 6xCH$_{Ar}$), 5.11 (d, $^{2}J_{PH}$ = 30.0

Hz, 1H, CHP), 4.85 (dd, $^{2}J_{HH}$ = 11.6 Hz, $^{3}J_{PH}$ = 7.5 Hz, 2H, C$\underline{H}_a H_b$), 4.66 (m, 2H, $CH_a\underline{H}_b$), 2.19 (s, 3H, 2xCH_3) ppm.

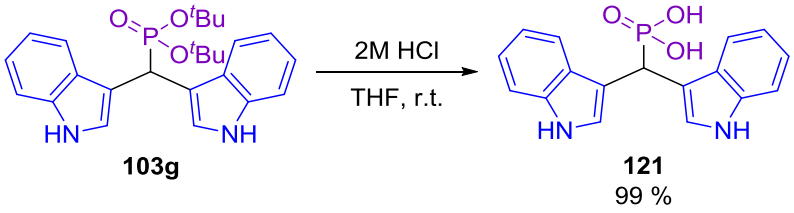
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.6 (d, $^{3}J_{PC}$ = 5.9 Hz, 2x$C_{quat}CH_2$), 134.9 (2xC7a indole), 133.6 (d, $^{3}J_{PC}$ = 10.1 Hz, 2xC2 indole), 128.6 (d, $^{2}J_{PC}$ = 6.7 Hz, 2xC3 indole), 128.4 (4xC_{Ar} Ph), 128.2 (4xC_{Ar} Ph), 128.1 (2xC_{Ar} Ph), 120.9 (2xC6 indole), 119.55 (2xC5 indole), 119.5 (2xC4 indole), 110.3 (2xC7 indole), 106.6 (d, $^{3}J_{PC}$ = 3.6 Hz, 2xC3a indole), 67.9 (d, $^{2}J_{PC}$ = 7.3 Hz, 2xCH_2), 33.2 (d, $^{1}J_{PC}$ = 146.2 Hz, CHP), 12.8 (2xCH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 28.4 ppm.

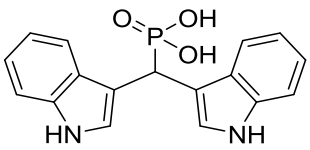
IR ν 3396 (N-H), 1451 (C-H_{Me}), 1227 (P=O) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{33}H_{31}N_2O_3PK$ $[M+K]^+$ 573.1704, found 573.1707.

Hydrolysis of phosphonate



(di(1*H*-indol-3-yl)methyl)phosphonic acid (121).



Di-*tert*-butyl (di(1*H*-indol-3-yl)methyl)phosphonate **103g** (438.5 mg, 1.0 mmol) was diluted in THF (3 mL) and 2M HCl (3 mL) was added. The reaction mixture was stirred at room temperature until the starting material was consumed (monitored by TLC). The mixture was diluted in CH_2Cl_2 and the combined organic phases were collected, dried with anhydrous $MgSO_4$ and concentrated at reduced pressure to yield the crude product which was crystallized in $CHCl_3$-MeOH to afford 323.4 mg (99%) as a pink solid.

Mp: 217-219 °C (dec.) ($CHCl_3$-MeOH).

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.52 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 7.33 (d, $^3J_{HH}$ = 2.2 Hz, 2H, 2xH2 indole), 7.26 (d, $^3J_{HH}$ = 8.1 Hz, 1H, 2xCH_{Ar}), 7.00 (ddd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ =7.1 Hz, $^4J_{HH}$ = 1.1 Hz, 2H, 2xCH_{Ar}), 6.90 (ddd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ =1.0 Hz, 2H, 2xCH_{Ar}), 4.95 (d, $^1J_{PH}$ = 24.8 Hz, 1H, CHP) ppm.

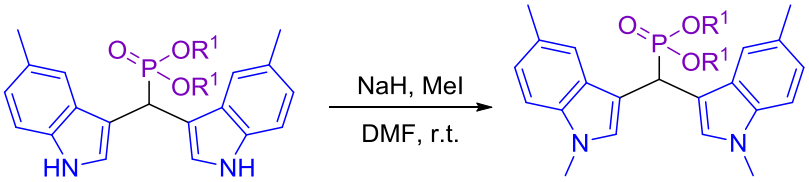
^{13}C {^{1}H} NMR (75 MHz, MeOH-d_4) δ 137.8 (2xC7a indole), 128.8 (d, $^{2}J_{PC}$ = 8.5 Hz, 2xC3 indole), 125.1 (d, $^{3}J_{PC}$ = 5.9 Hz, 2xC2 indole), 122.2 (2xC_{Ar}), 119.9 (2xC_{Ar}), 119.6 (2xC_{Ar}), 113.2 (d, $^{3}J_{PC}$ = 5.0 Hz, 2xC3a indole), 112.1 (2xC_{Ar}), 34.7 (d, $^{1}J_{PC}$ = 141.5 Hz, CHP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.4 ppm.

IR ν 3431 (N-H), 1216 (P=O) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{17}H_{15}N_2O_3PK$ $[M+K]^+$ 365.0452, found 365.0424.

General procedure for the synthesis *N*-methylated substrates

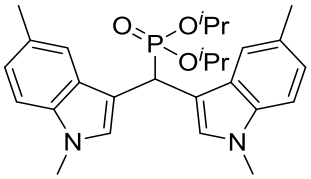


103f: R^1 = ^{i}Pr
103i: R^1 = ^{t}Bu

122: R^1 = ^{i}Pr 99 %
123: R^1 = ^{t}Bu 99 %

The corresponding dialkyl bis(1*H*-indol-3-yl)methyl phosphonate **103** (0.5 mmol) was diluted in freshly distilled DMF (3 mL) under nitrogen atmosphere and the reaction mixture was cooled to 0 °C. NaH (36.0 mg, 1.5 mmol) were added and the reaction was stirred at room temperature for 1h. Then, the reaction was cooled to 0 °C, methyl iodide (0.1 mL, 2.0 mmol) was added and stirring was continued at room temperature for 4h. The reaction mixture was quenched with saturated NH_4Cl solution (15 mL) and diluted in 10 mL of Et_2O. DMF was removed by multiple washing with saturated NH_4Cl solution (10x15 mL). The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure to yield the pure product in quantitative yield.

Diisopropyl (bis(1,5-dimethyl-1*H*-indol-3-yl)methyl)phosphonate (122).



The general procedure was followed to afford 231.5 mg (99%) of **122** as a pale brown solid.

Mp: 78-80 °C (dec.) (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2H, 2xCH_{Ar}), 7.28 (m, 2H, 2xCH_{Ar}), 7.14 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 7.00 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, 2xH6 indole), 4.91 (d, $^2J_{PH}$ = 25.2 Hz, 1H, CHP), 4.49 (m, 2H, 2xC<u>H</u>CH_3), 3.70 (s, 6H, 2xNCH_3), 2.44 (s, 6H, 2xCH_3 indole), 1.22 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3), 0.78 (d, $^3J_{HH}$ = 6.2 Hz, 6H, 2xCH_3) ppm.

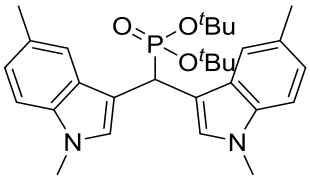
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.3 (2xC7a indole), 128.8 (d, $^3J_{PC}$ = 6.1 Hz, 2xC2 indole), 128.1 (d, $^2J_{PC}$ = 8.7 Hz, 2xC3 indole), 128.0 (2xC5 indole), 123.2 (2xC6 indole), 119.3 (2xC4 indole), 110.2 (d, $^3J_{PC}$ = 5.4 Hz, 2xC3a indole), 108.8 (2xC7 indole), 71.1 (d, $^2J_{PC}$ = 7.5 Hz, 2x<u>C</u>HCH_3), 33.0 (2xNCH_3), 32.4 (d, $^1J_{PC}$ = 145.2 Hz, CHP), 24.5 (d, $^3J_{PC}$ = 2.7 Hz, 2xCH<u>C</u>H_3), 23.4 (d, $^3J_{PC}$ = 5.5 Hz, 2xCH<u>C</u>H_3), 21.7 (2xCH_3 indole) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 25.5 ppm.

IR ν 1448 (C-H_{Me}), 1222 (P=O), 1098 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{31}H_{25}F_2N_2O_3PNa$ $[M+Na]^+$ 489.2277, found 489.2278.

Di-*tert*-butyl (bis(1,5-dimethyl-1*H*-indol-3-yl)methyl)phosphonate (123).



The general procedure was followed to afford 245.3 mg (99%) of **123** as a pale brown solid.

Mp: 82-85 °C (dec.) (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 2H, 2xH2 indole), 7.27 (m, 2H, 2xCH_{Ar}), 7.14 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar}), 7.00 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, 2xH6 indole), 4.84 (d, $^2J_{PH}$ = 25.5 Hz, 1H, CHP), 3.71 (s, 6H, 2xNCH_3), 2.44 (s, 6H, 2xCH_3 indol), 1.18 (s, 18H, 6xCH_3) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 135.2 (2xC7a indole), 129.1 (d, $^3J_{PC}$ = 6.0 Hz, 2xC2 indole), 128.44 (d, $^2J_{PC}$ = 8.5 Hz, 2xC3 indole), 127.8 (2xC5 indole), 123.0 (2xC6 indole), 119.3 (2xC4 indole), 111.1 (d, $^3J_{PC}$ = 5.4 Hz, 2xC3a indole), 108.7 (2xC7 indole), 82.3 (d, $^2J_{PC}$ = 10.5 Hz, 2x$\underline{C}(CH_3)_3$), 34.7 (d, $^1J_{PC}$ = 149.4 Hz, CHP), 32.9 (2xNCH_3), 30.3 (d, $^3J_{PC}$ = 3.8 Hz, 6xCH_3), 21.7 (2xCH_3 indol) ppm.

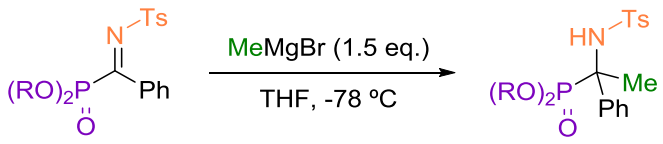
^{31}P NMR (120 MHz, $CDCl_3$) δ 18.1 ppm.

IR ν 1452 (C-H_{Me}), 1227 (P=O), 1101 (P-O-C) cm^{-1}.

HRMS (Q-TOF) m/z calcd. for $C_{29}H_{39}N_2O_3PNa$ $[M+Na]^+$ 517.2590, found 517.2589.

Chapter 4. Nucleophilic addition of organometalic reagents to α-ketiminophosphonates

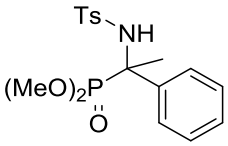
General procedure for the addition of methylmagnesium bromide to ketimines 49



49 **132a-135a**

The imine **49** (0.1 mmol) was dissolved in dry THF (2.0 mL), cooled to -78 °C and stirred for 10 min. Then methylmagnesium bromide was added (0.5 µL, 3M in Et_2O, 0.15 mmol) and the reaction was stirred for 1 h. After that, the reaction was quenched with saturated solution of NH_4Cl (1 mL) and extracted with CH_2Cl_2. The organic phase was dried in $MgSO_4$. The volatiles were distilled off at reduced pressure to give the crude product, which was crystallized in Et_2O/pentane.

Dimethyl (1-((4-methylphenyl)sulfonamido)-1-phenylethyl)phosphonate (132a).[55]



The general procedure was followed to give 32.6 mg (85 %) of **132a** as a white solid.

Mp: 163-164 °C (Et_2O/pentane). Lit.[55] 161–162 (Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.40–7.44 (m, 3H, 3xCH_{Ar}), 7.20 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar}), 7.11 (d, $^3J_{HH}$ = 8.0Hz, 2H, 2xCH_{Ar} *m*-Ts), 5.91 (d, $^3J_{PH}$ = 7.8 Hz, 1H, NH), 3.82 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.41 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.36 (s, 3H, CH_3 Ts), 1.99 (d, $^3J_{PH}$ = 16.9 Hz, 3H, CH_3CP) ppm.

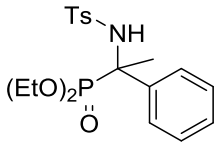
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.3 ($C_{quat}CH_3$ Ts), 141.8 (d, $^4J_{PC}$ = 1.7 Hz, $C_{quat}S$ Ts), 133.4 ($C_{quat}CP$), 128.6 (2xC_{Ar} Ts), 128.4 (d, $^3J_{PC}$ = 6.0 Hz, 2xC_{Ar} *o*-Ph), 128.1 (d, $^4J_{PC}$ = 2.2 Hz, 2xC_{Ar} *m*-Ph), 128.0 (d, $^5J_{PC}$ = 2.9 Hz, C_{Ar} *p*-Ph), 126.7 (2xC_{Ar} Ts), 61.1 (d, $^1J_{PC}$ = 152.2 Hz, CP), 54.5 (d, $^2J_{PC}$ = 7.1 Hz, CH_3O), 53.9 (d, $^2J_{PC}$ = 7.0 Hz, CH_3O), 21.3 (CH_3 Ts), 20.4 (d, $^2J_{PC}$ = 5.2 Hz $\underline{C}H_3CP$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 26.1 ppm.

IR ν 3315 (N-H), 1327 (O=S=O), 1242 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{17}H_{22}NO_5PS$ $[M+Na]^+$ 406.0848, found 406.0856.

Diethyl (1-((4-methylphenyl)sulfonamido)-1-phenylethyl)phosphonate (133a).



The general procedure was followed to give 31.2 mg (83 %) of **133a** as a white solid.

Mp: 113-114 °C (Et_2O/pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.41 – 7.36 (m, 2H, 2xCH_{Ar}), 7.21 – 7.15 (m, 3H, 3xCH_{Ar}), 7.10 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 5.83 (d, $^3J_{PH}$ = 8.0 Hz, 1H, NH), 4.12 – 3.94 (m, 2H, 2x$C\underline{H}_aH_b$), 3.80 (m, 1H, $CH_a\underline{H}_b$), 3.52 (m, 1H, $CH_a\underline{H}_b$), 2.35 (s, 3H, CH_3 Ts), 1.95 (d, $^3J_{PH}$ = 16.8 Hz, 3H, CH_3CP), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.03 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

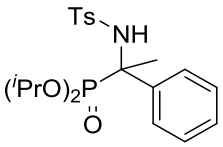
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.2 ($C_{quat}CH_3$ Ts), 139.5 (d, $^4J_{PC}$ = 1.3 Hz, $C_{quat}S$ Ts), 137.6 (d, $^2J_{PC}$ = 2.0 Hz, $C_{quat}CP$), 129.4 (2xC_{Ar} Ts), 128.1 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar} *m*-Ph), 127.7 (d, $^5J_{PC}$ = 3.0 Hz, C_{Ar} *p*-Ph), 127.5 (d, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *o*-Ph), 127.2 (2xC_{Ar} Ts), 64.1 (d, $^2J_{PC}$ = 6.0 Hz, CH_2), 64.1 (d, $^2J_{PC}$ = 6.0 Hz, CH_2), 60.0 (d, $^1J_{PC}$ = 152.4 Hz, CP), 21.9 (CH_3 Ts), 19.9 (d, $^2J_{PC}$ = 6.1 Hz, $\underline{C}H_3CP$), 16.5 (d, $^3J_{PC}$ = 5.8 Hz, $CH_2\underline{C}H_3$), 16.3 (d, $^3J_{PC}$ = 5.6 Hz, $CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.8 ppm.

IR ν 3323 (N-H), 1337 (O=S=O), 1245 (P=O), 1169 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{19}H_{27}NO_5PS$ $[M+H]^+$ 412.1342, found 412.1346.

Diisopropyl (1-((4-methylphenyl)sulfonamido)-1-phenylethyl)phosphonate (134a).



The general procedure was followed to give 37.4 mg (85 %) of **134a** as a white solid.

Mp: 138-140 °C (Et_2O/pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.42 – 7.38 (m, 2H, 2xCH_{Ar}), 7.18 – 7.13 (m, 3H, 3xCH_{Ar}), 7.08 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 4.58 (m, 1H, CH), 4.24 (m, 1H, CH), 2.34 (s, 3H, CH_3 Ts), 1.92 (d, $^3J_{PH}$ = 16.8 Hz, 3H, CH_3CP), 1.28 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHC$\underline{H}_3$), 1.21 – 1.17 (m, 6H, 2xCHC$\underline{H}_3$), 0.78 (d, $^3J_{HH}$ = 6.2 Hz, 3H, CHC$\underline{H}_3$) ppm.

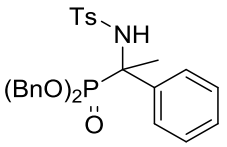
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.0 ($C_{quat}CH_3$ Ts), 139.6 (d, $^4J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 137.9 (d, $^2J_{PC}$ = 1.7 Hz, C_{quat}CP), 129.3 (2xC_{Ar} Ts), 127.9 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar} *m*-Ph), 127.7 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar} *o*-Ph), 127.5 (d, $^5J_{PC}$ = 3.1 Hz, C_{Ar} *p*-Ph), 127.2 (2xC_{Ar} Ts), 72.9 (d, $^2J_{PC}$ = 7.6 Hz, CH), 72.8 (d, $^2J_{PC}$ = 7.6 Hz, CH), 60.0 (d, $^1J_{PC}$ = 154.1 Hz, CP), 24.4 (d, $^3J_{PC}$ = 2.8 Hz, CH$\underline{C}H_3$), 24.3 (d, $^3J_{PC}$ = 2.8 Hz, CH$\underline{C}H_3$), 23.7 (d, $^3J_{PC}$ = 5.8 Hz, CH$\underline{C}H_3$), 23.1 (d, $^3J_{PC}$ = 6.4 Hz, CH$\underline{C}H_3$), 21.6 (CH_3 Ts), 19.9 (d, $^2J_{PC}$ = 6.5 Hz, $\underline{C}H_3$CP) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.2 ppm.

IR ν 3293 (N-H), 1334 (O=S=O), 1235 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{21}H_{31}NO_5PS$ $[M+H]^+$ 440.1655, found 440.1666.

Dibenzyl (1-((4-methylphenyl)sulfonamido)-1-phenylethyl)phosphonate (135a).



The general procedure was followed to give 42.3 mg (79 %) of **135a** as a white solid.

Mp: 80-82 °C (Et_2O/pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.48 – 7.43 (m, 2H, 2xCH_{Ar}), 7.36 – 7.31 (m, 3H, 3xCH_{Ar}), 7.29 – 7.20 (m, 8H, 8xCH_{Ar}), 7.05 – 7.01 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 5.90 (d, $^3J_{PH}$ = 7.9 Hz, 1H, NH), 4.93 (dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 6.7 Hz, 1H, C$\underline{H}_a$H$_b$), 4.87 (dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 8.6 Hz, 1H, CH$_a$$\underline{H}_b$), 4.70 (dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 6.7 Hz, 1H, C$\underline{H}_a$H$_b$), 4.38 (dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 8.6 Hz, 1H, CH$_a$$\underline{H}_b$), 2.34 (s, 3H, CH_3 Ts), 1.96 (d, $^3J_{PH}$ = 17.2 Hz, 3H, CH_3CP) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.11 ($C_{quat}CH_3$ Ts), 139.50 (d, $^4J_{PC}$ = 1.2 Hz, C_{quat}S Ts), 137.60 (d, $^2J_{PC}$ = 2.1 Hz, C_{quat}CP), 135.86 (d, $^3J_{PC}$ = 5.9 Hz, $C_{quat}CH_2$), 135.73 (d, $^3J_{PC}$ = 6.2 Hz, $C_{quat}CH_2$), 129.37 (2xC_{Ar} Ts), 128.74 (2xC_{Ar} Bn), 128.72 (C_{Ar} Bn), 128.62 (2xC_{Ar} Bn), 128.60 (C_{Ar} Bn), 128.25 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar} *m*-Ph), 128.19 (2xC_{Ar} Bn), 127.99 (2xC_{Ar} Bn), 127.89 (d, $^5J_{PC}$ = 3.0 Hz, C_{Ar} *p*-Ph), 127.58 (d, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *o*-Ph), 127.09 (2xC_{Ar} Ts), 69.29 (d, $^2J_{PC}$ = 7.3 Hz, CH_2), 69.11 (d, $^2J_{PC}$ = 7.5 Hz, CH_2), 60.21 (d, $^1J_{PC}$ = 152.2 Hz, CP), 21.59 (CH_3 Ts), 19.85 (d, $^2J_{PC}$ = 6.1 Hz, $\underline{C}H_3$CP) ppm.

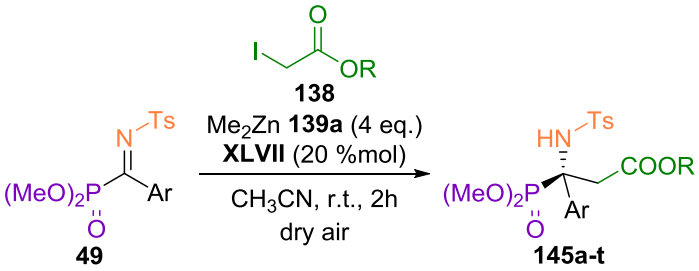
^{31}P NMR (120 MHz, $CDCl_3$) δ 23.6 ppm.

IR ν 3307 (N-H), 1329 (O=S=O), 1236 (P=O), 1159 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{29}H_{31}NO_5PS$ $[M+H]^+$ 536.1655, found 536.1664.

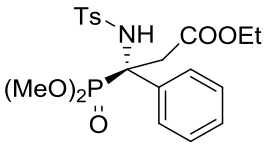
Chapter 5. Enantioselective aza-Reformatksy reaction of α-ketiminophosphonates

General procedure for the asymmetric synthesis of aza-Reformatsky products 145



A solution of the corresponding ketimine **49** (0.1 mmol) and (*R*)-3,3'-Di-9-anthracenyl-1,1'-bi-2-naphthol (12.8 mg, 0.02 mmol), in dry CH_3CN (2 mL) was stirred at room temperature under dry air atmosphere. To this mixture the corresponding iodoacetate (0.2 mmol) and Me_2Zn (0.33 mL, 1.2 M in toluene, 0.4 mmol) were added and the mixture was stirred for 2h at room temperature. The reaction was quenched with slow addition of saturated NH_4Cl solution (0.1 mL), dried with anhydrous $MgSO_4$. The solid was removed by filtration and washed with AcOEt, and the filtrate was concentrated at reduced pressure to yield the crude product, which was purified by column chromatography in silica gel (hexanes/AcOEt).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate (145a).



The general procedure was followed to give 41.4 mg (91 %) of **145a** as a white solid.

Mp: 98-99 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.34 (m, 2H, 2xCH_{Ar}), 7.18 (m, 1H, CH_{Ar}), 7.17 – 6.93 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 6.17 (d, $^3J_{PH}$= 11.2 Hz, 1H, NH), 4.14 (q, $^3J_{HH}$ = 7.1 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.59 (dd, $^3J_{PH}$ = 22.7 Hz, $^2J_{HH}$ = 16.4 Hz, 1H, C$\underline{H}_a$$H_b$CO),3.46 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.45 (dd, $^3J_{PH}$ = 7.5 Hz, $^2J_{HH}$ = 16.4 Hz, 1H, $CH_a$$\underline{H}_b$CO),3.38 (d, $^3J_{PH}$= 10.5 Hz, 3H, CH_3O), 2.36 (s, 3H, CH_3 Ts), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2 (d, $^3J_{PC}$ = 8.0 Hz, CO), 143.2 ($C_{quat}CH_3$ Ts), 139.2 (d, $^4J_{PC}$ = 1.5 Hz, C_{quat}S Ts), 134.4 (d, $^2J_{PC}$ = 7.3 Hz, C_{quat}CP), 129.1 (2xC_{Ar} Ts), 128.3 (d, $^5J_{PC}$ = 2.9 Hz, C_{Ar} *p*-Ph), 128.2 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar} *o*-Ph), 127.9 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar} *m*-Ph), 127.6 (2xC_{Ar} Ts), 62.1 (d, $^1J_{PC}$ = 153.8 Hz, CP), 61.0 ($\underline{C}H_2CH_3$), 54.5 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.0 (d, $^2J_{PC}$ = 7.7 Hz, CH_3O), 38.0 (CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

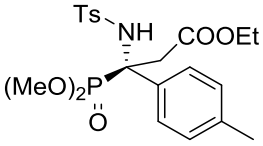
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.1 ppm.

IR ν 3259(N-H), 1741 (C=O), 1338 (O=S=O), 1247 (P=O), 1158 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{27}NO_7PS$ $[M+H]^+$ 456.1240, found 456.1245.

Ee (99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:47:3, 1 mL/min). Retention time (min): 21.3 (major) and 25.9 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(p-tolyl)propanoate (145b).



The general procedure was followed to give 40.3 mg (86 %) of **145b** as a white solid.

Mp: 117-118 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.24 (m, 2H, 2xCH_{Ar}), 7.13 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar}), 6.92 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.13 (d, $^3J_{PH}$ = 11.2 Hz, 1H, NH), 4.14 (q, $^3J_{HH}$= 7.1 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.61 – 3.34 (m, 2H, C$\underline{H}_a$$H_b$CO + $CH_a$$\underline{H}_b$CO), 3.49 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 3.41 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.38 (s, 3H, CH_3 Ts), 2.26 (s, 3H, CH_3-Ar), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.3 (d, $^3J_{PC}$ = 8.1 Hz, CO), 143.2 ($C_{quat}CH_3$ Ts), 139.2 (C_{quat}S Ts), 138.2 (d, $^5J_{PC}$ = 3.1 Hz, C_{quat} Ar), 131.3 (d, $^2J_{PC}$ = 7.3 Hz, C_{quat}CP), 129.0 (2xC_{Ar} Ts), 128.7 (d, $^4J_{PC}$ = 2.7 Hz, 2xC_{Ar} *o*-CH_3), 128.1 (d, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *m*-CH_3), 127.7 (2xC_{Ar} Ts), 61.9 (d, $^1J_{PC}$ = 154.8 Hz, CP), 61.0 ($\underline{C}H_2CH_3$), 54.6 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.0 (d, $^2J_{PC}$ = 7.6 Hz, CH_3O), 37.9 (CH_2CO), 21.6 (CH_3 Ts), 21.1 (CH_3 Ar), 14.2($CH_2\underline{C}H_3$) ppm.

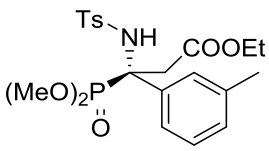
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.3 ppm.

IR ν 3311(N-H), 1732 (C=O), 1335 (O=S=O), 1244 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{21}H_{29}NO_7PS$ $[M+H]^+$ 470.1397, found 470.1403.

Ee (94 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 15.1 (major) and 18.3 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(m-tolyl)propanoate (145c).



The general procedure was followed to give 42.7 mg (91 %) of **145c** as a pale yellow solid.

Mp: 103-104 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.14 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.12 – 6.98 (m, 4H, CH_{Ar}), 6.19 (d, $^3J_{PH}$ = 10.3 Hz, 1H, NH), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.66 (dd, $^3J_{PH}$ = 24.4 Hz, $^2J_{HH}$ = 16.4 Hz, 1H, $C\underline{H}_aH_bCO$), 3.49 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.45 (m, 1H, $CH_a\underline{H}_bCO$), 3.42 (d, $^3J_{PH}$ = 10.5 Hz, 3H, CH_3O), 2.38 (s, 3H, CH_3 Ts), 2.09 (s, 3H, CH_3-Ar), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4 (d, $^3J_{PC}$ = 6.9 Hz, CO), 143.2 ($C_{quat}CH_3$ Ts), 139.4 (d, $^4J_{PC}$ = 1.0 Hz, C_{quat}S Ts), 137.5 (d, $^4J_{PC}$ = 2.9 Hz,

C_{quat} CH_3), 134.0 (d, $^2J_{PC}$ = 7.5 Hz, C_{quat}CP), 129.5 (d, $^3J_{PC}$ = 4.8 Hz, C_{Ar} *o*-CH_3), 129.2 (d, $^5J_{PC}$= 3.2 Hz, C_{Ar} *o*-CH_3), 129.1 (2xC_{Ar} Ts), 128.0 (d, $^4J_{PC}$ = 2.7 Hz, C_{Ar} *m*-CH_3), 127.6 (2xC_{Ar} Ts), 125.0 (d, $^3J_{PC}$ = 5.3 Hz, C_{Ar} *p*-CH_3), 62.2 (d, $^1J_{PC}$ = 153.8 Hz, CP), 61.1 ($\underline{C}H_2CH_3$), 54.6 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.1 (d, $^2J_{PC}$ = 7.7 Hz, CH_3O), 38.3 (CH_2CO), 21.6 (CH_3 Ts), 21.5 (CH_3 Ar), 14.3 ($CH_2\underline{C}H_3$) ppm.

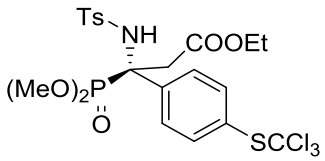
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.4 ppm.

IR ν 3276(N-H), 1735 (C=O), 1338 (O=S=O), 1241 (P=O), 1157 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{21}H_{29}NO_7PS$ $[M+H]^+$ 470.1397, found 470.1398.

Ee (93 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 12.4 (major) and 16.5 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-((trichloromethyl)thio)phenyl)propanoate (145d).



The general procedure was followed to give 52.5 mg (87 %) of **145d** as a pale yellow solid.

Mp: 123-124 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H¸2xCH_{Ar}), 7.53 – 7.46 (m, 4H, 2xCH_{Ar} + 2xCH_{Ar} *o*-Ts), 7.17 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.26 (d, $^{3}J_{PH}$ = 10.5 Hz, 1H, NH), 4.15 (m, 2H, C$\underline{H}_2CH_3$), 3.63 (dd, $^{3}J_{PH}$ = 23.5 Hz, $^{2}J_{HH}$ = 16.4 Hz, 1H, C$\underline{H}_a$$H_b$CO), 3.49 (d, 3H, $^{3}J_{PH}$ = 10.8 Hz, CH_3O), 3.46 (m, 1H, $CH_a\underline{H}_b$CO), 3.49 (d, 3H, $^{3}J_{PH}$ = 10.6 Hz, CH_3O), 2.38 (s, 3H, CH_3 Ts), 1.26 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9 (d, $^{3}J_{PC}$ = 7.1 Hz, CO), 143.7 ($C_{quat}CH_3$ Ts), 139.1 (d, $^{4}J_{PC}$ = 1.2 Hz, C_{quat}S Ts), 138.8 (d, $^{2}J_{PC}$= 7.3 Hz, C_{quat}CP), 136.5 (d, $^{4}J_{PC}$ = 2.8 Hz, 2xC_{Ar} *o*-$SCCl_3$), 130.8 (d, $^{5}J_{PC}$ = 3.6 Hz, $C_{quat}SCCl_3$), 129.4 (2xC_{Ar} Ts), 129.2 (d, $^{3}J_{PC}$ = 4.9 Hz, 2xC_{Ar} *m*-$SCCl_3$), 127.5 (2xC_{Ar} Ts), 98.5 (d, $^{7}J_{PC}$ = 3.2 Hz, CCl_3), 62.3 (d, $^{1}J_{PC}$ = 152.2 Hz, CP), 61.2 ($\underline{C}H_2CH_3$), 54.8 (d, $^{2}J_{PC}$ = 7.4 Hz, CH_3O), 54.4 (d, $^{2}J_{PC}$ = 7.6 Hz, CH_3O), 38.3 (CH_2CO), 21.7 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

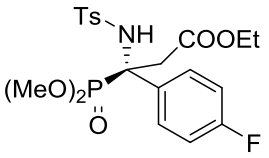
^{31}P NMR (120 MHz, $CDCl_3$) δ21.5 ppm.

IR ν 3291(N-H), 1733 (C=O), 1331 (O=S=O), 1258 (P=O), 1159 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{21}H_{26}Cl_3NO_7PS_2$ $[M+H]^+$ 605.9919, found 605.9928.

Ee (95 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:49:1, 1 mL/min). Retention time (min): 28.4 (major) and 31.9 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-(4-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (145e).



The general procedure was followed to give 42.1 mg (89 %) of **145e** as a white solid.

Mp: 111-112 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.37 – 7.29 (m, 2H, 2xCH_{Ar}), 7.15 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.79 (m, 2H, 2xCH_{Ar}), 6.21 (d, $^3J_{PH}$ = 9.9 Hz, 1H, NH), 4.17 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.74 – 3.34 (m, 2H, $C\underline{H}_aH_bCO$ + $CH_a\underline{H}_bCO$), 3.53 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3,45 (d,$^3J_{PH}$ = 10.5 Hz, 3H, CH_3O), 2.39 (s, 3H, CH_3 Ts), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.1 (d, $^3J_{PC}$ = 7.0 Hz, CO), 162.5 (dd, $^1J_{FC}$ = 248.9 Hz, $^5J_{PC}$ = 3.2 Hz, CF), 143.5($C_{quat}CH_3$ Ts), 139.1 (C_{quat}S Ts), 130.3 (dd, $^3J_{FC}$ = 8.3 Hz, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *m*-F), 130.1 (dd, $^2J_{PC}$ = 6.9 Hz, $^4J_{FC}$ = 3.3 Hz, C_{quat}CP), 129.2 (2xC_{Ar} Ts), 127.6 (2xC_{Ar} Ts), 114.8 (dd, $^2J_{FC}$ = 21.6 Hz, $^4J_{PC}$ = 2.7 Hz, 2xC_{Ar} *o*-F), 61.7 (d, $^1J_{PC}$ = 155.0 Hz, CP), 61.2 ($\underline{C}H_2CH_3$), 54.7 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.2 (d, $^2J_{PC}$ = 7.7 Hz, CH_3O), 38.2 (CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.2 ppm.

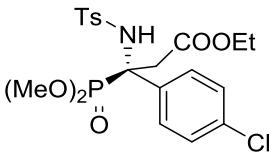
^{19}F NMR (282 MHz, $CDCl_3$) δ -113.8 ppm.

IR ν 3264(N-H), 1735 (C=O), 1335 (O=S=O), 1241 (P=O), 1161 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}FNO_7PS$ $[M+H]^+$ 474.1146, found 474.1148.

Ee (93 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 11.4 (major) and 15.7 (minor).

Ethyl (*S*)-3-(4-chlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145f).



The general procedure was followed to give 43.0 mg (88 %) of **145f** as a pale yellow solid.

Mp: 133-134 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.28 (dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{PH}$ = 2.3 Hz, 2H, 2xCH_{Ar} *m*-Cl), 7.15 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.06 (d, $^3J_{HH}$ = 8.9 Hz, 2H, 2xCH_{Ar} *o*-Cl), 6.19 (d, $^3J_{PH}$ = 10.2 Hz, 1H, NH), 4.15 (q, $^3J_{HH}$ = 7.2 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.62 (m, 1H, C$\underline{H}_a$$H_b$CO), 3.53 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.46 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 3.38 (dd, $^2J_{HH}$ = 16.4 Hz, $^3J_{PH}$ = 8.0 Hz, 1H, $CH_a$$\underline{H}_b$CO), 2.39 (s, 3H, CH_3 Ts), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.0 (d, $^3J_{PC}$ = 7.2 Hz, CO), 143.5 ($C_{quat}CH_3$ Ts), 139.0 (C_{quat}S Ts), 134.5 (d, $^5J_{PC}$ = 3.5 Hz, CCl), 133.0 (d, $^2J_{PC}$ = 7.0 Hz, C_{quat}CP), 129.7 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar} *m*-Cl), 129.2 (2xC_{Ar} Ts), 128.0 (d, $^4J_{PC}$ = 2.7 Hz, 2xC_{Ar} *o*-Cl), 127.6 (2xC_{Ar} Ts), 61.7 (d, $^1J_{PC}$ = 154.2 Hz, CP), 61.1 ($\underline{C}H_2CH_3$), 54.7 (d, $^2J_{PC}$ = 7.3 Hz, CH_3O), 54.2 (d, $^2J_{PC}$ = 7.5 Hz, CH_3O), 38.0 (CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

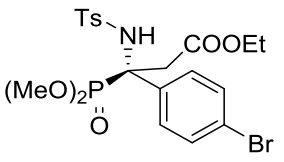
^{31}P NMR (120 MHz, $CDCl_3$) δ21.9 ppm.

IR ν 3256(N-H), 1732 (C=O), 1335 (O=S=O), 1246 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}ClNO_7PS$ $[M+H]^+$ 490.0851, found 490.0856.

Ee (>99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 11.3 (major) and 17.1 (minor).

Ethyl (*S*)-3-(4-bromophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145g).



The general procedure was followed to give 48.5 mg (91 %) of **145g** as a white solid.

Mp: 138-139 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.18 – 7.12 (m, 4H, 4xCH_{Ar}), 7.07 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.24 (d, $^3J_{PH}$ = 10.1 Hz, 1H, NH), 4.07 (m, 2H, $C\underline{H}_2CH_3$), 3.49 (m, 1H, $C\underline{H}_aH_bCO$), 3.47 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.39 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 3.32 (dd, $^2J_{HH}$ = 16.4 Hz, $^3J_{PH}$ = 8.0 Hz, 1H, $CH_a\underline{H}_bCO$), 2.32 (s, 3H, CH_3 Ts), 1.18 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.6 (d, $^3J_{PC}$ = 7.7 Hz, CO), 143.3($C_{quat}CH_3$ Ts), 138.8(m, C_{quat}S Ts), 133.4 (d, $^2J_{PC}$ = 6.7 Hz, C_{quat}CP), 130.6 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar} *o*-Br), 129.8 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar} *m*-Br),

129.0 (2xC_{Ar} Ts), 127.3 (2xC_{Ar} Ts), 122.5 (d, $^{5}J_{PC}$ = 3.6 Hz, CBr), 61.6 (d, $^{1}J_{PC}$ = 154.3 Hz, CP), 60.8 ($\underline{C}H_2CH_3$), 54.4 (d, $^{2}J_{PC}$ = 7.4 Hz, CH_3O), 54.0 (d, $^{2}J_{PC}$ = 7.7 Hz, CH_3O), 37.6 (CH_2CO), 21.36 (CH_3 Ts), 14.0 ($CH_2\underline{C}H_3$) ppm.

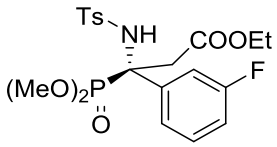
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.7 ppm.

IR ν 3293(N-H), 1729 (C=O), 1337 (O=S=O), 1245 (P=O), 1154 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}BrNO_7PS$ $[M+H]^+$ 534.0345, found 534.0311.

Ee (>99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 11.5 (major) and 16.1 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-(3-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (145h).



The general procedure was followed to give 42.1 mg (89 %) of **145h** as a white solid.

Mp: 111-112 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.17 – 7.09 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 7.01 (m, 1H, CH_{Ar}), 6.90 (m, 1H, CH_{Ar}), 6.22 (broad s, 1H, NH), 4.15 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.59 (dd, $^{3}J_{PH}$ = 23.5 Hz, $^{2}J_{HH}$ = 16.4 Hz, 1H, $C\underline{H}_aH_bCO$), 3.51 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.47 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.40 (dd, $^{2}J_{HH}$ = 16.4 Hz,

$^{3}J_{PH}$ = 7.5 Hz, 1H, CH_aH_bCO), 2.37 (s, 3H, CH_3 Ts), 1.25 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9 (d, $^{3}J_{PC}$ = 7.3 Hz, CO), 162.2 (dd, $^{1}J_{FC}$ = 246.1 Hz, $^{4}J_{PC}$ = 2.9 Hz, CF), 143.6 ($C_{quat}CH_3$ Ts), 139.0 (d, $^{4}J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 137.1 (t, $^{2}J_{PC}$ = $^{3}J_{FC}$ = 7.1 Hz, C_{quat}CP), 129.4 (dd, $^{3}J_{FC}$ = 8.1 Hz, $^{4}J_{PC}$ = 2.8 Hz, C_{Ar} *m*-F), 129.2 (2xC_{Ar} Ts), 127.5 (2xC_{Ar} Ts), 123.7 (dd, $^{3}J_{PC}$ = 5.2 Hz, $^{4}J_{FC}$ = 2.9 Hz, C_{Ar} *p*-F), 116.0 (dd, $^{2}J_{FC}$ = 24.1 Hz, $^{3}J_{PC}$ = 4.9 Hz, C_{Ar} *o*-F), 115.3 (dd, $^{2}J_{FC}$ = 21.0 Hz, $^{5}J_{PC}$ = 3.0 Hz, C_{Ar} *o*-F), 61.9 (dd, $^{1}J_{PC}$ = 153.6 Hz, $^{4}J_{FC}$ = 1.9 Hz, CP), 61.1 (CH_2CH_3), 54.6 (d, $^{2}J_{PC}$= 7.4 Hz, CH_3O), 54.3 (d, $^{2}J_{PC}$= 7.6 Hz, CH_3O), 38.1 (CH_2CO), 21.6 (CH_3 Ts), 14.2 (CH_2CH_3) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.7 ppm.

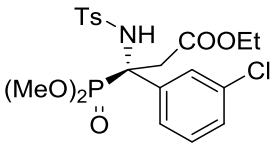
^{19}F NMR (282 MHz, $CDCl_3$) δ -113.0 ppm.

IR ν 3281(N-H), 1732 (C=O), 1333 (O=S=O), 1244 (P=O), 1157 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{20}H_{26}FNO_7PS$ $[M+H]^+$ 474.1146, found 474.1155.

Ee (>99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 10.5 (major) and 14.7 (minor).

Ethyl (*S*)-3-(3-chlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145i).



The general procedure was followed to give 44.0 mg (90 %) of **145i** as a pale yellow solid.

Mp: 88-89 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.27 – 7.22 (m, 2H, 2xCH_{Ar}), 7.19 – 7.09 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 6.20 (d, $^3J_{PH}$ = 9.4 Hz, 1H, NH), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.65 (dd, $^3J_{PH}$ = 24.9 Hz, $^3J_{HH}$ = 16.2 Hz, 1H, C$\underline{H}_a$$H_b$CO), 3.54 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.51 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 3.42 (dd, $^3J_{HH}$ = 16.2 Hz, $^3J_{PH}$ = 7.6 Hz, 1H, $CH_a$$\underline{H}_b$CO), 2.40 (s, 3H, CH_3 Ts), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1 (d, $^3J_{PC}$ = 6.1 Hz, CO), 143.7 ($C_{quat}CH_3$ Ts), 139.0 (C_{quat}S Ts), 136.5 (d, $^2J_{PC}$ = 7.7 Hz, C_{quat}CP), 134.1 (d, $^4J_{PC}$ = 3.3 Hz, CCl), 129.4 (2xC_{Ar} Ts), 129.2 (d, $^4J_{PC}$ = 2.9 Hz, C_{Ar} *m*-Cl), 129.2 (d, $^3J_{PC}$ = 4.9 Hz, C_{Ar} *o*-Cl), 128.6 (d, $^5J_{PC}$ = 2.9 Hz, C_{Ar} *o*-Cl), 127.5 (2xC_{Ar} Ts), 126.2 (d, $^3J_{PC}$ = 5.1 Hz, C_{Ar} *p*-Cl), 62.0 (d, $^1J_{PC}$ = 153.2 Hz, CP), 61.2 ($\underline{C}H_2CH_3$), 54.7 (d, $^2J_{PC}$ = 7.3 Hz, CH_3O), 54.4 (d, $^2J_{PC}$ = 7.6 Hz, CH_3O), 38.3 (CH_2CO), 21.7 (CH_3 Ts), 14.3 ($CH_2\underline{C}H_3$) ppm.

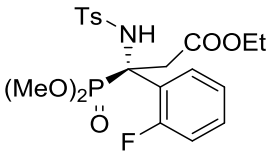
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9 ppm.

IR ν 3276(N-H), 1732 (C=O), 1341 (O=S=O), 1238 (P=O), 1161 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}ClNO_7PS$ $[M+H]^+$ 490.0851, found 490.0857.

Ee (93 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 10.2 (major) and 14.9 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-(2-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (145j).



The general procedure was followed to give 44.0 mg (93 %) of **145j** as a pale yellow solid.

Mp: 140-141 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.44 (m, 1H, CH_{Ar}), 7.21 (m, 1H, CH_{Ar}), 7.16 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.99 (m, 1H, CH_{Ar}), 6.80 (dd, $^3J_{FH}$ = 12.8 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, CH_{Ar} *o*-F), 6.21 (d, $^3J_{PH}$ = 13.1 Hz, 1H, NH), 4.09 (m, 2H, $C\underline{H}_2CH_3$), 3.63 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.72 – 3.51 (m, 2H, $C\underline{H}_aH_bCO$ + $CH_a\underline{H}_bCO$), 3.54 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.38 (s, 3H, CH_3 Ts), 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2 (d, $^3J_{PC}$ = 10.8 Hz, CO), 160.6 (dd, $^1J_{FC}$ = 249.9 Hz, $^3J_{PC}$ = 5.8 Hz, CF), 143.3($C_{quat}CH_3$ Ts), 138.8 (d, $^4J_{PC}$ = 1.3 Hz, C_{quat}S Ts), 130.4 (dd, $^3J_{FC}$ = 9.4, $^3J_{PC}$ = 2.8 Hz, C_{Ar} *m*-F), 130.3 (dd, $^3J_{FC}$ = 4.8 Hz, $^5J_{PC}$ = 2.9 Hz, C_{Ar} *m*-F), 129.2 (2xC_{Ar} Ts), 127.6 (2xC_{Ar} Ts), 123.9 (dd, $^4J_{FC}$ = 3.3 Hz, $^4J_{PC}$ = 2.5 Hz, C_{Ar} *p*-F), 123.2 (m, C_{quat}CP), 116.4 (dd, $^2J_{FC}$ = 24.6 Hz, $^4J_{PC}$ = 2.5 Hz, C_{Ar} *o*-F), 61.4 (dd, $^1J_{PC}$ = 154.0,

$^{3}J_{FC}$ = 3.4 Hz, CP), 60.9 ($\underline{C}H_2CH_3$), 54.7 (d, $^{2}J_{PC}$ = 7.6 Hz, CH_3O), 54.5 (d, $^{2}J_{PC}$= 7.4 Hz, CH_3O), 38.6 (d, $^{4}J_{FC}$ = 6.8 Hz, CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.1 ppm.

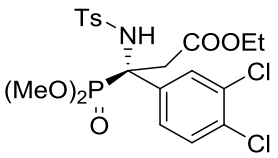
^{19}F NMR (282 MHz, $CDCl_3$) δ -107.6 ppm.

IR ν 3236(N-H), 1755 (C=O), 1328 (O=S=O), 1239 (P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}FNO_7PS$ $[M+H]^+$ 474.1146, found 474.1126.

Ee (>99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 15.3 (major) and 16.7 (minor).

Ethyl (*S*)-3-(3,4-dichlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145k).



The general procedure was followed to give 45.0 mg (86 %) of **145k** as a white solid.

Mp: 109-110 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.33 (s, 1H, CH_{Ar}), 7.23 – 7.18 (m, 2H, 2xCH_{Ar}), 7.15 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.24 (d, $^{3}J_{PH}$ = 9.3 Hz, 1H, NH), 4.17 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 3.59 (m, 1H, $C\underline{H}_aH_bCO$), 3.58 (d, $^{3}J_{HH}$ = 10.8 Hz, 3H, CH_3O), 3.54

(d, $^{3}J_{HH}$ = 10.7 Hz, 3H, CH_3O), 3.36 (dd, $^{2}J_{HH}$ = 16.2 Hz, $^{3}J_{PH}$ = 8.3 Hz, 1H, $CH_a\underline{H}_bCO$), 2.38 (s, 3H, CH_3 Ts), 1.27 (t, $^{3}J_{HH}$ = 7.5 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7 (d, $^{3}J_{PC}$ = 6.4 Hz, CO), 143.9 ($C_{quat}CH_3$ Ts), 138.7 (d, $^{4}J_{PC}$= 1.4 Hz, C_{quat}S Ts), 134.7 (d, $^{2}J_{PC}$ = 6.6 Hz, C_{quat}CP), 132.7 (d, $^{5}J_{PC}$ = 3.7 Hz, CCl), 132.1 (d, $^{4}J_{PC}$ = 2.9 Hz, CCl), 130.9 (d, $^{3}J_{PC}$ = 5.1 Hz, C_{Ar} *o*-3Cl), 129.7 (d, $^{4}J_{PC}$ = 2.6 Hz, C_{Ar} *o*-4Cl), 129.4 (2xC_{Ar} Ts), 127.4 (d, $^{3}J_{PC}$ = 5.1 Hz, C_{Ar} *p*-3Cl), 127.3 (2xC_{Ar} Ts), 61.4 (d, $^{1}J_{PC}$ = 153.7 Hz, CP), 61.2 ($\underline{C}H_2CH_3$), 54.7 (d, $^{2}J_{PC}$ = 7.3 Hz, CH_3O), 54.5 (d, $^{2}J_{PC}$ = 7.6 Hz, CH_3O), 38.0 (CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

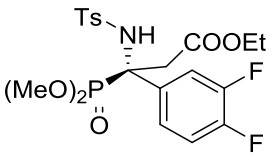
^{31}P NMR (120 MHz, $CDCl_3$) δ 21.7 ppm.

IR ν 3251(N-H), 1738 (C=O), 1338 (O=S=O), 1261(P=O), 1160 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{25}Cl_2NO_7PS$ $[M+H]^+$ 524.0461, found 524.0465.

Ee (99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 9.2 (major) and 13.8 (minor).

Ethyl (*S*)-3-(3,4-difluorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145l).



The general procedure was followed to give 44.7 mg (91 %) of **145l** as a white solid.

Mp: 98-99 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.16 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.14 – 7.04 (m, 2H, 2xCH_{Ar}), 6.93 (m, 1H, CH_{Ar}), 6.24 (br d, $^3J_{PH}$= 9.5 Hz, 1H, NH), 4.16 (q, $^3J_{HH}$= 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.76 (m, 1H, $C\underline{H}_aH_bCO$), 3.57 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.50 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.35 (dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{PH}$ = 7.8 Hz, 1H, $CH_a\underline{H}_bCO$), 2.38 (s, 3H, CH_3 Ts), 1.25 (t, $^3J_{HH}$= 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8 (d, $^3J_{PC}$ = 6.8 Hz, CO), 150.2 (ddd, $^1J_{FC}$ = 250.6 Hz, $^2J_{FC}$ = 11.8 Hz, $^5J_{PC}$ = 3.1 Hz, CF), 149.5 (ddd, $^1J_{FC}$ = 246.0 Hz, $^2J_{FC}$ = 10.6 Hz, $^4J_{PC}$ = 3.0 Hz, CF), 143.9 ($C_{quat}CH_3$ Ts), 139.0 (d, $^4J_{PC}$ = 1.3 Hz, C_{quat}S Ts), 131.6 (m, C_{quat}CP), 129.3(2xC_{Ar} Ts), 127.5 (2xC_{Ar} Ts), 124.4 (m, C_{Ar} *p*-3F), 118.4 (dd, $^2J_{FC}$= 19.6 Hz, $^3J_{PC}$ = 4.8 Hz, C_{Ar} *o*-3F), 116.5 (dd, $^2J_{FC}$ = 17.4 Hz, $^4J_{PC}$ = 2.7 Hz, C_{Ar} *o*-4F), 61.5 (d, $^1J_{PC}$ = 154.6 Hz, CP), 61.3 ($\underline{C}H_2CH_3$), 54.7 (d, $^2J_{PC}$= 7.3 Hz, CH_3O), 54.4 (d, $^2J_{PC}$= 7.6 Hz, CH_3O), 38.2 (CH_2CO), 21.6 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.7 ppm.

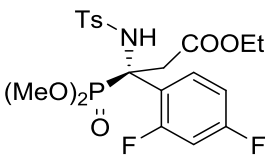
^{19}F NMR (282 MHz, $CDCl_3$) δ -137.6, -138.0 ppm.

IR ν 3262(N-H), 1738 (C=O), 1338 (O=S=O), 1249 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{25}F_2NO_7PS$ $[M+H]^+$ 492.1052, found 492.1060.

Ee (99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 8.8 (major) and 13.6 (minor).

Ethyl (*S*)-3-(2,4-difluorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145m).



The general procedure was followed to give 45.7 mg (93 %) of **145m** as a white solid.

Mp: 135-136 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.39 (m, 1H, CH_{Ar}), 7.15 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.68 (m, 1H, CH_{Ar}), 6.52 (m, 1H, CH_{Ar}), 6.25 (broad d, $^3J_{PH}$ = 8.9 Hz, 1H, NH), 4.09 (m, 2H, C$\underline{H}_2$$CH_3$), 3.65 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.57 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.57 – 3.47 (m, 2H, C$\underline{H}_a$$H_b$CO + $CH_a$$\underline{H}_b$CO), 2.37 (s, 3H, CH_3 Ts), 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.0 (d, $^3J_{PC}$ = 10.9 Hz, CO), 162.9 (ddd, $^1J_{FC}$ = 251.3 Hz, $^3J_{FC}$ = 12.7 Hz, $^5J_{PC}$ = 2.9 Hz, CF), 160.7 (ddd, $^1J_{FC}$ = 252.9 Hz, $^3J_{FC}$ = 11.7 Hz, $^3J_{PC}$ = 5.7 Hz, CF), 143.5 ($C_{quat}CH_3$ Ts), 138.6 (C_{quat}S Ts), 131.4 (m, C_{Ar} *m*-2F), 129.2 (2xC_{Ar} Ts), 127.5 (2xC_{Ar} Ts), 119.4

(m, $C_{quat}CP$), 110.8 (br d, $^2J_{FC}$ = 21 Hz, C_{Ar} *p*-2F), 104.5 (ddd, $^2J_{FC}$ = 27.9 Hz, $^2J_{FC}$ = 25.3 Hz, $^4J_{PC}$ = 2.5 Hz, C_{Ar} *o*-2F), 60.9 ($\underline{C}H_2CH_3$), 60.9 (dd, $^1J_{PC}$ = 154.6 Hz, $^3J_{FC}$ = 3.7 Hz, CP), 54.6 (br d, $^2J_{PC}$= 7.6 Hz, CH_3O), 54.6 (broad d, $^2J_{PC}$= 7.3 Hz, CH_3O), 38.5 (d, $^4J_{FC}$ = 6.9 Hz, CH_2CO), 21.6 (CH_3 Ts), 14.1 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.0ppm.

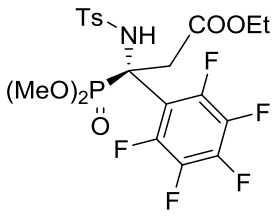
^{19}F NMR (282 MHz, $CDCl_3$) δ -103.0, -110.3 ppm.

IR ν 3248(N-H), 1741 (C=O), 1335 (O=S=O), 1247 (P=O), 1155 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{25}F_2NO_7PS$ $[M+H]^+$ 492.1052, found 492.1058.

Ee (94 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 12.8 (major) and 15.1 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(perfluorophenyl)propanoate (145n).



The general procedure was followed to give 50.1 mg (92 %) of **145n** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.16 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.23 (d, $^3J_{PH}$ = 10.5 Hz, 1H, NH), 4.13 (m, 2H, $C\underline{H}_2CH_3$), 3.98 (m, 1H, $C\underline{H}_aH_bCO$), 3.80 (d, $^3J_{PH}$ = 10.9 Hz, 3H, CH_3O), 3.75 (d, $^3J_{PH}$

= 10.9 Hz, 3H, CH_3O), 3.45 (m, 1H, $CH_a\underline{H}_bCO$), 2.36 (s, 3H, CH_3 Ts), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1 (d, $^3J_{PC}$ = 8.4 Hz, CO), 145.9 (m, 2xCF), 144.1 ($C_{quat}CH_3$ Ts), 140.8 (m, CF), 137.7 (d, $^4J_{PC}$ = 1.9 Hz, $C_{quat}S$ Ts), 137.5 (m, 2xCF), 129.2 (2xC_{Ar} Ts), 127.1 (2xC_{Ar} Ts), 111.2 (m, $C_{quat}CP$), 61.0 ($\underline{C}H_2CH_3$), 60.0 (d, $^1J_{PC}$ = 153.3 Hz, CP), 55.7 (d, $^2J_{PC}$ = 7.2 Hz, CH_3O), 54.9 (d, $^2J_{PC}$ = 7.8 Hz, CH_3O), 40.3 (d, $^4J_{FC}$ = 5.3 Hz, CH_2CO), 21.4 (CH_3 Ts), 14.1 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ21.7 ppm.

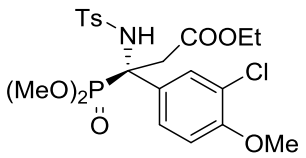
^{19}F NMR (282 MHz, $CDCl_3$) δ -135.0, -154.3, -162.8 ppm.

IR ν 3284(N-H), 1741 (C=O), 1333 (O=S=O), 1254 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{22}F_5NO_7PS$ $[M+H]^+$ 546.0769, found 546.0781.

Ee (98 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 6.4 (major) and 10.5 (minor).

Ethyl (*S*)-3-(3-chloro-4-methoxyphenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145o).



The general procedure was followed to give 42.0 mg (81 %) of **145o** as a white solid.

Mp: 153-154 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.24 – 7.18 (m, 2H, 2xCH_{Ar}), 7.15 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.71 (d, $^3J_{HH}$= 8.7 Hz, 1H, CH_{Ar}), 6.17 (d, $^3J_{PH}$= 9.0 Hz, 1H, NH), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.86 (s, 3H, CH_3OAr), 3.62 (dd, $^3J_{PH}$ = 25.6 Hz, $^2J_{HH}$ = 16.1 Hz, 1H, C$\underline{H}_a$$H_b$CO), 3.55 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3OP), 3.52 (d, $^3J_{PH}$= 10.7 Hz, 3H, CH_3OP), 3.36 (dd, $^2J_{HH}$ = 16.1 Hz, $^3J_{PH}$ = 7.6 Hz, 1H, $CH_a$$\underline{H}_b$CO), 2.39 (s, 3H, CH_3 Ts), 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1 (d, $^3J_{PC}$ = 5.9 Hz, CO), 154.9 (d, $^5J_{PC}$ = 2.7 Hz, $C_{quat}$$OCH_3$), 143.7 ($C_{quat}$$CH_3$ Ts), 138.9 (d, $^4J_{PC}$ = 1.7 Hz, C_{quat}S Ts),130.9 (d, $^3J_{PC}$ = 4.8 Hz, C_{Ar} *o*-Cl), 129.3 (2xC_{Ar} Ts), 127.7 (d, $^3J_{PC}$= 5.5 Hz, C_{Ar} *p*-Cl), 127.5 (2xC_{Ar} Ts), 126.8 (d, $^2J_{PC}$= 7.4 Hz, C_{quat}CP), 122.0 (d, $^4J_{PC}$ = 3.0 Hz, CCl), 111.0 (d, $^4J_{PC}$ = 2.6 Hz, C_{Ar} *o*-OCH_3), 61.3 (d, $^1J_{PC}$ = 155.4 Hz, CP), 61.2 ($\underline{C}H_2CH_3$), 56.2 (CH_3OAr), 54.7 (d, $^2J_{PC}$ = 7.3 Hz, CH_3OP), 54.3 (d, $^2J_{PC}$ = 7.7 Hz, CH_3OP), 38.2 (CH_2CO), 21.7 (CH_3 Ts), 14.3 ($CH_2\underline{C}H_3$) ppm.

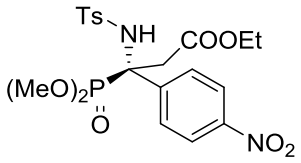
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.2 ppm.

IR ν 3275(N-H), 1732 (C=O), 1333 (O=S=O), 1263 (P=O), 1158 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{21}H_{28}ClNO_8PS$ $[M+H]^+$ 520.0956, found 520.0959.

Ee (97 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 12.6 (major) and 18.0 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-nitrophenyl)propanoate (145p).



The general procedure was followed to give 42.5 mg (85 %) of **145p** as a white solid.

Mp: 129-130 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $^3J_{HH}$= 9.0 Hz, 2H, 2xCH_{Ar} *o*-NO_2), 7.56 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{PH}$ = 2.3 Hz, 2H, 2xCH_{Ar} *m*-NO_2), 7.50 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.17 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.30 (d, $^3J_{PH}$ = 10.3 Hz, 1H, NH), 4.16 (m, 2H, C$\underline{H}_2$$CH_3$), 3.62 (dd, $^2J_{HH}$ = 16.5 Hz, $^3J_{PH}$ = 6.2 Hz,1H, C$\underline{H}_a$$H_b$CO), 3.58 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.55 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.48 (dd, $^2J_{HH}$ = 16.5 Hz, $^3J_{PH}$ = 8.2 Hz, 1H, $CH_a\underline{H}_b$CO), 2.41 (s, 3H, CH_3 Ts), 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7 (d, $^3J_{PC}$ = 7.6 Hz, CO), 147.4 (d, $^5J_{PC}$= 3.4 Hz, $C_{quat}NO_2$), 144.1 ($C_{quat}CH_3$ Ts), 142.5 (d, $^2J_{PC}$ = 6.6 Hz, C_{quat}CP), 138.8 (d, $^4J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 129.4 (2xC_{Ar} Ts), 129.3 (d, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *m*-NO_2), 127.5 (2xC_{Ar} Ts), 122.8 (d, $^4J_{PC}$= 2.6 Hz, 2xC_{Ar} *o*-NO_2), 62.3 (d, $^1J_{PC}$ = 152.2 Hz, CP), 61.4 ($\underline{C}H_2CH_3$), 54.9 (d, $^2J_{PC}$ = 7.3 Hz,

CH_3O), 54.6 (d, $^2J_{PC}$ = 7.5 Hz, CH_3O), 38.3 (CH_2CO), 21.7 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

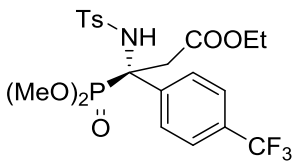
^{31}P NMR (120 MHz, $CDCl_3$) δ21.2 ppm.

IR ν 3272(N-H), 1743 (C=O), 1349 (O=S=O), 1244 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{20}H_{26}N_2O_9PS$ $[M+H]^+$ 501.1091, found 501.1098.

Ee (99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 11.8 (major) and 15.0 (minor).

Ethyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-(trifluoromethyl)phenyl)propanoate (145q).



The general procedure was followed to give 45.5 mg (87 %) of **145q** as a white solid.

Mp: 114-115 °C (hexanes/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H, 2xCH_{Ar}), 7.42 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.33 (d, $^3J_{HH}$ = 8.5 Hz, 2H, 2xCH_{Ar}), 7.12 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.24 (d, $^3J_{PH}$ = 10.1 Hz, 1H, NH), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.68 (dd, $^3J_{PH}$ = 23.6 Hz, $^2J_{HH}$ = 16.4 Hz, 1H, $C\underline{H}_aH_bCO$), 3.58 (d, $^3J_{PH}$ = 10.8 Hz, 3H, CH_3O), 3.50 (d, $^3J_{PH}$ = 10.7 Hz, 3H,

CH_3O), 3.44 (m, 1H, $CH_a\underline{H}_bCO$), 2.39 (s, 3H, CH_3 Ts), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.0 (d, $^3J_{PC}$ = 6.8 Hz, CO), 143.7 ($C_{quat}CH_3$ Ts), 138.9 (C_{quat}S Ts), 138.6 (d, $^2J_{PC}$ = 6.6 Hz, C_{quat}CP), 130.4 (dq, $^2J_{FC}$ = 32.8 Hz, $^5J_{PC}$ = 3.0 Hz, $C_{quat}CF_3$), 129.3 (2xC_{Ar} Ts), 128.8 (d, $^3J_{PC}$ = 5.0 Hz, 2xC_{Ar} *m*-CF_3), 127.5 (2xC_{Ar} Ts), 124.7 (m, 2xC_{Ar} *o*-CF_3), 123.9 (q, $^1J_{FC}$ = 272.4 Hz, CF_3), 62.0 (d, $^1J_{PC}$ = 152.8 Hz, CP), 61.3 ($\underline{C}H_2CH_3$), 54.8 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.4 (d, $^2J_{PC}$ = 7.6 Hz, CH_3O), 38.1 (CH_2CO), 21.6 (CH_3 Ts), 14.3 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ21.9 ppm.

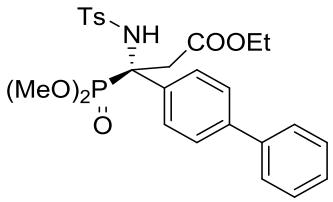
^{19}F NMR (282 MHz, $CDCl_3$) δ -63.4 ppm.

IR ν 3261(N-H), 1735 (C=O), 1327 (O=S=O), 1263 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{21}H_{26}F_3NO_7PS$ $[M+H]^+$ 524.1114, found 524.1121.

Ee (93 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 8.6 (major) and 12.4 (minor).

Ethyl (*S*)-3-([1,1'-biphenyl]-4-yl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145r).



The general procedure was followed to give 47.8 mg (90 %) of **145r** as a white solid.

Mp: 112-113 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 4H, 2xCH_{Ar}+ 2xCH_{Ar} *o*-Ts), 7.45 – 7.40 (m, 5H, 5xCH_{Ar}), 7.36 (m, 2H, 2xCH_{Ar}), 7.13 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.21 (d, $^3J_{PH}$ = 10.5 Hz, 1H, NH), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 2H, C$\underline{H}_2$$CH_3$), 3.69 (dd, $^3J_{PH}$ = 23.4 Hz, $^2J_{HH}$= 16.4 Hz, 1H, C$\underline{H}_a$$H_b$CO), 3.56 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.49 (m, 1H, $CH_a$$\underline{H}_b$CO), 3.46 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.38 (s, 3H, CH_3 Ts), 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.3 (d, $^3J_{PC}$ = 7.3 Hz, CO), 143.3 ($C_{quat}$$CH_3$ Ts), 141.0 (d, $^5J_{PC}$ = 3.1 Hz, C_{quat}Ph), 140.1 (d, $^4J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 139.2 (C_{quat}CP), 129.2 (2xC_{Ar} Ts), 129.0 (2xC_{Ar}), 128.8 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar}), 128.3 (C_{quat}Ar), 127.8 (C_{Ar}), 127.7 (2xC_{Ar} Ts), 127.1 (2xC_{Ar}), 126.5 (d, $^4J_{PC}$ = 2.8 Hz, 2xC_{Ar}), 62.1 (d, $^1J_{PC}$ = 153.9 Hz, CP), 61.1 ($\underline{C}H_2CH_3$), 54.7 (d, $^2J_{PC}$ = 7.4 Hz, CH_3O), 54.2 (d, $^2J_{PC}$ = 7.6 Hz, CH_3O), 38.2 (CH_2CO), 21.7 (CH_3 Ts), 14.3 ($CH_2\underline{C}H_3$) ppm.

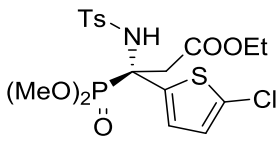
^{31}P NMR (120 MHz, $CDCl_3$) δ 22.2 ppm.

IR ν 3308(N-H), 1729 (C=O), 1332 (O=S=O), 1241 (P=O), 1161 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{26}H_{31}NO_7PS$ $[M+H]^+$ 532.1553, found 532.1555.

Ee (99 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 14.1 (major) and 17.9 (minor).

Ethyl (*S*)-3-(5-chlorothiophen-2-yl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (145s).



The general procedure was followed to give 37.8 mg (76 %) of **145s** as a pale brown solid.

Mp: 93-94 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.17 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 6.79 (dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{PH}$ = 3.4 Hz, 1H, CH_{Ar}), 6.61 (d, $^3J_{HH}$ = 4.0 Hz, 1H, CH_{Ar}), 6.23 (d, $^3J_{PH}$ = 7.2 Hz, 1H, NH), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 3.68 (d, $^3J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.66 (d, $^3J_{PH}$ = 10.5 Hz, 3H, CH_3O), 3.61 (m, 1H, C$\underline{H}_a$H$_b$CO), 3.21 (dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{PH}$ = 7.1 Hz, 1H, CH$_a\underline{H}_b$CO), 2.40 (s, 3H, CH_3 Ts), 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5 (d, $^3J_{PC}$ = 5.6 Hz, CO), 143.6 ($C_{quat}CH_3$ Ts), 138.7 (d, $^4J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 135.9 (d, $^2J_{PC}$ = 7.7 Hz, C_{quat}2-thiophene), 132.3 (d, $^4J_{PC}$ = 3.6 Hz, CCl), 129.3 (2xC_{Ar} Ts), 128.6 (d, $^3J_{PC}$ = 7.3 Hz, C_{Ar} 3-thiophene), 127.5 (2xC_{Ar} Ts), 125.3 (d, $^4J_{PC}$ = 2.8 Hz, C_{Ar} 4-thiophene), 61.4 ($\underline{C}H_2CH_3$), 60.0 (d, $^1J_{PC}$ = 161.5 Hz, CP), 55.2

(d, $^{3}J_{PC}$ = 7.3 Hz, CH_3O), 54.5 (d, $^{3}J_{PC}$ = 7.6 Hz, CH_3O), 39.0 (CH_2CO), 21.7 (CH_3 Ts), 14.2 ($CH_2\underline{C}H_3$) ppm.

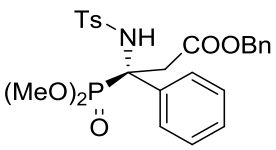
^{31}P NMR (120 MHz, $CDCl_3$) δ 20.3 ppm.

IR ν 3270(N-H), 1735 (C=O), 1341 (O=S=O), 1243 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{24}ClNO_7PS_2$ $[M+H]^+$ 496.0415, found 496.0444.

Ee (98 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 9.1 (major) and 16.8 (minor).

Benzyl (*S*)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate (145t).



The general procedure was followed to give 47.6 mg (92 %) of **145t** as a white solid.

Mp: 84-85 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.37 – 7.29 (m, 7H, 7xCH_{Ar}), 7.18 (m, 1H, CH_{Ar}), 7.12 – 7.06 (m, 4H, 2xCH_{Ar} *m*-Ts + 2xCH_{Ar}), 6.22 (d, $^{3}J_{PH}$ = 11.1 Hz, 1H, NH), 5.14 (d, $^{2}J_{HH}$ = 12.2 Hz, 1H, $C\underline{H}_aH_bPh$), 5.09 (d, $^{2}J_{HH}$ = 12.2 Hz, 1H, $CH_a\underline{H}_bPh$), 3.65 (dd, $^{3}J_{PH}$ = 22.3 Hz, $^{2}J_{HH}$ = 16.6 Hz, 1H, $C\underline{H}_aH_bCO$), 3.49 (dd, $^{2}J_{HH}$ = 16.6 Hz, $^{3}J_{PH}$ = 7.5 Hz, 1H, $CH_a\underline{H}_bCO$), 3.37 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 3.31 (d, $^{3}J_{PH}$ = 10.7 Hz, 3H, CH_3O), 2.34 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8 (d, $^{3}J_{PC}$ = 8.1 Hz, CO), 143.1 ($C_{quat}CH_3$ Ts), 139.0 (d, $^{4}J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 135.5 ($C_{quat}CH_2Ph$), 134.1 (d, $^{2}J_{PC}$ = 7.3 Hz, C_{quat}CP), 129.0 (2xC_{Ar} Ts), 128.4 (2xC_{Ar} Bn), 128.4 (2xC_{Ar} Bn), 128.2 (C_{Ar} Bn), 128.2 (C_{Ar} Ph), 128.0 (d, $^{3}J_{PC}$ = 5.0 Hz, 2xC_{Ar} *m*-Ph), 127.8 (d, $^{4}J_{PC}$ = 2.6 Hz, 2xC_{Ar} *o*-Ph), 127.4 (2xC_{Ar} Ts), 66.5 (CH_2Ph), 61.9 (d, $^{1}J_{PC}$ = 154.1 Hz, CP), 54.4 (d, $^{2}J_{PC}$ = 7.4 Hz, CH_3O), 53.8 (d, $^{2}J_{PC}$ = 7.7 Hz, CH_3O), 37.7 (CH_2CO), 21.4 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 22.0 ppm.

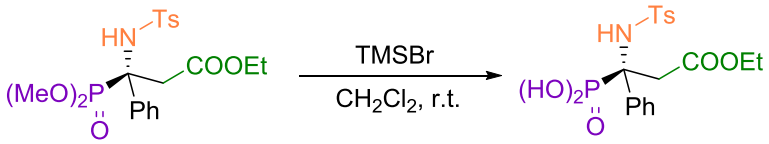
IR ν 3322(N-H), 1739 (C=O), 1337 (O=S=O), 1248 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{25}H_{28}NO_7PS$ $[M+H]^+$ 518.1397, found 518.1372.

Ee (96 %) was determined by HPLC analysis (Chiracel-IC, Heptane/CH_2Cl_2/Ethanol 50:45:5, 1 mL/min). Retention time (min): 12.7 (major) and 14.3 (minor).

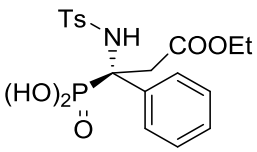
Gram scale reaction: Using the general procedure, 1.0 g of ketimine **93a** reacted with benzyl iodoacetate in the presence of 20 mol % of BINOL ligand **XLVII** to afford 1.2 g of the aza-Reformatsky product **145t** in 84% yield and 86 % ee.

Selective hydrolysis of phosphonate



145a **146**

(*S*)-(3-Ethoxy-1-((4-methylphenyl)sulfonamido)-3-oxo-1-phenylpropyl)phosphonic acid (146).



To a solution of aminophosphonate **145a** (228.1 mg, 0.5 mmol) in dry $CHCl_3$ (2 mL), TMSBr (0.33 mL, 2.5 mmol) was added and the mixture was stirred at room temperature for 24h. After that, MeOH (2 mL) was added and the volatiles were distilled off at reduced pressure to yield the crude product, which was purified by crystallization in MeOH to give 209.3 mg (98 %) of **146** as a white solid.

Mp: 144-145 °C (MeOH).

^{1}H NMR (400 MHz, Acetone) δ 7.49 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.37 (d, $^3J_{HH}$ = 7.9 Hz, 2H, 2xCH_{Ar}), 7.20 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 7.15 (m, 1H, CH_{Ar}), 7.06 (t, $^3J_{HH}$ = 7.6 Hz, 2H, 2xCH_{Ar}), 4.11 (m, 2H, $C\underline{H}_2CH_3$), 3.63 (d, $^2J_{HH}$ = 17.9 Hz, 2H, $C\underline{H}_aH_bCO$ + $CH_a\underline{H}_bCO$), 2.38 (s, 3H, CH_3 Ts), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CH_2C\underline{H}_3$) ppm.

^{13}C {^{1}H} NMR (100 MHz, Acetone) δ 173.21 (d, $^3J_{PC}$ = 5.6 Hz, CO), 143.8 ($C_{quat}CH_3$ Ts), 140.8 (d, $^4J_{PC}$ = 1.3 Hz, C_{quat}S Ts), 137.0 (d, $^2J_{PC}$ = 5.3 Hz, C_{quat}CP), 129.9 (2xC_{Ar} Ts), 129.1 (d, $^3J_{PC}$ = 4.4 Hz, 2xC_{Ar} *o*-Ph), 128.2 (d,

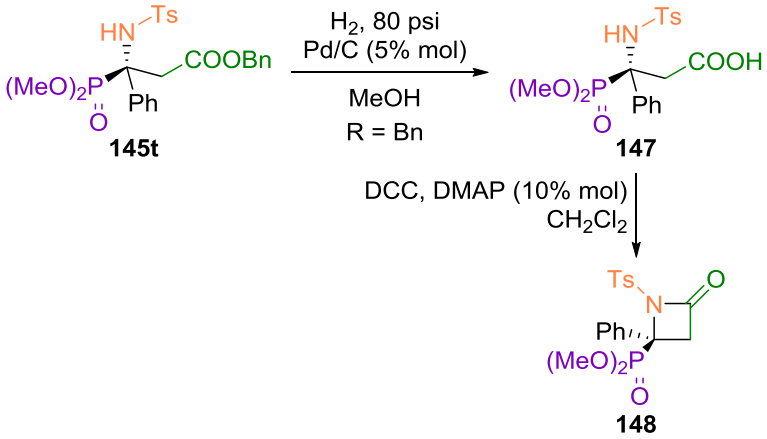
$^{4}J_{PC}$ = 2.2 Hz, 2xC_{Ar} *m*-Ph), 128.2 (d, $^{5}J_{PC}$ = 2.6 Hz, C_{Ar} *p*-Ph), 128.1 (2xC_{Ar} Ts), 62.3 (d, $^{1}J_{PC}$ = 145.2 Hz, CP), 62.1 ($\underline{C}H_2CH_3$), 39.5 (CH_2CO), 21.4 (CH_3 Ts), 14.3 ($CH_2\underline{C}H_3$) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 20.7 ppm.

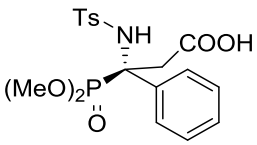
IR ν 3500-2500 (O-H), 3275(N-H), 1733 (C=O), 1330 (O=S=O), 1243 (P=O), 1165 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m*/*z* calcd. for $C_{18}H_{23}NO_7PS$ $[M+H]^+$ 428.0927, found 428.0899.

Synthesis of β-lactam derivative 148



(*S*)-3-(Dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoic acid (147).



A mixture of aminophosphonate **145t** (258.9 mg, 0.5 mmol) and Pd-C 10% (53.0 mg, 0.05 mmol) in MeOH (50 mL) was stirred for 12h under H_2 atmosphere (75 psi) at room temperature. The mixture was then filtered on celite and concentrated under reduced pressure to yield the crude product **147** as a white solid, 201.3 mg (94 %), after crystallization in MeOH.

Mp: 145-146 °C (MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ9.91 (broad s, 1H, COOH), 7.48 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.33 (d, $^3J_{HH}$ = 7.6 Hz, 2H, 2xCH_{Ar}), 7.20 (m, 1H, CH_{Ar}), 7.17 – 7.09 (m, 4H, 2xCH_{Ar} + 2xCH_{Ar} *m*-Ts), 6.60 (d, $^3J_{PH}$ = 10.6 Hz, NH), 3.67 (dd, $^3J_{PH}$ = 23.9 Hz, $^2J_{HH}$ = 16.0 Hz, 1H, C$H_a$$H_b$CO), 3.52 (d, $^3J_{PH}$

= 10.8 Hz, 3H, CH_3O), 3.49 (m, 7H, CH_aH_bCO), 3.47 (d, $^3J_{PH}$ = 10.6 Hz, 3H, CH_3O), 2.38 (s, 3H, CH_3 Ts) ppm.

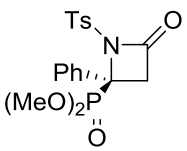
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5 (d, $^3J_{PC}$ = 7.7 Hz, CO), 143.3 ($C_{quat}CH_3$ Ts), 139.2 (d, $^4J_{PC}$ = 1.4 Hz, C_{quat}S Ts), 134.1 (d, $^2J_{PC}$ = 7.6 Hz, C_{quat}CP), 129.2 (2xC_{Ar} Ts), 128.4 (d, $^5J_{PC}$ = 3.0 Hz, C_{Ar}), 128.3 (d, $^3J_{PC}$ = 5.1 Hz, 2xC_{Ar}), 128.0 (d, $^4J_{PC}$ = 2.6 Hz, 2xC_{Ar}), 127.6 (2xC_{Ar} Ts), 62.1 (d, $^1J_{PC}$ = 155.6 Hz, CP), 55.1 (d, $^2J_{PC}$ = 7.3 Hz, CH_3O), 54.5 (d, $^2J_{PC}$ = 7.9 Hz, CH_3O), 38.0 (CH_2CO), 21.6 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 21.8 ppm.

IR ν 3500-2500 (O-H), 3271(N-H), 1714 (C=O), 1337 (O=S=O), 1235 (P=O), 1163 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{23}NO_7PS$ $[M+H]^+$ 428.0927, found 428.0901.

(*S*)-Dimethyl (4-oxo-2-phenyl-1-tosylazetidin-2-yl)phosphonate (148).



A mixture of aminophosphonate **147** (213.7 mg, 0.5 mmol), DCC (123.8 mg, 0.6 mmol), and DMAP (6.1 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was stirred for 12 h at room temperature. The mixture was then filtered on celite and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography (hexanes/AcOEt) to give 182.1 mg (89 %) of **148** as a white solid.

Mp: 120-121 °C (hexanes/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *o*-Ts), 7.84 – 7.76 (m, 2H, 2xCH_{Ar}), 7.46 – 7.37 (m, 3H, 3xCH_{Ar}), 7.34 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2xCH_{Ar} *m*-Ts), 3.74 (dd, $^2J_{HH}$ = 15.6 Hz, $^3J_{PH}$ = 9.3 Hz, 1H, C$\underline{H}_a$$H_b$CO), 3.59 (d, $^3J_{PH}$ = 10.8 Hz, 6H, 2xCH_3O), 3.24 (dd, $^2J_{HH}$ = 15.6 Hz, $^3J_{PH}$ = 6.8 Hz, 1H, C$H_a$$\underline{H}_b$CO), 2.44 (s, 3H, CH_3 Ts) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.9 (d, $^3J_{PC}$= 7.4 Hz, CO), 145.5 ($C_{quat}CH_3$ Ts), 135.9 (d, $^4J_{PC}$ = 2.9 Hz, C_{quat}S Ts), 135.2 (d, $^2J_{PC}$ = 7.3 Hz, C_{quat}CP), 129.5 (2xC_{Ar} Ts), 129.0 – 128.7 (m, 2xC_{Ar} Ts + 3xC_{Ar}), 127.3 (d, $^3J_{PC}$ = 4.5 Hz, 2xC_{Ar}), 66.3 (d, $^1J_{PC}$ = 164.7 Hz, CP), 54.7 (d, $^2J_{PC}$ = 7.1 Hz, CH_3O), 53.8 (d, $^2J_{PC}$= 7.1 Hz, CH_3O), 50.3 (CH_2CO), 21.9 (CH_3 Ts) ppm.

^{31}P NMR (120 MHz, $CDCl_3$) δ 20.7 ppm.

IR ν1799 (C=O), 1369 (O=S=O), 1258 (P=O), 1166 (O=S=O) cm^{-1}.

ESI-HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{21}NO_6PS$ $[M+H]^+$ 410.0822, found 410.0801.

The absolute *S* configuration of lactam **148** was determined by X-Ray diffraction.

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