Attempted Enantioselective Preparation of α-Aminophosphonic Acids and a Mechanistic Investigation of the Coupling Agent Mediated Phosphonamidation Reaction

Dissertation for the degree of Philosophiae Doctor

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2016
“The important question is, after the work is done, what do you know that you didn’t know before?”

- Gilbert Stork

1 Cope Symposium Lecture, ACS Anaheim, March, 1999; C & EN, April 5, 1999, p.33.
ACKNOWLEDGMENTS

As the process of writing this thesis comes to an end, and the goal of completion seems within reach, it is only appropriate to thank the individuals whom have been instrumental for bringing me to this moment in time. From a slightly awkward beginning in this Department some 10 years ago and without really knowing what I was heading into, the fact that 10 years has flown by this quickly is a good indication that I have been fortunate to have met some truly wonderful people. As much as anything this thesis is dedicated to you, since its existence would not have been possible without you.

I would like to convey my sincerest gratitude to my supervisor Mohamed “Mamou” Amedjkouh for giving me the opportunity to pursue the degree of PhD. I was fortunate to be part of the group from its inception which has been an exciting journey, but also a challenging one. Throughout the numerous challenging phases of the project he has always stayed positive. Additionally he has encouraged and supported me in pursuing new directions. I would also like to highlight the generous group-dinners I have had the pleasure of going to, which has been a wonderful treat. Lastly, thank you for bringing to my attention and allowing me to participate on the winter-school e-WISPOC at Bressanone which were a great experience both scientifically and socially.

To my co-supervisor Tore Bonge-Hansen, even though his involvement in this project has been more to fulfill the formal requirement for the PhD-application, I am sincerely grateful for the time he has invested in me since I started on a Bachelor project in his group some 8 years ago. Those years spent under his guidance in both the Bachelor-project and eventually in the Master’s project were not only highly educational and rewarding, but it fuelled my interest for chemistry even further.

Tor Erik Kristensen, Åsmund Kaupang Martin Hennum and Kristian Vestli deserve a special mentioning not only for their friendship through 8 years, which I highly appreciate, but also for the fruitful scientific and non-scientific discussions we have had. The importance of unhealthy food, beer and stomach pain induced by too much laughter obtained in their company can’t be underestimated! A special thanks to Tor Erik and Åsmund is highly deserved for their contribution of proof-reading the draft for the published paper. Few people I know master the art of scientific writing and presentation of data like them, and being able to get their input and suggestions has been of tremendous help.

Peter Molesworth deserves a special mentioning for his comments, corrections and suggestions for the written part of this thesis. His feed-back and suggestions improved the quality and readability of the thesis significantly.
Håkon “Baby-face” Gulbrandsen also deserves a mentioning for his contribution to the proof-reading of this thesis.

Franziska Ihlefeldt also deserves a mentioning for her constructive feed-back and suggested changes for the schemes and figures featured in this thesis. The readability and aesthetics has much improved thanks to her.

I also want to thank the current and former members of the organic chemistry section for the numerous social and scientific exchanges over the last 8 years. This includes amusing lunches with politically incorrect statements, weird facts and theories, puns and more. There has also been the annual organic section Christmas party, weekly floorball battles, practical jokes, BBQs, game-nights, development of mischievous contraptions for the annual dry-ice curling event (Sadly termed cheating by those empowered to ban us), quizzes (with excessive drinking), paintball excursions and so much more.

A special thanks to the current and former members of the Mamou-group, including Bora Sieng, Matias Funes Maldonado, Carlo Romagnoli, Jakob Wåhlander and Eirik Mydske Thoresen for making the day-to-day life in the lab a fun and social arena.

Hui-Chung Wen and Pierre Paolo, deserves thanks for their efforts and contribution to the project which was undertaken during their Erasmus studies.

I would like to thank Frode Rise and Dirk Pettersen, for their excellent services by both maintaining and somehow even improving upon the already impressive NMR facility here at the Chemistry Department. Their services and dedication has not only benefitted myself but numerous others. I also highly appreciate their willingness to answer NMR-relevant questions and give practical assistance when in need of it and friendly chatter in the hallways.

To Osamu Sekiguchi and the rest of the MS-team, thank you for the service you have provided during my stay at the Department. The MS-team also deserves as special thanks for their willingness to answer questions.

To my family, thank you for you continuous support over the last 10 years and for providing me with a safe port for to rest, in a safe distance away from academia and all of its issues. The comfort of having a home cooked meal once in a while and hikes around the mountain tops surrounding our cabin has been of great importance to me.

To my swinging friends at Bårdar Swing Club (Not swingers friends/club), thank you for introducing me to the fantastic world of swing dance, and for being such lovely people to hang out with!
My childhood friends, Magnus, Jonas, Thomas and Lars, deserve thanks for reminding me of the life that exists outside of Blindern. I really enjoyed our trips together (including mountain hiking, fishing and trips abroad), game nights, watching sports with the appropriate food and drinks among so many other things.

Possibly on a stranger note, I feel the urge to thank the 300 and 200 MHz NMR instrument of the Chemistry Department. Thank you for your relentless dedication and your keen eye for details, which is impressive considering your age. Without you, chapter 3 and 4 of this thesis would undoubtedly have been more frustrating than it was.

And lastly to my favourite inanimate object, my Moomin cup, thank you for the caffeine buzz you have helped me achieve in all of these years.

Sincerely

Kim Alex Fredriksen, Blindern, 23.11.2016
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Investigation of Reactive Intermediates and Reaction Pathways in the Coupling Agent-Mediated Phosphonamidation Reaction.

Kim Alex Fredriksen, Mohamed Amedjkouh

AIM OF STUDY

The aim of the study was to advance the chemistry related to aminophosphonic acids. After reviewing the available literature, our attention was drawn towards the preparation of chiral \( \alpha \)-aminophosphonic acids and derivatives thereof. The first objective was to investigate their preparation, with a special emphasis on enantioselective methods. This investigation prompted us to explore whether chiral phase-transfer catalysis could be used in the key step to prepare chiral \( \alpha \)-aminophosphonic acids in an enantioselective manner (see Chapter 2).

The second objective was to promote a phosphonamidation reaction between monoesters of phosphonic acids and amines \textit{via} a coupling agent-mediated reaction. Upon the eventual establishment of such a method an extended goal would be to attempt a phosphonamidation reaction on adequately protected aminophosphonic acids attempting to form small peptides (see Chapter 3). The peptides themselves could be interesting targets to study by means of NMR spectroscopy and X-ray crystallography, to investigate how the geometry of the phosphonoamidate groups affects the folding of the peptide.

Once a methodology for the synthesis of phosphonamidates had been developed it became an important objective to control the stereochemistry at the phosphorous atom. Different strategies to achieve stereoselective phosphonamidation reaction were investigated. This feature necessitated the development of a new subclass of coupling agents that were themselves chiral (see Chapter 4).
Chapter 2 - This section includes our attempted preparation of enantioenriched aminophosphonic acids employing phase-transfer catalysis. The chapter includes the attempted preparation of new chiral crown ethers and synthesis of well-known ammonium-type phase-transfer catalysts. The latter was employed in enantioselective alkylation reactions on a phosphoglycine Schiff base.

Chapter 3 and Paper 1 - These sections detail our investigation of the coupling agent mediated phosphonamidation reaction. The investigation includes an exploration of the mechanism, reaction pathways, and the activated species formed during the reaction and the impact they have on the reaction.
Chapter 4 - This section includes our exploration towards an enantioselective phosphonamidation using chiral coupling agents.
<table>
<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AMBN</td>
<td>Azobisisobutyronitrile (Radical initiator)</td>
</tr>
<tr>
<td>Anth</td>
<td>Anthracenylmethyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Buthyloxy carbonyl</td>
</tr>
<tr>
<td>BOP</td>
<td>(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>CDMT</td>
<td>2-Chloro-4,6-dimethoxy-1,3,5-triazine</td>
</tr>
<tr>
<td>COLOC</td>
<td>Correlation via Long range Coupling (NMR-sequence)</td>
</tr>
<tr>
<td>COMU</td>
<td>(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy) dimethylamino-morpholino-carbenium hexafluorophosphate</td>
</tr>
<tr>
<td>COSY</td>
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</tr>
<tr>
<td>CPA</td>
<td>Carboxypeptidase A</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-p-benzoquinone</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N'-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DMT</td>
<td>4,6-Dimethoxy-1,3,5-triazin-2-yl</td>
</tr>
<tr>
<td>DMTMM</td>
<td>4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate</td>
</tr>
<tr>
<td>HBTU</td>
<td>O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate</td>
</tr>
<tr>
<td>HETCOR</td>
<td>Heteronuclear correlation (NMR-sequence)</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation (NMR-sequence)</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramidate</td>
</tr>
<tr>
<td>HOAt</td>
<td>1-Hydroxy-7-azabenzotriazole</td>
</tr>
</tbody>
</table>
HOBt  1-Hydroxybenzotriazole
HPLC  High-performance liquid chromatography
HSQC  Heteronuclear single-quantum correlation (NMR-sequence)
Oxyma  2-Cyano-2-(hydroxyimino)acetic acid ethyl ester
PT  Phase-transfer
p-TsOH  para-Toluenesulfonic acid
PyBOP  (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyOxim  [Ethyl cyano(hydroxyimino)acetato-O\(\cdot\)]tri-1-pyrrolidinylphosphonium hexafluorophosphate
K-Oxyma  2-Cyano-2-(hydroxyimino)acetic acid ethyl ester, potassium salt
MS  Mass spectrometry
LAP  Leucine aminopeptidase
NMR  Nuclear-Magnetic Resonance
SPPS  Solid-phase peptide synthesis
TBAB  tetra-\(n\)-Buthylammonium bromide
TBAC  tetra-\(n\)-Buthylammonium chloride
TBAI  tetra-\(n\)-Buthylammonium iodide
TBME  tert-Buthyl methyl ether
THF  Tetrahydrofuran
THP  2-tetrahydropyranyl
TLC  Thin-layer chromatography
CHAPTER 1 – GENERAL INTRODUCTION

The intention of Chapter 1 is to provide a general introduction to the chemistry in which the thesis is built upon. The work presented, is mainly divided between organic synthesis and phase-transfer catalysis methodology, with the latter being presented as a whole in Chapter 2. Since the overall aim of the project was to advance the chemistry related to chiral $\alpha$-aminophosphonic acids, some of their key characteristics and favoured preparation methods are highlighted in this chapter.

1.1 – Synthesis from a Historic Perspective

The advent of the field of organic synthesis is often referenced back to Wöhlers preparation of urea (1) in 1828.[1] This accomplishment was unique at the time since living matter had not been prepared from “dead” inorganic materials, nor was it believed to be possible. “...I cannot, so to say, hold my chemical water, and must tell you that I can make urea, without thereby needing to have kidneys, or anyhow, an animal, be it human or dog...”[2] In the years to follow, chemists started to synthesise natural products rather than analysing them, which necessitated a deeper understanding of both molecular structure and chemical reactivity. The synthesis of molecules such as acetic acid (2),[3] tert-butanol (4),[4, 5] along with synthetic dyes such as alizarin (5), mauvine (4) (serendipitous discovery by Perkin) and indigo (6) surfaced (Figure 1.1).[6, 7, 8] The elegant work on both the structure elucidation and synthesis of glucose (8) by Emil Fischer and the biocatalytic synthesis of fructose (7) by Brown in the 19th century,[9, 10] among many contributions to new named reactions,[11, 12] helped set the stage for the explosive growth of synthetic organic chemistry experienced following Woodwards and Döring synthesis of quinine (10) in 1944.[13, 14] Synthesis, or “the intentional construction of molecules by chemical means”,[15] as defined by Cornforth in 1998 has since Wöhlers discovery allowed the preparation of some truly complex molecules exemplified here by compounds such as Taxol (11), Palytoxin (12) and Brevetoxin B (13) (Figure 1.1).[16, 17, 18, 19, 20] Even though molecular complexity and difficulty in preparation is not necessarily synonymous with molecular size, the synthesis of as Taxol (11), Palytoxin (12) and Brevetoxin B (13) indicate the extent to which the field has progressed since 1828.
Figure 1.1 – Achievements in total synthesis from its inception up until recent.

The construction of complex compounds has necessitated the application of general guidelines and strategies to improve the planning phase of synthesis. One of these tools is retrosynthetic analysis which was formalised by E. J. Corey,[21] but the concept had already been introduced by Robert Robinson in 1917, with the introduction of “imaginary hydrolysis”.[22] Retrosynthetic analysis is based on deconstructing the target molecule into smaller building blocks in order to find logical reactions and starting materials for the synthesis. This method may help to reduce the number of steps required for a target molecule. Brevity in synthesis, the ability to compose a synthesis with few chemical
transformations are among the most important guidelines that are taught in modern day synthesis. A famous, yet old example is the synthesis of Tropinone (9), which was first synthesised by Wilstätter in 1901 in 15 steps in a total yield of 0.75%.\cite{23} The same compound was synthesised by Robinson in 1917 in 2 steps in a total yield of 17%.\cite{22} The yield was improved further by Schöpf who modified the pH of the reaction mixture.\cite{24}

Organic synthesis was often the main tool in order to elucidate the molecular structure of isolated natural products. With technological advances such as NMR spectroscopy, X-ray crystallography, mass spectrometry among other techniques, a complete structure elucidation can often be undertaken in matter of days. The effort required to synthesise a particular natural product however can be extremely time consuming and costly. As an example, Brevotoxin B (13) took 12 years to complete.\cite{16} As a consequence of the technical advances related to structure elucidation instrumentation, the role of organic synthesis have shifted from being primarily that of synthesis of natural products to involve catalysis and methods for asymmetric synthesis. In the book “The Way of Synthesis” it is stated that “over the last 50 years the perceptions and expectations of the synthetic community with regard to what constitutes acceptable levels of accomplishments in synthesis has undergone major changes”.\cite{11} Among these accomplishments is the ability to not only synthesise molecules with the correct connectivity of atoms, but also to synthesise molecules with the right arrangement of atoms in space. This became especially important after the infamous Thalidomide incident during the late 1950s and it is connected to stereochemistry (see Section 1.2).
1.2 - Stereochemistry

Synthetic organic chemistry entails several important aspects, such as the understanding of chemical reactivity and stability of molecules, and subsequently the connectivity and arrangement of atoms in space. Investigations concerning the dynamic and static behaviour of three-dimensional shapes of molecules fall under the category - stereochemistry. The chemistry related to this category is extensively studied because several important building blocks found in nature, including our own bodies, have this integral property. Stereochemistry is important because molecules that share the same chemical connectivity, but differ in the arrangement of their atoms in space can have significantly different properties when placed in a chiral environment, such as the human body. Receptors in the human body can have different affinities for molecules with different connectivity in space, which in turn can trigger different responses. These responses can be harmless such as difference in taste or smell (see Carvone, Figure 1.2), but it can also have a more tragic outcome as was experienced with the Thalidomide incident.\cite{25} Thalidomide which has two stereoisomers, (The enantiomers, \textit{15}\textbullet-(R) and \textit{15}\textbullet-(S)) was sold as racemate (50/50 mixture of the enantiomers) (Figure 1.2). The drug was prescribed to cure morning sickness for pregnant women but it was later found to cause serious malformations on the limbs of the infants and tragically, several deaths. It was found that the (S)-stereoisomer caused the side-effects, but also that the (R)-stereoisomer would undergo transformation to the harmful (S)-stereoisomer \textit{in vivo}. As a consequence, being able to prepare molecules in a stereoselective manner became important as well as obtaining a deeper understanding of how molecules behave \textit{in vivo}.

A molecule or an object is said to be chiral if it is non-superimposable with its mirror image. To evaluate this, the concept of stereogenic center or more precise, stereogenic unit was introduced. Using this concept, a molecule is said have stereoisomers if the interchange of two atoms or groups of atoms that are connected to a stereogenic unit produce a new stereoisomer. Stereoisomers can either be enantiomers; which is non-superimposable with its mirror image, or diastereomers; which are stereoisomers that are not enantiomers. A stereogenic unit is often introduced as being a tetrahedral carbon atom with four different

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.2.png}
\caption{Examples of different stereoisomers of carvone (14) and thalidomide (15) and their characteristics.}
\end{figure}
substituents, but it also includes olefins, hexa- or tetra-coordinated phosphorous atoms, allenes, spiro compounds and substituted biphenyls among other compounds (Figure 1.3). In this thesis, tetrahedral carbon and phosphorous species will be covered (see chapter 2, 3 and 4). Subsequently, the definition stereogenic center instead of stereogenic unit will be used since all of the chiral molecules that are prepared have a stereogenic center at an atom and not of a group of atoms.

![Figure 1.3](image_url) – A figure showing examples of different types of stereogenic units. The stereogenic unit is marked in red.
1.3 - Phosphorous Analogues of Amino Acids and Derivatives thereof

The aim of the project was to advance the chemistry related to chiral α-aminophosphonic acids and derivatives thereof (Figure 1.4). These compounds are included in a diverse class of phosphorous analogues of amino acids to which the carboxylic acid group is replaced by either a phosphonic or phosphinic acid moiety.

![Diagram of phosphorous analogues of α-aminocarboxylic acids relevant for this thesis.](image)

Phosphonic and phosphinic acid analogues are significantly different to their carboxylic acid counterparts when comparing characteristics such as size (Atomic radii values for C = 0.67 Å and P = 0.98 Å), geometry and acidity (Table 1.1). As will be evident in later sections, these characteristics may be important when trying to evaluate and understand their reactivity. All of the phosphorous acid analogues covered in this thesis have a tetrahedral-like geometry of the acid functional group compared to the pseudo-flat geometry of the carboxylic acids. Additionally, the pKa values are consistently lower for organic acids where the carboxylic acid functionality has been isosterically replaced with a phosphonic or phosphinic acid (Table 1.1).
### Table 1.1 – Comparison of the pKa and geometry of some of carboxylic, phosphinic and phosphonic acids.

<table>
<thead>
<tr>
<th>Acid</th>
<th>pKa₁</th>
<th>pKa₂</th>
<th>Geometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>4.20</td>
<td>-</td>
<td>Flat</td>
</tr>
<tr>
<td>Phenylphosphonic acid</td>
<td>1.85</td>
<td>7.1</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>4.76</td>
<td>-</td>
<td>Flat</td>
</tr>
<tr>
<td>Methylphosphonic acid</td>
<td>2.38</td>
<td>7.74</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>Dimethylphosphinic acid</td>
<td>3.08</td>
<td>-</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>Phenylacetic acid</td>
<td>4.3</td>
<td>-</td>
<td>Flat</td>
</tr>
<tr>
<td>Benzylphosphonic acid</td>
<td>2.3</td>
<td>7.6</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>O-Phenyl cyclohexylphosphonic acid</td>
<td>3.6</td>
<td>-</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>Cyclohexyl phosphonic acid</td>
<td>4.8</td>
<td>-</td>
<td>Tetrahedral</td>
</tr>
</tbody>
</table>

[a] The pKa values were determined from EtOH: H₂O (75:25) solvent mixture. The pKa values for the other acids were determined from H₂O (100%).

These phosphorous analogues influence a broad range of physiologic and pathologic processes, which has helped this particular branch of phosphorous chemistry to be regarded as an own discipline. Together with their negligible toxicity in mammalian cells, aminophosphonic acids function as important metabolites that compete with other compounds for active sites of enzymes and other cell receptors. Consequently, several biologically active phosphorous-containing compounds have been prepared, incorporating the free acid or their esters and amides (Figure 1.5). These motifs have also been incorporated as individual segments in peptides. Application of these compounds include uses such as enzyme inhibitors, antiviral agents, antibiotics, antibacterial agents, antifungal agents, herbicides, antitumor agents, antibody generation and as metal chelators.
Figure 1.5 – Examples of biologically active aminophosphonic acids.

Typical examples in which the binding affinity of aminophosphonic acids towards receptors has been used are for compounds structurally similar to the known neurotransmitters glutamic acid and gamma-aminobuturic acid (GABA (22)). GABA-analogues are interesting targets of synthesis since they are involved in regulating important processes in the central nervous system. GABA interacts with three major subtypes of receptors, designated GABA<sub>A</sub>, GABA<sub>B</sub> and GABA<sub>C</sub>.[33] Phosphorous analogous of GABA have shown to be potent and selective effectors of these receptors (Figure 1.6).[31, 34, 35, 36, 37]

Figure 1.6 – The neurotransmitter GABA (22), and various phosphorous analogous of GABA.
However, the main protagonists of this thesis are α-aminophosphonic acids and the derivatives thereof, including phosphonamidates and phosphonates (see Figure 1.4). These compounds can be regarded as structural analogous of α-aminocarboxylic acids. The applications of these compounds, either as their free acids, esters, amides or as part of a peptide, often promote enzyme inhibition, where the compounds act as false substrates in the active sites of enzymes (see below).[38, 39] Particularly their natural tetrahedral geometry and ability to form strong electrostatic interactions with metals make these compounds interesting inhibitors of hydrolytic enzymes and especially of metalloproteases, where metals serve an important mechanistic role in the active site of the enzyme (Scheme 1.1).

![Scheme 1.1](image)

**Scheme 1.1** – Phosphorous analogous of amino acids can often promote enzyme inhibition by forming a stable mimic of high-energy intermediates.

The inhibition of these enzymes is explained by the ability of the phosphorous acid analogues to mimic the high-energy intermediates that would normally form during the hydrolytic cleavage (of ester or amide bonds) of carboxylates and carboxamidates (Scheme 1.1). Examples using phosphonic acids and their derivatives appears to be limited to leucine aminopeptidase (LAP) and carboxypeptidase A (CPA),[40, 41] while compounds derived from aminophosphinic acids are more frequently studied.[42] The availability of the crystal structures of the LAP enzyme bound to the phosphorous analogue of leucine, LeuP (Figure 1.7), was used in cooperation with molecular modelling to design new inhibitors (Figure 1.8).[43]

![Figure 1.7](image)

**Figure 1.7** - The molecular modelling of LeuPLeu in the active site of the LAP enzyme.[43]
It was found that the phosphonamidate N-H-bond increased the binding affinity with the active site of the enzyme by forming a hydrogen bond to Leu360 in the LAP-enzyme (Figure 1.7). Compounds without this binding interaction, such as phosphinate analogues (33 and 34), had a lower affinity for the active site (Figure 1.8). However, the chemical instability found in most P-N bonds of phosphonamidic acids (30 and 31) currently limits the application of these compounds. This may explain why the more robust phosphinate analogues have received more attention for enzyme inhibition studies.[42, 43, 44, 45] Some efforts have been attempted to prepare phosphonamidic acids which are stable at physiological pH but they were not effective inhibitors of LAP (Compound 32, Figure 1.8).[46]

![Phosphonamidic acids](image)

**Figure 1.8** – Synthesised inhibitors of the LAP enzyme.

The characteristics of α-aminophosphonic acids and their derivatives make them interesting targets in medicinal chemistry and for further studies.

### 1.4 - Synthesis of α-Aminophosphonic Acids and Phosphonates

Chiral α-aminophosphonic acids can be prepared *via* numerous routes, and primarily by those in which the phosphonic acid group is masked as a phosphonate throughout the key steps of the synthesis. During the finalisation of the product, the phosphonic acid is normally obtained after hydrolysis of the phosphonate group. The majority of the strategies that have been developed depend on a stereoselective P-N, C-C, C-N or a double C-H bond formation reaction as the key step (Figure 1.9). All of these strategies have been undertaken with control of stereochemistry which have been summarised in the following review.[32] The work presented in this thesis contain both C-C (see Chapter 2) and P-N (see Chapter 3) bond
formation reactions to afford α-aminophosphonic acids precursors. P-N bond formation reactions are arguably the most popular strategy used to obtain α-aminophosphonic acid precursors and are briefly covered in the following section.

![Scheme 1.2](image)

**Figure 1.9** – The different strategies used to obtain α-aminophosphonic acids precursors using retrosynthetic synthons.

Nucleophilic substitution or addition reactions using dialkylphosphites as the nucleophile, are frequently employed strategies used to incorporate the phosphonate group into organic molecules. Among these strategies, the Kabachnik-Fields reaction is currently the most popular method in order to synthesise α-aminophosphonates. The original Kabachnik-Fields reaction is a three-component domino reaction between an amine, an aldehyde or ketone, and a dialkylphosphite, which is facilitated by a catalyst (Scheme 1.2). The key step of the reaction is the nucleophilic addition of the dialkylphosphite to the imine, which subsequently furnishes the C-P bond formation step and generates the stereogenic centre when aldehydes and unsymmetrical ketones are used. The imines can either be pre-formed or be generated in situ. The substitution on the α-carbon of the finished product originates from the choice of the carbonyl (Scheme 1.2).

![Kabachnik-Fields Reaction](image)

**Kabachnik-Fields Reaction**

\[ R_1 = \text{alkyl, aryl} \quad R_2 = H, \text{alkyl, aryl} \]

**Scheme 1.2** – The three-component Kabachnik-Fields reaction.
Enantioselective Kabachnik-Fields reactions have been studied in which chiral catalysts are able to produce enantioenriched material (Scheme 1.3). The reactions are catalysed by several types of catalysts, here exemplified by aminoalcohol 10, hydrogen bond-type 45 and Brønsted acid-type 46 organocatalysts.

Scheme 1.3 – Enantioselective Kabachnik-Fields reactions catalysed by quinine (10), a hydrogen bond-type organocatalyst 45 and a Brønsted-acid type organocatalyst 46.
Other representative methods used to prepare enantioenriched $\alpha$-aminophosphonic acids and/or $\alpha$-aminophosphonates are shown in Scheme 1.4.[52, 53, 54]

C-N bond formation

Our study was initiated by investigating an alternative route to afford the $\alpha$-aminophosphonates which does not rely on the Kabachnik-Fields reaction, but rather on the strategy commonly used to synthetically afford $\alpha$-amino acids. This strategy involves the use of phase-transfer catalysts in order to alkylate phosphoglycine Schiff bases. This strategy has been employed occasionally but there is currently no description of an enantioselective preparation method using a chiral catalyst.[55, 56, 57] Our strategy regarding this topic is discussed in Chapter 2.
1.6 – References

The aim of this chapter is to give an introduction to the field of phase-transfer catalysis (PT-catalysis) and to present some of the existing theories used to describe the mechanism involved. The field of asymmetric PT-catalysis will be introduced with special emphasis on the alkylation of glycine Schiff bases. In this context, some highlights from the development of chiral PT-catalysts will be briefly covered. This development process in particular was used as a guide in our own attempt to advance the field of asymmetric PT-catalysis of phosphoglycine Schiff bases.

2.1 - The Concept of Phase-Transfer Catalysis

The conceptualisation of what is now known as phase-transfer catalysis stems from several individual efforts provided during the 1960s. During this period, several authors were detailing the rate enhancement obtained when quaternary ammonium and arsonium salts were used as a catalyst in biphasic systems. Names such as “extractive alkylations” and “catalysis in heterogeneous systems” began to surface, and eventually the phrase “phase-transfer catalysis” was coined by Charles M. Stark in 1971. PT-catalysis is an alternative solution to what is known as the heterogeneity problem, which inhibits a chemical reaction between two chemical species when they are located in different phases (i.e. immiscible liquids and between solids and liquids). The heterogeneity problem occurs in systems where compounds with a significant difference in polarity (i.e. inorganic salts and organic compounds) are required to react. Traditionally, this problem has been circumvented by the use of a solvent or solvent mixture that allows both components to dissolve. PT-catalysis serves as an alternative solution to the heterogeneity problem by utilising a biphasic system (i.e. a mixture of water and an organic solvent) and a catalyst. The role of the catalyst is to bring the two, initially separated, chemical species together in the same phase, which allows the species to react with each other. This can be accomplished in several ways, and the mechanism for these transfers will be presented in more depth in the following sections.

2.2 - The Principles of Phase-Transfer Catalysis

In most reactions employing PT-catalysis, the nucleophile and/or base is dissolved in an aqueous phase while the organic reactant or reactants are dissolved in an organic solvent. Since the reactions occur in the organic phase, an important feature of the PT-catalyst is to make the water-soluble reactant sufficiently lipophilic in order for it to enter the organic phase. Theories on how this can be achieved and the structure of the catalyst-salt/anion complexes will be discussed shortly (Section 2.4.). The pathway that generates these
complexes is debated and consists mainly of Stark’s *Extraction Mechanism* and Makosza’s *Interface Mechanism* (Figure 2.1). The disagreement between the two mechanisms originates from where the complex is generated. In Stark’s proposed mechanism, the catalyst is required to physically enter the aqueous phase to form the complex, while Makosza proposed that the complex is formed at the interface of the two immiscible solvents. In cases were the catalysts are significantly lipophilic, Makosza’s proposed mechanism appears to be the most plausible alternative while the opposite stands with sufficiently hydrophilic catalysts. Most of the catalysts that are covered in the following sections however are considerably lipophilic, thus Makosza’s mechanistic suggestion will be emphasised in this study.

**Stark’s Extraction Mechanism**

![Stark's Extraction Mechanism Diagram](image)

**Makosza’s Interface Mechanism**

![Makosza's Interface Mechanism Diagram](image)

**Scheme 2.1** – Two different mechanisms used to explain how the PT-catalysts extract the water-soluble reactants into the organic phase.
A more detailed mechanism of PT-catalysed processes in general depends on several factors, which is extensively covered in reviews and books,[8, 9, 10, 11, 12] thus a brief explanation will be covered here.

At this point in time, it is important to discuss how the anion (organic or inorganic) which has been extracted in the organic phase is affected by its surroundings. The surroundings experienced by the anion consist primarily of neighbouring solvent molecules and of the PT-catalyst.

### 2.3 - Solvation

A factor that can have a dramatic influence on the nucleophilicity and basicity of an anion is the solvation. Nucleophilicity is normally evaluated from the structure of the nucleophile (shape, polarizability, basicity, and the $\alpha$-effect) and how it is solvated. If the organic phase is an aprotic solvent of low polarity, rate enhancements may be observed in nucleophilic substitution reactions. The observed rate enhancement is partly attributed to the lack of stabilising interactions between the anion and the surrounding solvent molecules. Such anions are commonly referred to as “naked” even though this description has been criticized for being inaccurate.[13] In polar protic solvents, nucleophiles are commonly hindered by the formation of a solvent cage surrounding the nucleophile. This solvent cage is the result of hydrogen bonds caused by the solvent molecules. For dilute aqueous solutions, hydration of the anion in the organic phase can affect the nucleophilicity and basicity of the extracted anions via an analogous explanation.[14, 15, 16] Saturated salt solutions have shown to improve the rate of such reactions by minimising the degree of hydration of the organic phase.[8] This is often referred to as desiccation, which can be accomplished by employing aqueous 60 wt% KOH or 50 wt% NaOH solutions; this is even beneficial for reactions that do not require deprotonation. An explanation for this will be given in Section 2.6. Traditionally, prior to the introduction of PT-catalysis, solvents such as DMF, DMSO, acetonitrile and HMPA would often help to facilitate reactions between inorganic salts and organic reactants. However, these solvents are hampered by several disadvantages such as difficulty in removing the solvent from the product mixture, the cost and sometimes by the toxicity (HMPA is carcinogenic). These disadvantages have encouraged the development of PT-catalysed processes.
2.4 - Catalyst Structure

PT-catalysed processes are commonly catalysed by either onium species which include, ammonium, phosphonium and arsonium-salts or by neutral species such as crown ethers, cryptands and others structures (Figure 2.1).[8, 17]

**Figure 2.1** - A PT-catalyst overview, displaying some of the structural diversity of currently used PT-catalyst.

A common feature for both classes of catalysts is that they extract the required anion into the organic phase by the formation of an ion-pair with a sufficiently lipophilic catalyst cation. Onium type catalysts are by themselves permanently charged species (salts) and may necessitate an anion exchange with the anion required for the reaction before it is extracted into the organic phase (Exchange of chloride with cyanide in Scheme 2.2). Neutral catalyst such as crown ethers on the other hand, work by forming a tight non-covalent bond with the cation of the salt, making it sufficiently lipophilic in order to extract the anion into the organic phase (Scheme 2.2).

**Scheme 2.2** – Different PT-catalysts extract the inorganic salt differently. Onium species undergoes anion exchange with the salt, while neutral species extracts the entire salt during the PT-process.
To ensure a sufficiently tight interaction between the crown ether and the cation, the size of the crown ether ring should be chosen to ensure the best fit with the cation (Table 2.1).[18]

Table 2.1 - An overview of various cations and the crown ether most suitable to form a sufficient chelation. [18]

<table>
<thead>
<tr>
<th>Preferred anion size (diameter)</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 – 1.5 Å</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7 – 2.2 Å</td>
<td>Zn²⁺</td>
<td>Ca²⁺</td>
<td>Ag⁺</td>
<td>Fr⁺</td>
</tr>
<tr>
<td>2.6 – 3.2 Å</td>
<td>Cu²⁺</td>
<td></td>
<td>Au⁺</td>
<td>Cs⁺</td>
</tr>
<tr>
<td>3.4 – 4.3 Å</td>
<td></td>
<td>Hg²⁺</td>
<td>NH₄⁺</td>
<td></td>
</tr>
</tbody>
</table>

2.5 - Phase Transfer Catalysed Process under Neutral Conditions

Typical examples of PT-catalysed processes that proceed under neutral conditions are nucleophilic substitution reactions, which were featured in Stark's original paper from 1971 (Scheme 2.1).[7] Fundamental to his proposed mechanism was that the inorganic anion originating from the aqueous phase would be transported into the organic phase by complexing with the PT-catalyst. The anion of the catalyst-anion complex would then participate in a rapid substitution reaction with the organic substrate, which is accelerated by an aprotic solvent of low polarity. The displaced anion originating from the organic substrate is then transported to the aqueous phase by the PT-catalyst. Reactions occurring at the interface were evaluated as unlikely since the reaction rates are largely unaffected by the stir rate which increases the surface area by emulsifying the two phases. For PT-catalysed processes where a deprotonation is required, stir rates appear to be more important, suggesting that a different mechanism may be active (Section 2.6).

As mentioned previously, since most PT-catalysts consist of lipophilic building blocks, it is assumed that the catalyst does not physically enter the aqueous phase. Further evidence for this has been found from kinetic measurements where the concentration of the catalyst-anion complex in the organic phase was directly related to the rate of reaction.[19] An important mechanistic feature of PT-catalysed processes, which had to be evaluated, was if the chemical reactivity was caused by dissociated ions or by onium ion-pairs. In typical
low-polarity solvents routinely used for PT-processes (dielectric constant 10 – 15 or lower), the dissociation constant for quaternary ammonium salts are of the order $10^{-4} – 10^{-5}$, thus the probability is higher that the reaction occurs from ion-pairs than from dissociated ions. From rate measurements, Brandström provided evidence supporting that the ion-pairs are indeed the main reactive species.\cite{19} Another important feature to evaluate in PT-catalysed processes is related to the extraction of ions, and the catalysts ability to discriminate between different ions. It should be stressed that this particular subject has been extensively studied and depends on many different aspects such as, dilution and choice of anion and cation. For PT-catalysed processes under neutral conditions, the experimental setup should be designed to suppress catalyst poisoning.\cite{8, 20} Catalyst poisoning occurs in systems were the PT-catalyst has a significantly higher extraction coefficient for the displaced anion originating from the targeted reaction rather than for the anion required for the intended reaction. Thus, as the reaction progresses an increasing number of the catalyst cations forms a complex with the wrong ion. As a consequence, the reaction rate of the intended reaction will decrease during the course of the reaction and potentially stop entirely.

2.6 - Phase Transfer Catalysed Processes of Alkali Metal Hydroxides

Unlike the extraction of neutral anions which were covered in the previous section, PT-catalysts does not readily extract the hydroxide anion featured in PT-catalysis process where a deprotonation is required. Onium hydroxides are known to be unstable, leading to degradation of the catalyst.\cite{21, 22, 23} Additionally, the poor extraction selectivity of onium hydroxides compared to other ions (i.e. $K_{el Cl/OH} = ca$ 10\(^3\)),\cite{23, 24, 25} questions whether the role of the catalyst is mechanistically different to what was described in Section 2.5. To compensate for the less efficient extraction of hydroxides by onium salts, an alternative mechanism was proposed. Makosa hypothesised that the deprotonation of the weak carbon acids (C-H deprotonations, i.e. formation of enolates) occurs mainly via an direct interaction between the hydroxide and the reagent at the interface of the immiscible solvents, and not from extracted onium-hydroxides into the organic phase.\cite{26} This may explain why these types of PT-catalysed processes are more affected by the stir rate of the experimental setup than for processes with sufficiently lipophilic anions that have higher extraction coefficients than hydroxides. Interestingly, deprotonation of acids with a higher pKa than hydroxide may occur. A possible explanation to why the basicity of hydroxides is increased in the interface of aprotic polar solvents may be the absence of stabilising factors of the hydroxide by the surrounding solvent molecules. The same analogy was used to explain the elevated basicity observed for hydroxides in dry (desiccated) compared to wet organic solvents. The deprotonated carbon acid is then anchored to the interface until it is made sufficiently lipophilic by complexation with the PT-catalyst (Relevant mechanisms in Scheme 2.3). Once
the carbon acid is extracted into the organic phase, the reaction between the reactants is made accessible. The following section will attempt to briefly cover one of the main reactions frequently used in PT-catalysed processes with alkali metal hydroxides, namely the alkylation of glycine Schiff bases.

2.7 - Achiral and Chiral Alkylation Reactions of Glycine Schiff Bases\^[12]\]

Having already mentioned the unlikelihood of extracting hydroxide with PT-catalysts in the previous section, the main pathway considered for the deprotonation of the glycine Schiff bases is via the interface of the immiscible liquids. Due to mutual insolubilities of the metal enolate in both the aqueous and the organic phase, the metal enolate is regarded as being “anchored” to the interface with limited chance of reacting with the alkyl halide (Scheme 2.3, Step 1). For a chiral PT-catalysed process this mutual insolubility is crucial since it prevents the racemic background reaction from occurring that would diminish the enantioselectivity of the reaction. On this note, racemic product would also be obtained if the observed reactions were undertaken by fully dissociated ions which was disproved by Brandström.\^[19]\]

Scheme 2.3 – The proposed mechanism for a PT-catalysed alkylation reaction, using Makosza’s interface mechanism. The given example is between a glycine Schiff base and an alkyl halide (R-X) using an ammonium-type catalyst.

The PT-catalyst can then extract the enolate into the organic phase (Scheme 2.3, Step 2), which allows the nucleophilic reaction with the alkyl halide to occur (Scheme 2.3, Step 3). After the reaction is completed, the PT-catalyst can extract another enolate in order to complete the catalytic cycle. In enantioselective PT-catalysis the enantioinduction may originate from the use of a chiral PT-catalyst or a chiral auxiliary. The chiral PT-catalyst
discriminates one enantiomer over the other in the nucleophilic substitution reaction (Step 3), by the formation of a chiral ion-pair with the enolate.[9, 10, 12]

2.8 - The Development of Asymmetric Phase-Transfer Catalysts - Ammonium Salts

The increased popularity of PT-catalysis as a tool in organic synthesis eventually encouraged the development of chiral PT-catalysts. Several attempts were undertaken to achieve high stereoselectivity using chiral ammonium salts,[27, 28, 29, 30] and the first real breakthrough was presented by a Merck research group in 1984 (Scheme 2.4).[31] Utilising a chiral ammonium-type PT-catalyst 69, obtained from N-alkylation of the natural product cinchonine (70, Figure 2.2), they were able to obtain alkylated derivatives of the indanone with high enantioselectivity, especially for compound 68 (92% ee). Their decision to utilise the natural compound cinchonine, which is part of a class of compounds which is often referred to as the cinchona alkaloids, would later on have a significant impact on the development of new PT-catalysts.

1984 - Dolling, Davies and Grabowski

Scheme 2.4 – A PT-catalysed alkylation reaction using catalyst 69.

A few years later, O'Donnel and co-workers presented a new strategy to prepare enantioenriched α-amino acids, with the key step being an enantioselective PT-catalysed alkylation reaction.[32] The main protagonist in their strategy was the newly introduced glycine Schiff base 72, which can be viewed upon as a general α-amino acid precursor. The PT-catalyst employed by the O'Donnel group where obtained by N-alkylation of the the natural products cinchonine (70) and cinchonidine (71) (Figure 2.2). It is worth highlighting that cinchonine and cinchonidine are structurally similar with each other with the exception of the stereochemistry located at carbon 8 and 9. It is worth noting that the different epimers give predominantly different stereochemical outcome in alkylation reactions of glycine Schiff bases. PT-catalysts prepared from cinchonine (70) give predominantly the R-enantiomer while the opposite enantiomer is obtained from cinchonidine (71).
Figure 2.2 – The chiral natural products cinchonine and cinchonidine.

Each of the enantiomers of product 73 could be prepared with moderate stereoselectivity depending by which natural product that was used to prepare the PT-catalyst (Scheme 2.5).

1989 - O'Donnel and co-workers

Scheme 2.5 - PT-catalysed alkylation reactions using catalyst 74 and 75.

In the context of controlled preparation of natural and unnatural \( \alpha \)-amino acids, the introduction of glycine Schiff bases in combination with PT-catalysis is arguably a valuable tool. The glycine Schiff bases represent a chemically modifiable precursor for \( \alpha \)-amino acids and derivatives thereof which can be obtained by varying the electrophile.\(^9\) An important feature of this amino acid precursor is that the \( \alpha \)-proton of the mono-alkylated product has a significantly higher pKa value compared to the \( \alpha \)-protons found in the starting material. For the monomethylated and monobenzylated products the pKa-value of the products was approximately 4.1 and 4.5 pKa units higher than that of the starting materials.\(^{33}\) The pKa difference between the mono-alkylated product and the starting material is thought to suppress racemisation pathways and prevent a secondary alkylation of the mono-alkylated product from occurring. Considerable effort was undertaken to further improving this
methodology since it allowed for a controlled synthesis of both natural and unnatural amino acids.[9, 10, 34]

The O'Donnel group also included a racemisation study which demonstrated that the free alkoxide of the PT-catalyst can racemise the product.[35] Racemisation was not observed when catalysts unable to form lipophilic alkoxides in solution were used. The same paper described that the actual catalyst responsible for the results were in fact the O-benzylated catalyst 77 and 78 which is formed in situ during the alkylation of the Schiff base. It is likely that the same phenomenon occurred during the paper presented by the Merck research group which would generate the O-methylated catalyst 76 (Figure 2.3).

![Figure 2.3](image) – In situ generated PT-catalysts that are formed from the alkyl halide reacting with the free hydroxyl group of the PT-catalysts.

The catalyst design was further improved by two individual groups (Scheme 2.6). The group led by Lygo increased the steric bulk near the ammonium group by synthesising the N-antracenylmethyl ammonium salt 79.[36] This led to an improved enantioselectivity in the alkylation reaction of glycine Schiff bases compared to previous attempts.[32] The group led by Corey used the same N-antracenylmethyl ammonium salt but they allylated the alcohol functional group (catalyst 80, Scheme 2.6), presumably to avoid in situ O-alkylation that had previously been observed by O'Donnel and co-workers. This catalyst design gave comparable results to the catalyst prepared by Lygo and Wainwright.[37]
Maruoka and co-workers developed monomeric PT-catalysts which were not derived from the cinchona alkaloids. These C2-symmetric, chiral spiro ammonium salts proved to be effective catalysts in asymmetric PT-catalysed reactions and required only 1 mol% of the catalyst. The best results were obtained with catalyst 81 (Scheme 2.7). A disadvantage experienced with these catalysts is that they are not as readily available as the catalyst derived from cinchona alkaloids depicted in Figure 2.2. The catalyst 81 and derivatives thereof require a 16-step synthesis to be obtained.

Influenced by the work of Sharpless regarding the development of dimeric catalysts for the Sharpless asymmetric dihydroxylation, Jew and Park introduced the first dimeric species of the catalyst, introducing a spacer unit in-between the two ammonium groups (Scheme 2.8). It was observed that the enantioselectivity varied according to the

Scheme 2.6 - PT-catalysed alkylation reactions using catalyst 79 and 80.

Scheme 2.7 - A PT-catalysed alkylation reaction using catalyst 81.
choice of linker and the orientation of the two ammonium species (Catalysts 82 - 85, Scheme 2.8).

In a third paper, Jew and Park studied PT-catalysts containing electron-deficient N-fluorobenzyl substituents and how they affected the outcome in the same alkylation reaction as they had tested earlier (Scheme 2.9). Evidence supporting that electron-deficient substituent in certain positions could be beneficial was established. Additionally, the position of the fluorine substituent and the number of fluorines had a significant influence on the results obtained.

Scheme 2.8 - PT-catalysed alkylation reactions using dimeric PT-catalysts 82 - 85.

Scheme 2.9 - PT-catalysed alkylation reactions using electron-deficient PT-catalysts 86 - 89.

2.9 - The Development of Asymmetric Phase-Transfer Catalysts – Crown Ethers

The first characterisation and recognition of crown ethers as a unique chemical entity were the result of a serendipitous observation by Charles Pedersen while attempting to prepare a phenolic multidendate ligand intended for Vanadium (Scheme 2.10). From an unsuccessful purification attempt of an “unattractive goo” Pedersen was able to recover a small quantity (0.4%) of mysterious crystalline compound. This compound would later be recognised
as the crown ether 94, resulting from the reaction between catechol (93), a minor impurity in the starting material 90, and bis(2-chloroethyl) ether (91) (Scheme 2.10).

Scheme 2.10 – The first crown ether that was synthesised and structure elucidated was prepared by Charles Pedersen’s by a serendipitous discovery.

Pedersen’s seminal paper, which included the synthesis, characterisation, naming and properties of 33 cyclic polyethers, can be considered to be the starting point of host-guest chemistry which led to the field of supramolecular chemistry. From the seminal paper by Charles Pedersen,[46] the crown ethers were given their name from the visual picture they resemble while complexing with a cation, “I applied the epithet “crown” to the first member of this class of macrocyclic polyethers because its molecular model looked like one and, with it, cations could be crowned and uncrowned without physical damage to either...”[18] The research topic of host-guest interactions in chemistry received the Nobel Prize in chemistry in 1987, which was equally shared between Cram, Lehn and Pedersen. In asymmetric synthesis, it was the pioneering efforts of Cram and Sogah,[47] which recognised that the host-guest properties of crown ethers could be utilised. In their study, crown ethers prepared from 3,3'-methylated BINOL derivatives 96 and 99 could be used to achieve enantioselective Michael additions between indenone and methylvinyl ketone and between methyl acrylate and esters. In these reactions, good to excellent enantioselectivity (62 – 99% ee) was achieved with good to excellent yields (48 – 100%).

The concept of host-guest interactions in PT-catalysis mediated by chiral crown ethers was eventually recognised by several other research groups. Since then, several new chiral crown ethers derived from sugars,[48, 49] chiral diols,[47, 50, 51] nucleoside bases and other chiral natural products have been developed (Figure 2.4).[51, 52, 53]
Figure 2.4 - Examples of crown ethers prepared from different chiral sources.
2.10 - Related Studies

The starting point for this project was the realisation that no enantioselective alkylation reaction of phosphoglycine Schiff bases catalysed by a chiral PT-catalyst existed. This was surprising since PT-catalysed alkylation reactions of the similar glycine Schiff bases have been investigated thoroughly after their introduction by the O’Donnel group in 1978.\(^{[54]}\) We envisioned that phosphoglycine Schiff base 104 could be utilised as a precursor for the synthesis of \(\alpha\)-aminophosphonic acids via a similar strategy to that developed by the O’Donnel group.\(^{[32, 54]}\) Evidence supporting this methodology as a viable strategy was found in 2009, when the group led by Alfredo Ricci presented the first enantioselective PT-catalysed Mannich reactions between the phosphoglycine Schiff base 104 and \textit{in situ} generated Boc-imines, obtained from \(\alpha\)-amidosulfones 103 (Scheme 2.11).\(^{[55]}\) Their efforts demonstrated that the phosphoglycine Schiff base 104 could be readily deprotonated and subsequently solubilised into the organic phase with catalysts commonly used for glycine Schiff bases. Additionally, the catalysts provided the product with a satisfactory yield (up to 96\%) and enantioselectivity (up to 94\% \textit{ee}). Almost simultaneously, the group of Töke published a procedure in which chiral crown ethers under PT-catalysis conditions could mediate an enantioselective Michael addition between electron deficient alkenes 107a-e and the phosphoglycine Schiff base 104 (Scheme 2.11).\(^{[56]}\)

\textbf{Alfredo Ricci and co-workers}

\begin{equation}
\text{Boc}-\text{NH}-\text{Ar-SO}_{2}\text{Ph} \quad \text{Ph-Ph-P-O} \quad \text{106 (5 mol\%)} \quad \text{CsOH-H}_{2}\text{O} \\
\text{103} \quad \text{104} \quad \text{PhMe-TBME (9:1)} \\
\text{60 - 96\% yield} \\
\text{50 - 94\% ee} \\
\text{105} \quad \text{106}
\end{equation}

\textbf{László Töke and co-workers}

\begin{equation}
\text{R}_1\text{X} \quad \text{Ph-Ph-P-O} \quad \text{109a-d (10 mol\%)} \quad \text{NaOtf-Bu} \\
\text{107a-e} \quad \text{104} \quad \text{PhMe} \quad \text{-75 \degree C} \\
\text{108a-e} \quad \text{109a-d}
\end{equation}

\(\text{R}_1=\text{H, Me, R}_2=\text{H, Ph, X=CN, CO}_2\text{Me, CO}_2\text{f-Bu}\)

\textbf{Scheme 2.11 - PT-catalysed procedures for the preparation of chiral \(\alpha\)-aminophosphonates.}
With these results in mind, two separate strategies were initiated that were targeting both types of PT-catalyst. The first strategy was aimed at developing new crown ethers prepared from chiral building blocks already popularised in asymmetric synthesis, and subsequently test them in Michael-type reactions. The second strategy was aimed towards testing already established ammonium-type catalyst in an alkylation type reaction. The results obtained from these strategies will be presented in the remaining part of this chapter.
2.11 – Results and Discussion

The starting point was to develop new chiral crown ethers derived from chiral natural products which were already frequently utilised in asymmetric catalysis. This included molecules derived from the amino acid trans-4-hydroxy-L-proline (115) and from the cinchona alkaloid quinine (10) (Section 2.12 and 2.13). In parallel an attempted alkylation reaction of phosphoglycine Schiff bases using known ammonium type PT-catalysts were investigated (Section 2.15).

2.12 - Attempted Crown Ether Synthesis, Inspired by the Trost Dinuclear Zinc Catalyst-System

We wanted to prepare crown ethers based around the structural motif found in the dinuclear zinc catalyst developed by Barry Trost in 2001.\cite{57} To prepare the crown ethers directly from the original design of the Trost catalyst ligand 110 was evaluated to not be synthetically feasible. Phenoxides are considered as more nucleophilic than sterically congested tertiary alkoxides, which are more likely to act as a base. Thus, an attempted crown ether formation of the unmodified Trost ligand design was expected to generate a dimer between two molecules of the ligand and the dichloro alkane. Simplifying the Trost catalyst design by removal of the phenol functional group alone would still be a difficult target to alkylate since tertiary alkoxides are normally not nucleophilic enough to facilitate substitution reactions. To accommodate these issues we decided to replace the diphenyl-prolinol scaffold with a trans-diphenyl-4-hydroxyprolinol scaffold since it includes a secondary alcohol that has been alkylated on previous occasions (Scheme 2.7).\cite{58, 59, 60}

Trost ligand

![Scheme 2.12 - Preparation of chiral diols that may undergo dialkylation to form crown ethers.](image)
Additionally, trans-4-hydroxy-L-proline (115, Figure 2.5) can be converted into the cis-4-hydroxy-D-proline (116) upon treatment with Ac₂O.[61, 62, 63] Having the flexibility to prepare 116 could be beneficial upon an eventual establishment of a working synthesis of the crown ethers 112 and 114, since the crown ethers 112 and 114 are diastereomers of each other.

![Figure 2.5 - Diastereomers of 4-hydroxy-proline](image)

The target molecules 112 and 114 could be viable catalysts for Michael and Michael-type addition reactions. A retrosynthetic analysis of compound 111 provided the following disconnections as seen in Scheme 2.13.

![Scheme 2.13 – Retrosynthetic analysis of the chiral diol 111.](image)

From the retrosynthetic analysis, the chiral diol 111 could be obtained from an N-alkylation between dibromo m-xylene (118) and the trans-diphenyl-4-hydroxy-L-prolinol (97) (Scheme 2.13). The dibromo m-xylene (118) was obtained from a radical bromination protocol of m-xylene (117) using N-bromosuccinimide (NBS) with benzoyl peroxide as the radical initiator. Pure dibromo m-xylene (118) was then obtained from a selective precipitation procedure of the crude reaction mixture when immersed in cold petroleum ether. The trans-diphenyl-4-hydroxy-L-prolinol (120) was obtained directly from a Grignard reaction on the unprotected methyl prolinate·HCl 119.[64] The product was purified by recrystallisation from EtOH. The N-alkylated product 111 was readily obtained when the reaction was undertaken in DMF. The product was purified by recrystallization from EtOH.
Scheme 2.14 – Chromatography free synthesis of the chiral diol 111.

Generally, the synthesis of macrocyclic structures mark a significant challenge since linear polymerisation has to be supressed. As a consequence, sufficiently dilute conditions are required in order to facilitate the *intramolecular* cyclisation reaction over the *intermolecular* polymerisation. Examples detailing such conditions can be found in natural product synthesis where Yamaguchi macrolactonisation and olefin/alkyne metathesis have been popular tools.[65, 66, 67] In the synthesis of crown ethers however, such dilute conditions are normally not required. In these procedures, an inorganic base is typically chosen to have the same cation that the finished crown ether would extract during the PT-catalysed process. Consequently, the multiple interactions of the ether-oxygens/heteroatoms facilitate the *intramolecular* cyclisation reaction by bringing the reactive sites together (Scheme 2.15). This is referred to as template assisted synthesis.

Scheme 2.15 – Template assisted synthesis of 18-crown-6 (59) using a potassium ion to bring the reactive sites together.

The ring-closing dialkylation was attempted with 1,2-bis(2-chloroethoxy) ethane (123) and 1,2-bis(2-tosyloxyethyl)ether (124) using bases such as KOT-Bu, K-HMDS and NaH. It soon became evident that substrate 111 did not readily undergo alkylation reactions, as 2-3 days at elevated temperatures with varying conditions did not provide an observable conversion of the starting material to any alkylated products (see Table 2.1). This conclusion was reached after $^1$H-NMR and TLC analysis of the quenched reaction mixtures.
Table 2.1 – Attempted cyclisation of the chiral diol 111 to afford the chiral crown ether 112.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp. [°C]</th>
<th>X</th>
<th>Solvent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOt-bu</td>
<td>20</td>
<td>O-Ts</td>
<td>THF</td>
<td>1 day</td>
</tr>
<tr>
<td>2</td>
<td>KOt-bu</td>
<td>80</td>
<td>O-Ts</td>
<td>DMF</td>
<td>2 days</td>
</tr>
<tr>
<td>3</td>
<td>K-HMDS</td>
<td>80</td>
<td>O-Ts</td>
<td>THF</td>
<td>2 days</td>
</tr>
<tr>
<td>4[a]</td>
<td>NaH</td>
<td>80</td>
<td>Cl</td>
<td>THF</td>
<td>2 days</td>
</tr>
<tr>
<td>5[b]</td>
<td>NaH</td>
<td>80</td>
<td>Cl</td>
<td>DMF</td>
<td>2 days</td>
</tr>
<tr>
<td>6[b]</td>
<td>NaH</td>
<td>80</td>
<td>O-Ts</td>
<td>PhMe</td>
<td>3 days</td>
</tr>
</tbody>
</table>

[a] TBAI as additive  [b] 0.5 M dilution

A possible explanation for the lack of crown ether formation may be explained by an inaccessibility or lack of reactivity of the secondary alkoxide formed after the deprotonation step. The electrophiles 123 and 124 have been used on numerous occasions on similar reactions. Structures similar to 123 and 124 have an increased electrophilicity compared to regular alkyl halides due to a neighbouring group participation effect imposed by the ether-oxygens, which is often referred to as anchimeric assistance.[13] The inability of the alkoxides of 111 to react with the electrophiles could be explained by the sterically demanding phenyl groups contained within the compound. Alternatively, the phenyl groups may impose a conformation of 111 that encapsulates or otherwise prevent the secondary alkoxides from reacting with the electrophiles 123 and 124. A source of critique for how the initial of the cyclisation attempts were conducted is that quite dilute conditions were undertaken. However two experiments were undertaken with high concentration (0.5 M) without any noticeable difference to the results. The lack of any detectable O-alkylated products supports our claim that the alcohol groups are not readily accessible.

A different strategy was envisioned in which the order of the N- and O-alkylations was reversed compared to the original strategy. An obvious disadvantage when finalising the crown ether synthesis with an N-alkylation is the lack of chelation between the heteroatoms of the crown ether precursor and an alkali metal cation during the ring-closing step. This may necessitate significantly dilute conditions in order to supress linear polymerisation over the desired cyclisation. To avoid the more favourable N- rather than O-alkylation in the first step of the synthesis, it was believed necessary to protect the secondary amine. This was undertaken by the formation of a carbamate protecting group using ethyl chloroformate (120 to 125, Scheme 2.16).
Scheme 2.16 – An alternative strategy to synthesise chiral crown ethers.

The isolated yield of the carbamate protected prolinol 125 was less than satisfactory (<20%), which may be a consequence of the incompatibility between the elevated temperatures required to dissolve the diphenyl-hydroxyprolinol (120) and the reduced temperatures typically used in chloroformate protection of amines. Carbamate protection using chloroformates on structurally similar monomeric prolinols had been successfully achieved before,[60] and after our attempt.[58] After the carbamate protection of the amine, a brief attempt to alkylate the prolinol 125 with dibromo m-xylene (118) was initiated. Even though a full structure elucidation was not undertaken, evidence supporting O-alkylation of the prolinol 125 was obtained by both MS (ESI+) and NMR analysis of the crude reaction mixture. Using 4.5 eq. of NaH in the alkylation step promoted an intramolecular substitution reaction between the tertiary alkoxide and the ethyl carbamate, affording compound 126.[68, 69] The attempted synthesis of 128 however ended with an unsuccessful purification attempt following the hydrolysis of the cyclic carbamate group to give the unprotected bis[aminoalcohol] 127.[58, 68]
2.13 - Attempted Crown Ether Synthesis of Cinchonidine Alkaloids

The cinchona alkaloids have been a popular structural motifs for catalysts used in asymmetric catalysis.\textsuperscript{[70]} We wanted to check whether the cinchona alkaloids could be incorporated into a crown ether design. Having previous experience with an thiol-alkene radical polymerisation technique,\textsuperscript{[71]} we wanted to attempt a radical thiol-ene cyclisation reaction between \textit{O}-allylated quinine 129 and PEG-dithiol 130 (Scheme 2.17). The \textit{O}-allylated quinine 129 was obtained in 66\% yield following a scaled down literature procedure.\textsuperscript{[72]}

The radical thiol-ene cyclisation reaction was attempted using AMBN as the radical initiator under dilute conditions to suppress linear polymerisation. However, the crude reaction mixture that was obtained was not easily purified due to excessive tailing of multiple products with similar \textit{Rf}-values. MS (ESI+) of the crude reaction mixture indicated that the correct product 131 was synthesised along with other unidentified products.

\textbf{Scheme 2.17} – Attempted synthesis of a crown ether designed from quinine (10) using a thiol-ene radical addition reaction.
2.14 - Asymmetric PT-Catalysed Alkylation Reactions of Phosphoglycine Schiff Bases

Seeing that the attempted preparation and isolation of crown ethers based on the Trost ligand (110) and quinine (10) were unsuccessful, it was decided to evaluate known chiral ammonium salts instead. As a first approach to this new strategy, both the catalysts and the phosphoglycine Schiff base had to be prepared.

The phosphoglycine Schiff base 104 needed for the evaluation of the PT-catalysts were obtained in 48% yield over three steps (Scheme 2.18), following a literature procedure.[73]

Scheme 2.18 – The synthesis of the phosphoglycine Schiff base 104

As a starting point for our investigation of the PT-catalysed alkylation reaction of 104, it was decided to prepare and evaluate chiral PT-catalysts that were frequently used in similar alkylation reactions of glycine Schiff bases. Thus, from existing literature procedures the following chiral PT-catalysts 80, 136 and 138 were prepared (Scheme 2.19). The PT-catalysts were prepared over two steps, in which cinchonidine (71) was first N-alkylated with the appropriate alkyl halide to afford the ammonium species 79, 135 and 137.[36, 37, 44, 45] Selective O-allylation of the hydroxy group was achieved under PT-conditions, in which the ammonium salt of both the product and starting material can catalyse the allylation reaction.
It was decided to use benzyl bromide as the alkyl halide since it historically appears frequently in the evaluation of newly developed PT-catalyst for the analogous glycine Schiff base 72 (see Schemes 2.4 - 2.9). In order to evaluate the performance of the chiral catalysts by HPLC analysis, a racemic reference sample was prepared. The racemate was prepared from a TBAC and TBAB catalysed reaction. Full conversion to the product 139 was observed after five hours as was evidenced by NMR analysis of the crude reaction mixture. The product mixture was purified by column chromatography, which allowed us to establish the HPLC-conditions required to separate the enantiomers of the afforded racemate. As already mentioned in Section 2.6 and 2.7, the mechanism in PT-catalysed reactions of hydroxyl anions differ from that of neutral anions. Due to the low extraction coefficient of hydroxylonium species into the organic phase the reaction rate is dependent on the intermixing of the two phases which is dependent on the rate of stirring. As a consequence, the stir rate that was used for the preparation of the racemate was used in the asymmetric alkylations that are presented in the sections below.

The dimeric chiral PT-catalyst 137 with free hydroxyl groups was tested using similar conditions to that used in the TBAC and TBAB catalysed reaction. After 24 hours reaction time, only trace an amount of the intended product 139 could be observed from 1H-NMR analysis. MS (ESI+) analysis of the crude reaction mixture displayed a strong signal that
could originate from a product resulting from dichlorocarbene (DCC) addition to the imine of 140 (Scheme 2.20).[^74] Not unexpectedly, an MS (ESI+)-analysis of the crude reaction mixture revealed that the catalyst had become alkylated to the double O-benzylated PT-catalyst 141, (Scheme 2.20).[^35] Measures to avoid both of these issues were implemented in the future experiments.

**Scheme 2.20** – Attempted PT-catalysed alkylation reaction using PT-catalyst 137. An O-benzylated catalyst 141 and a by-product 140 were observed in addition to the intended product 139 from the reaction mixture.

The attempted isolation of the DCC addition by-product 140 by column chromatography was unsuccessful. The addition of *in situ* generated DCCs to alkenes, obtained through PT-catalysis conditions is well known and was one of the first applications published by Makosza in the late 1960–early 1970s.[^75, 76, 77] Structurally similar addition products between DCCs and imines are also found in literature. However, the required *in situ* generation of DCCs from CHCl₃ is normally obtained at slightly elevated temperatures and not under room temperature.[^74, 75] Since the majority of PT-catalysed reactions that use CHCl₃ as the solvent are normally carried out under reduced temperatures (<0 °C) and short reaction times (<5 h), the formation of DCCs is negligible compared to product formation.

The strong signal observed from the MS analysis in our example, led us to believe that the generation and subsequent addition of DCCs to the phosphoglycine Schiff base 104 was significant. At this point during the investigation, ³¹P-NMR measurements had not been
implemented. With $^{31}$P-NMR measurements at hand, quantifying the relative amount of the reaction products would be readily available. As a consequence, the PhMe:CHCl$_3$ (30:70) solvent mixture was replaced with PhMe:CH$_2$Cl$_2$ (80:20) to avoid the *in situ* formation of DCCs. After 7 days reaction time, 55% conversion was reached (Table 2.3, Entry 3). HPLC-analysis of the purified material revealed that the product 139 was obtained as an racemate.

Assuming that the alkylation of the PT-catalyst is faster than the alkylation of the phosphoglycine Schiff base, the *in situ* generated catalyst 141 is considered the main catalytic species responsible for the racemate that was obtained (Scheme 2.20). The rate in which catalyst 137 was O-benzylated was not investigated, yet the occurrence of it impacted the decisions to which catalysts to use for the remainder of the study. As a consequence, this led us to exclusively use the O-allylated catalysts found in Scheme 2.19 to avoid having several catalysts (mono- and di-O-benzylated and free hydroxyl catalysts) operational during the PT-catalysed process. We then proceeded by testing the dimeric catalyst 138, under similar conditions. Again the conversion of starting material was slow compared to the achiral TBAC/TBAB catalyst (Table 2.3, Entry 1), but full conversion was achieved after 2 days at 0 °C (Table 2.3, Entry 4). HPLC-analysis of the mono-alkylated product 139 displayed 17% ee. The enantioselectivity was reduced to 8% ee when the reaction was carried out at room temperature (20 °C) (Table 2.3, Entry 6). Cooling the reaction mixture to -15 °C or lower slowed down the reaction to such an extent that only trace amount of product formation was observed after two days (Table 2.3, Entry 5).

We then proceeded by testing the PT-catalyst 80 developed by Corey and co-workers. The catalyst did not effectively catalyse the reaction and a low conversion to product (20%) was observed after seven days of stirring at room temperature (Table 2.3, Entry 9). It’s worth highlighting that the catalyst effectivity drops significantly after 1 day, which may indicate catalyst degradation (Table 2.3, Entry 8 and 9). Changing the base to CsOH had no obvious effect on outcome of the reaction (Table 2.3, Entry 7).

Changing the $N$-anthracenylmethyl group to a sterically less demanding $N$-(2-flurobenzyl) group improved the rate of the reaction affording approximately 30% conversion to product after one day, but the afforded product was racemic (Table 2.3, Entry 10). Cooling the reaction mixture in order to improve the enantioselectivity led to a strongly reduced rate of reaction and only a trace amount of the product was obtained.
Table 2.3 – Evaluation of chiral PT-catalysts and their performance in the alkylation reaction of phosphoglycine Schiff base 104.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp. [°C]</th>
<th>Conv. [%]a</th>
<th>% ee[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAB (20 mol%)</td>
<td>CHCl3-PhMe (30:70)</td>
<td>5h</td>
<td>20</td>
<td>&gt;95</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>137/141 (5 mol%)</td>
<td>CHCl3-PhMe (30:70)</td>
<td>5h</td>
<td>-10</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>137/141 (20 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>7 days</td>
<td>20</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>138 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>48h</td>
<td>0</td>
<td>&gt;95</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>138 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>48h</td>
<td>-15</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>138 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>48h</td>
<td>20</td>
<td>&gt;95</td>
<td>8</td>
</tr>
<tr>
<td>7†</td>
<td>80 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>24h</td>
<td>0</td>
<td>16</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>80 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>24h</td>
<td>20</td>
<td>18</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>80 (20 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>7 days</td>
<td>20</td>
<td>20</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>136 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>24h</td>
<td>20</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>136 (5 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>24h</td>
<td>0</td>
<td>Trace</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>143 (20 mol%)</td>
<td>CH2Cl2:PhMe (20:80)</td>
<td>3 days</td>
<td>20</td>
<td>&gt;95</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Measured by 1H- and 31P-NMR of the crude reaction mixtures.  [b] Measured from HPLC analysis of the purified material.  [c] CsOH used as the base.
Inspiration for a new catalyst design came during the work which is presented in Chapter 4 and where undertaken several years after the initial study. Due to the poor performance of the PT-catalysts derived from cinchonidine (71), it was decided to prepare a PT-catalyst from another natural compound, namely brucine (142). Brucine consists of tertiary bridgehead nitrogen which can be transformed into an ammonium salt by direct N-alkylation with a suitable alkyl halide.

A brucine derived PT-catalyst 143 was prepared in one step by N-alkylation with benzyl bromide (Figure 2.4). The catalyst afforded full conversion of the glycine Schiff base 104 to product 139 as evidenced from 31P-NMR analysis of the crude reaction mixture, but the product was racemic (Table 2.3, Entry 12).

As previously mentioned, the rate at which the biphasic solution is stirred can sometimes be important. To compensate for this, the stir speed used in the TBAB/TBAC catalysed reactions was used as a guideline for the asymmetric PT-catalysis experiments. Thus it seems reasonable that the low reaction rate of the alkylation reaction does not originate from an inability of the reaction mixture to generate the potassium phosphoenolate under the given conditions, but more likely by an inability of the catalysts to effectively extract the phosphoenolate into the organic phase.

In order for the PT-catalyst to extract the phosphoenolate into the organic phase, the close contact ion-pair between the catalyst and the anion needs to be sufficiently strong. This can in simplistic terms, be evaluated from the magnitude of the electrostatic force acting between the cation and anion, and the distance separating them. The latter may be affected by both the geometry of the anions by steric repulsions imposed by neighbouring groups of the catalyst. The magnitude of the individual catalyst cation in TBAB, 80, 136, 138, 141 and 143 is expected to be comparable since there is no electron withdrawing or electron donating groups in close proximity to the ammonium group. The fluorinated PT-catalyst 136 which has an electron deficient benzyl group is described by its authors to have a more electrophilic cation due to the position and electronegativity of the fluorine. Since TBAB, which is void of any electron withdrawing groups, effectively manages to catalyse the
reaction it seems unlikely that the problem can be explained on terms of insufficient ion-strength of the phosphoenolate and the PT-catalyst.

Unlike the pseudo-planar glycine Schiff bases introduced by the O’Donnel group, the phosphoenolates have a tetrahedral geometry around the phosphorous atom. Consequently, the phosphoenolates takes up more physical space than their carbon-enolate counterpart, thus getting both the phosphoenolate and the ammonium species in close proximity of each other to form the active onium specie may be more challenging. Of the catalysts prepared, the sterically congested \( N \)-anthracenylmethyl \( O \)-allyl cinchonidinium catalyst \( (80) \) did not effectively catalyse the reaction which may be attributed to the size of the anthracenylmethyl group, which may prevent the extraction of the phosphoenolate. The \( N \)-(2-flurobenzyl) \( O \)-allyl cinchonidinium catalyst \( (136) \) provided an improved yield compared to catalyst \( 80 \) but the afforded product was racemic. The enhanced reactivity of the dimeric catalyst \( 138 \) compared to catalysts \( 80 \) and \( 138 \) may be attributed to the two ammonium groups. Whether one or two ammonium groups actively participate in the formation of the ion-pair with the phosphoenolate is unknown.

At this point we chose not to continue with this part of the project due to the uncertainties associated with this chemistry.
2.15 - Summary and Conclusion

In this work, PT-catalysed C-C bond formation reactions of the achiral phosphoglycine Schiff base 104 has been investigated as to evaluate if this method is viable to prepare enantioenriched α-aminophosphonates. The effort was divided in two parts, one which included the attempted preparation of new crown ether derivatives, and one which included testing well-known ammonium type PT-catalysts. Inspiration to the design of the crown ether catalysts was taken from chiral ligands and building blocks such as the natural product quinine (10) and the Trost ligand 110 (see Section 2.12 and 2.13). However, none of the crown ethers were readily obtained even though evidence for the quinine derived crown ether 131 was obtained from MS (ESI+). As a result this strategy was abandoned and it was decided to prepare known PT-catalysts and evaluate them in alkylation reactions of the phosphoglycine Schiff base 104. It was found that PT-catalysts 80, 136, 138, 141 (prepared in situ from cat. 137), and 143, prepared from either from cinchonidine (71) or from brucine (142) were able to catalyse the formation of the product. The enantioselectivities obtained from these catalysts were in the range of 0 – 17% ee.

The conclusion that can be drawn from this work suggests that PT-catalysts prepared from cinchonidine (71), are not effective catalysts in alkylation reactions of phosphoglycine Schiff base 104. The main hypothesis is that the size and geometry of the phosphonoate enolate do not fit the active site of the catalysts. This is likely to account for the reduced reaction rate; since less of the enolate is transferred into the organic phase from the interface, and it may explain the reduced enantioselectivity of the resulting product.
2.16 - References


CHAPTER 3 – INVESTIGATION OF THE MECHANISM, SCOPE AND LIMITATIONS OF THE COUPLING AGENT-MEDIATED PHOSPHONAMIDATION REACTION

The aim of this chapter is to briefly describe our attempts to facilitate the phosphonamidation reaction between monoalkyl phosphonic acids and various amines, mediated by coupling agents popularised in the analogous amidation reactions of carboxylic acids. A significant portion of the work presented in this chapter has been published,\cite{paper1} and Paper I provides a more in-depth description of the proposed mechanism (see Paper I in the Appendix). This chapter is structured differently than the published work, furthermore the chapter includes some additional results that did not make it into Paper I (see Section 3.4 to 3.7). The changes to the layout of this chapter compared to the article were undertaken with the intention to more clearly demonstrate the impact each change to the reaction conditions had to the outcome of the reactions.

3.1 - History and Recent Development of Phosphonamidation Reactions

Reactions in which phosphonamidates are formed have received limited attention within the organic chemistry community, and their methods of preparation are by and large still reliant upon aminolysis of chlorinated intermediates. These intermediates can in turn be obtained through numerous routes.\cite{route1, route2, route3, route4, route5, route6, route7, route8, route9, route10} Aminolysis of activated phosphonates, obtained through the use of coupling agents are also reported,\cite{route11, route12, route13, route14, route15} but they occur less frequently than the aforementioned strategies. The limited number of methods by which phosphonamidates can be generated may partially be explained by a natural preference towards preparation of carboxamidates, which are essential in our lives and in numerous medicinal compounds.\cite{medicinal} Through decades of research and development, new coupling agents and methods have been developed that combine efficient coupling of amines and carboxylic acids with a low degree of racemisation/epimerisation of neighbouring stereogenic centres. Robert Merrifield’s genius introduction of solid-phase peptide synthesis (SPPS) advanced the field even further,\cite{merrifield} allowing large peptides to be prepared relatively effortlessly by simplifying the purification of the targeted peptides. This strive to improve and expand upon the number of existing methods does not appear to have been transferred into improving the amidation reactions of phosphonic acids. A survey of the relevant literature indicated that most methods that weren’t obtained through aminolysis of phosphonochloridates employed coupling agents such as DIC, DCC, BOP and PyBOP (Figure 3.1).\cite{route11, route12, route13, route14, route15}

For the benefit of the reader, an overview of the coupling agents relevant for this thesis are summarised in Figure 3.1 and Table 3.1. They include information regarding their chemical
structure in addition to the reactive intermediates and activated esters they generate with carboxylic acids. These coupling agents include those derived from 1-hydroxybenzotriazole (HOBt) (144), PyBOP (145) and HBTU (147); recently developed coupling agents derived from Oxyma (148), PyOxim (149) and COMU (150); carbodiimides, DCC (151) and DIC (152); and lastly, the triazine-based coupling agent DMTMM 153 (Figure 3.1).

![Phosphonium and Guanidinium Salts of 1-Hydroxybenzotriazole (HOBt)](image)

![Phosphonium and Uronium Salts of Oxyma](image)

![Carbodiimides](image)

![Triazine-Type Coupling Agent](image)

**Figure 3.1** – An overview of coupling agents and additives used in this study.

The coupling agents depicted in Figure 3.1 activate carboxylic acids via different mechanisms which depend on the identity of the activating group (red) and of the leaving group (black) (Table 3.1.) The proposed intermediate structures and the activated esters that are obtained during an amidation of carboxylic acids are summarised in Table 3.1. Reaction pathways leading to racemisation or that would otherwise complicate the reaction have been omitted. One complication that the reader may familiarise themselves with is the notion that the anhydrides may form when activated esters react with carboxylates (Table 3.1, Entry 9). This reaction pathway appears to be more important for phosphonic acids rather than carboxylic acids as will become more evident in Section 3.3.


Table 3.1 – An overview of key intermediates and activated esters of carboxylic acids obtained through the use of the coupling agents depicted in Figure 3.1. The activating group of the coupling agents is coloured red while the leaving group is black.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Coupling reagents</th>
<th>Intermediate structures</th>
<th>Activated esters applicable for aminolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBTU</td>
<td><img src="image1" alt="Intermediates" /></td>
<td><img src="image2" alt="Activated esters" /></td>
</tr>
<tr>
<td>2</td>
<td>Phosphonium</td>
<td><img src="image3" alt="Intermediates" /></td>
<td><img src="image4" alt="Activated esters" /></td>
</tr>
<tr>
<td>3</td>
<td>COMU</td>
<td><img src="image5" alt="Intermediates" /></td>
<td><img src="image6" alt="Activated esters" /></td>
</tr>
<tr>
<td>4</td>
<td>PyOxim</td>
<td><img src="image7" alt="Intermediates" /></td>
<td><img src="image8" alt="Activated esters" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Reagents" /></td>
<td><img src="image10" alt="Intermediates" /></td>
<td><img src="image11" alt="Activated esters" /></td>
</tr>
<tr>
<td>6</td>
<td>R = cyclohexyl (DCC) R = isopropyl (DIC)</td>
<td><img src="image12" alt="Intermediate" /></td>
<td><img src="image13" alt="Activated esters" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image14" alt="Reagents" /></td>
<td><img src="image15" alt="Intermediate" /></td>
<td><img src="image16" alt="Activated esters" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="image17" alt="Reagents" /></td>
<td><img src="image18" alt="Intermediate" /></td>
<td><img src="image19" alt="Activated esters" /></td>
</tr>
<tr>
<td>9</td>
<td>Lg = Oxyma (From COMU, PyOxim) Lg = hydroxybenzotriazole (From PyBOP, HBTU) Lg = O-acylsoura (From DIC, DCC)</td>
<td><img src="image20" alt="Intermediate" /></td>
<td><img src="image21" alt="Activated esters" /></td>
</tr>
</tbody>
</table>

---

Lg = Oxyma (From COMU, PyOxim) Lg = hydroxybenzotriazole (From PyBOP, HBTU) Lg = O-acylsoura (From DIC, DCC)
To the best of our knowledge, the first phosphoamidation procedure was established already in 1957 by Burger and Anderson.\cite{15} Their effort helped elucidate an important mechanistic feature of the reaction that appears to have been overlooked by the majority of the synthetic organic community, us included, for a long period of time. The authors discovered that a preactivation period without the amine coupling partner was necessary when using DCC in order to obtain the phosphonamidate product instead of guanidinium compounds 155 (Scheme 3.2). These compounds were generated from an unwanted reaction between the amines and the DCC coupling agent.

Scheme 3.1 – The first coupling agent-mediated phosphonamidation using DCC. A preactivation was necessary to avoid guanidinium compounds 155.

This important mechanistic feature has been overlooked by the synthetic chemistry community and can probably explain why other groups struggled in their attempted coupling agent mediated phosphonamidation reactions.\cite{14, 18} Several years later, Dumy and co-workers employed BOP and PyBOP coupling agents in order to prepare short dipeptides between the α-aminophosphonic acid 158 and protected aminocarboxylic acids 160 - 162.\cite{13}

Scheme 3.2 – Phosphonamidation reaction mediated by BOP or PyBOP coupling agent.
Unlike Burger and Anderson, Dumy and co-workers achieved excellent conversion to product without the implementation of a preactivation period (Scheme 3.2). $^{31}$P-NMR of a crude reaction mixture, recorded four hours into the reaction, displayed reactive phosphonates that were evaluated to be the HOBt-phosphonate and pyrophosphonates along with unconsumed coupling agent and phosphonic acid. This indicated that both BOP and PyBOP do not suffer from the unwanted reaction pathway between the coupling agent and the amine seen in previous phosphoamidation attempts.$^{[14, 15, 18]}$

Coste and co-workers adapted this methodology in a mixed phosphonate synthesis and included one example in which an phosphonamidation reaction was successfully achieved.$^{[12]}$ Interestingly, they conducted competition experiments that demonstrated that amines are significantly less reactive towards the activated phosphonates than alcohols, which is the opposite of what is observed in for activated carboxylate esters.

As recent as in 2009, Ishibashi and Kitamura developed a SPPS-methodology to afford oligomers of $\alpha$-aminophosphonates using DIC as the coupling agent together with HOAt $^{[165]}$ as the additive (Scheme 3.3).$^{[11]}$ Their procedure also included a preactivation strategy, but this detail was not emphasised in the article, nor was the Burger/Anderson paper mentioned.

Scheme 3.3 – Phosphonamidation developed using an SPPS-methodology.
3.2 - RESULTS AND DISCUSSION

During the early stages of this project, different coupling agents were screened in order to evaluate their ability to generate phosphonamidates from amines and monoesters of phosphonic acids. The initial screening was performed following procedures that are typically used in analogous carboxamidation reactions, in which the coupling agent is added last to a solution containing the remaining reagents and additives (Table 3.2). Monoethyl benzylphosphonic acid (171) was chosen for the screening to suppress any potential complications that could occur from a protected α-aminophosphonate derivatives.

Scheme 3.4 – Preparation of monoethyl benzylphosphonic acid (171).

This decision was made to check if the results obtained by the groups led by Imoto and Martell were dependent on the substrate or the coupling agent.[14, 18] The monoethyl benzylphosphonic acid (171) was obtained in two chromatography-free steps starting from commercially available starting materials and following known literature procedures (Scheme 3.4).[19] The results from the initial screening of coupling agents depicted in Figure 3.1 is summarised in Table 3.2.

As shown in Table 3.2, only PyBOP afforded the product with acceptable efficiency when procedures originally developed for amidation of carboxylic acids were used. Interestingly, HBTU, where the hydroxybenzotriazole is activated as a guanidinium N-oxide salt rather than a phosphonium salt, inflicted a drastic negative change to the outcome of the reaction (from >95 to 0% yield as seen in Table 3.2, Entry 5 and 6). Following the same line of thought, it was anticipated that if COMU was replaced with PyOxim; which is activated by the same group as PyBOP, that a positive result could be achieved (Table 3.2, Entry 7 and 8). This line of thought however did not provide the right solution, since PyOxim were largely unable to mediate the phosphonamidation reaction. The attempted phosphonamidations using carbodiimide-type coupling agents were unsuccessful which was explained by Burger and Anderson in 1957.[15] The same negative result was observed using the triazine-type coupling agent DMTMM (153).
Table 3.2. Screening of available coupling agents in the phosphonamidation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Coupling agent (1.15 eq.)</th>
<th>Additive (0.5 eq.)</th>
<th>Conversion [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCC</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DIC</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>DCC</td>
<td>HOBt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Triazine</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>5[b]</td>
<td>PyBOP</td>
<td>-</td>
<td>&gt;95</td>
</tr>
<tr>
<td>6</td>
<td>HBTU</td>
<td>HOBt</td>
<td>0</td>
</tr>
<tr>
<td>7[b]</td>
<td>COMU</td>
<td>-</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>PyOxim</td>
<td>-</td>
<td>Trace</td>
</tr>
</tbody>
</table>

[a] Conversion was measured by $^{31}$P-NMR analysis of the crude reaction mixtures. [b] Similar results were obtained when cyclohexylamine was replaced with benzylamine.

The first clue that helped explain why PyBOP outperformed the other coupling agents was obtained during the work-up of the reaction mixture resulting from the COMU mediated phosphonamidation reaction. From several EtOAc-extractions of the combined aqueous phase, obtained from the work-up, a relatively pure sample of a reaction product was obtained. Analysis by NMR spectroscopy and MS suggested that the structure was likely to be the guanidinium salt 173. A logical assumption is that this compound is the product of the amine reacting with the coupling agent. This observation is similar to that made by Burger and Andersons in 1957 (see Scheme 3.1).[15] A similar guanidinium salt 174 was detected when cyclohexylamine was replaced with benzylamine (Figure 3.2).
Figure 3.2 – The guanidinium salts 173 and 174 that were detected from the initial phosphonamidation reactions using COMU as the coupling agent.

We suspect that a similar reaction pathway between the amine and the coupling agent could explain why the majority of the coupling agents depicted in Figure 3.1 were unable to afford the product in an acceptable yield. This indicated that the choice and combination of both the activator group (carbodiimide, phosphonium, triazine-ammonium, guanidinium N-oxide, or uronium) and the leaving group (O-acylurea, 4-hydroxybenzotriazole, DMT or Oxyma) of the coupling agent are important in order to achieve successful phosphonamidation reactions. This appears to be especially important when following standardised procedures popularised in traditional peptide chemistry. The optimal combination of the activator- and leaving group is not easily rationalised from the results summarised in Table 3.2 and would serve as a valuable objective in future studies.
3.3 - Improved Reaction Conditions by the Introduction of a Preactivation Period

In an attempt to suppress the irreversible side reaction between the amine and the coupling agent, a preactivation period without the amine was introduced. Incorporating a preactivation period to the procedures provided a significant improvement to the phosphonamidation reactions, especially those mediated by coupling agents that initially suffered from trace conversion to product (Table 3.3). The crude reaction mixtures originating from the preactivation periods in Table 3.3 were analysed by $^{31}$P-NMR before the aminolysis step. This allowed us to determine the number of activated phosphonate species responsible for the observed reactivity and the ratio between them (Figure 3.2).

![Activated phosphonate species observed by $^{31}$P-NMR after the preactivation period.](image)

**Figure 3.2 -** Activated phosphonate species observed by $^{31}$P-NMR after the preactivation period.

**Table 3.3 -** Improved phosphoamidation reactions by the introduction of a preactivation period.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Coupling agent (CA)</th>
<th>Eq. CA</th>
<th>Activated Phosphonates</th>
<th>Conversion [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PyBOP</td>
<td>1.1</td>
<td>$^{176}$a-b and $^{175}$ (50:50)[b]</td>
<td>$&gt;95$</td>
</tr>
<tr>
<td>2</td>
<td>COMU</td>
<td>1.5</td>
<td>$^{176}$a-b and $^{177}$ (50:50)[b]</td>
<td>69</td>
</tr>
<tr>
<td>3[b]</td>
<td>PyOxim</td>
<td>1.5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>DIC</td>
<td>1.5</td>
<td>$^{176}$a-b</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>DCC</td>
<td>1.5</td>
<td>$^{176}$a-b</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>HBTU</td>
<td>2</td>
<td>$^{176}$a-b</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>DMTMM[c]</td>
<td>1.5</td>
<td>$^{176}$a-b</td>
<td>25</td>
</tr>
</tbody>
</table>

[a] Conversion was measured by $^{31}$P-NMR analysis of the crude reaction mixtures. [b] PyOxim was not evaluated but future studies with slightly different reaction conditions have shown the presence of both pyrophosphonates and the Oxyma-phosphonate in the preactivation reaction mixture. [c] A 24 hour preactivation was necessary to obtain full conversion to the pyrophosphonates.
It was considered necessary to elucidate the structures of the activated phosphonates 175 - 177, and to be able to synthesise them separately in order to investigate the reaction systematically. The structures of the activated phosphonates were confirmed by comparison of their spectral data to that of the individually synthesised materials (Figure 3.3). The phosphonochloridate 178 was used to prepare the activated phosphonates, which is explained in more detail in the published material.\(^1\) The only exception was the OBt-phosphonate 175 which we were unable to obtain in high yield and in sufficient purity for a full structure elucidation. The \(^{31}\text{P}-\text{NMR}\) spectrum of the crude reaction mixture of the attempted synthesis of 175 did match that of the expected OBt-phosphonate obtained from the preactivation. This effort allowed us to prove the existence of pyrophosphonates 176a-b, and the activated phosphonates 175 and 177 in the reaction.

Information regarding the \(^{31}\text{P}-\text{NMR}\) shifts and shift areas of specific phosphorous-containing compounds such activated phosphonates, reagents, by-products and eventually phosphonamidates were a helpful tool during this study. Evaluation of the reaction mixtures could then be undertaken based of the \(^{31}\text{P}-\text{NMR}\) analysis. This technique has been utilised to obtain details of the reactions including; conversion of specific compounds, purity of isolated material, measuring the stability of reaction products and to monitor reactions.

\textbf{Figure 3.3} – An overview of the specific shift values and shift areas of the observed activated phosphonates, reagents and products encountered in the study.

The investigation of the preactivation period demonstrated that pyrophosphonates 176a-b either occurred exclusively (Table 3.3, Entry 4, 5, 6 and 7) or in a substantial amount compared to the other activated-phosphonates 175 or 177 (Table 3.3, Entry 1 and 2).
to contradicting reports regarding the reactivity between pyrophosphonates and amines,[6] aminolysis of the individually synthesised pyrophosphonates 176a-b was attempted. This demonstrated that the pyrophosphonates investigated in our study could readily undergo aminolysis under similar reaction conditions used in the phosphonamidation experiments. During the aminolysis of pyrophosphonates 176a-b, the product 172 and the anion of the phosphonic acid 171 was obtained in near equal quantities.[1] This is a concern since the amine reacts faster with the coupling agent than the anion of the starting material 171. As a result, the remaining coupling agent reacts to form guanidinium salts while the remaining anion of the starting material 171 is unable to reactivate which is necessary in order to form the product. Thus, to ensure a high conversion of the starting material to product, the concentration of the pyrophosphonate should to be low prior to the addition of the amine. It was thought that this could be achieved by changing the addition order of the reagents, adding an appropriate additive and/or by adjusting the rate in which the reagents were added.[1] These changes were tested systematically for the coupling agents, and the results are provided in Table 3.4.

For COMU and PyOxim, the best results of the phosphoamidation reactions were obtained using a preactivation step consisting of a slow addition of the phosphonic acid 171 and Et3N to a stirred solution of the coupling agent with additional Oxyma (148) (Method B, Table 3.4, Entry 2 and 4). This was not observed for HBTU with additional HOBt (144) as additive. It is likely that the crystal lattice water from the HOBt caused hydrolysis of the activated phosphonates that was generated during the preactivation period. The slower preactivation procedure provided no significant improvement over the regular preactivation when using DIC (Table 3.4, Entry 6 and 8). Method B was not applied when using DCC as the coupling agent. The triazine-type coupling agent DMTMM 153 was not an ideal reagent choice when employing the time-consuming preactivation procedure since it reacted slowly with the phosphonic acid and generated exclusively the pyrophosphonates 176a-b.
Table 3.4 – The variation in the conversion to product in the phosphonamidation reactions depending on which preactivation method and coupling agent that were used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Coupling agent (CA)</th>
<th>Eq. CA</th>
<th>Method</th>
<th>Additive</th>
<th>Eq. additive</th>
<th>Conversion [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COMU</td>
<td>1.5</td>
<td>A[b]</td>
<td>Oxyma</td>
<td>0.5</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>COMU</td>
<td>1.5</td>
<td>B[c]</td>
<td>Oxyma</td>
<td>0.5</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>COMU</td>
<td>1.5</td>
<td>B[c]</td>
<td>-</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>PyOxim</td>
<td>1.5</td>
<td>B[c]</td>
<td>Oxyma</td>
<td>0.5</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>PyOxim</td>
<td>1.5</td>
<td>B[c]</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>DIC</td>
<td>1.5</td>
<td>A[b]</td>
<td>Oxyma</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>DCC</td>
<td>1.5</td>
<td>A[b]</td>
<td>Oxyma</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>DIC</td>
<td>1.5</td>
<td>B[c]</td>
<td>Oxyma</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>HBTU</td>
<td>2</td>
<td>B[c]</td>
<td>HOBt</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10[d]</td>
<td>DMTMM</td>
<td>1.5</td>
<td>B[c]</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
</tbody>
</table>

[a] Conversion was measured by 31P-NMR analysis of the crude reaction mixtures.  
[b] Preactivation method A; Coupling agent, additive, phosphonic acid 171 and Et3N (2.15 eq.) were mixed for 2 hours before the amine is added.  
[c] Preactivation method B; dropwise addition of the phosphonic acid 171 and Et3N (2.15 eq.) into a CH2Cl2 solution of the coupling agent and additive. After approximately 5.5 h the amine is added dropwise over 2 h.  
[d] A 24h preactivation was need in order to get a sufficient conversion to the pyrophosphonates.
3.4 - Scope of the COMU-Mediated Phosphonamidation Reaction

The scope of the COMU mediated phosphonamidation reaction was investigated by evaluating several primary and secondary amines (Table 3.5). Primary amines, with the exception of allylamine (Table 3.5, Entry 7) and glycine methyl ester·HCl (Table 3.5, Entry 8), were transformed into the corresponding phosphonamidates with high conversions (85 – 91%). The reduced conversion found for the secondary amines in the COMU mediated phosphonamidation was found to occur during the aminolysis step of the Oxyma-phosphonate 177. This conclusion was reached after a control experiment in which pure Oxyma-phosphonate 177 underwent aminolysis with morpholine (43% yield) under similar conditions to what was used in the phosphonamidation experiments. A similar aminolysis of the Oxyma-phosphonate was undertaken with benzylamine (75% yield) in which the product was afforded in a higher yield compared to morpholine. These experiments demonstrated how the outcome of the aminolysis step of Oxyma-phosphonates can be significantly affected depending on the choice of amine.

Phosphonamidations were also attempted on the monomethyl- and monoisopropyl benzylphosphonic acids 180 and 181 (Table 3.5, Entries 1, 2, 12 and 13). Neither the monomethyl- nor the monoisopropyl benzylphosphonic acids 180 and 181 were suitable substrates in the COMU mediated phosphonamidation reaction (Figure 3.4).

![Figure 3.4](image)

Figure 3.4 – The monomethyl- and monoisopropyl benzylphosphonic acid 180 and 181 were not suitable acids in the COMU mediated phosphonamidation reaction.

The preparation of monoisopropyl benzylphosphonic acid from was only achieved through the hydrolysis of the monoisopropyl benzylphosphonochloridate 182. This substrate can undergo aminolysis directly, which renders any phosphonamidation attempt through coupling agent mediated protocols redundant, unless a stereoselective approach is wanted (see Chapter 4). The monomethyl benzylphosphonic acid 180 was not a suitable substrate, since the starting material or the activated phosphonates decomposed during the preactivation period. Signals corresponding to breakdown products were subsequently observed by 31P-NMR analysis of the preactivation mixture.
Table 3.5 - A comparison of the conversion obtained when varying the method and reagents used in the phosphonamidation reaction

![Chemical structure diagram]

Table:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>R</th>
<th>Amine</th>
<th>Prod.</th>
<th>Conversion [%][b]</th>
<th>Yield [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A[a]</td>
<td>i-Pr</td>
<td></td>
<td>183</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>A[a]</td>
<td>i-Pr</td>
<td></td>
<td>184</td>
<td>85</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>A[a]</td>
<td>Et</td>
<td>172</td>
<td></td>
<td>89</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>185</td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>186</td>
<td>91</td>
<td>49</td>
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<td>7</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>188</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>A[a][d]</td>
<td>Et</td>
<td></td>
<td>189</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>190</td>
<td>65</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>191</td>
<td>53</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>A[a]</td>
<td>Et</td>
<td></td>
<td>192</td>
<td>48</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>A[a]</td>
<td>Me</td>
<td></td>
<td>193</td>
<td>50</td>
<td>15</td>
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<tr>
<td>13</td>
<td>A[a]</td>
<td>Me</td>
<td></td>
<td>194</td>
<td>54</td>
<td>18</td>
</tr>
</tbody>
</table>

[a] Preactivation protocol; dropwise addition of the phosphonic acid and Et₃N (2.15 eq.) into a CH₂Cl₂ solution of COMU (1.5 eq.) and Oxyma (0.5 eq.). After approximately 5.5 h the amine (2 eq.) is added dropwise over 2 h. [b] The conversion was measured by ³¹P-NMR. [d] Yields are measured after column chromatography and Kügelrohr distillation. [e] 3.15 eq. of Et₃N was used.
3.5 - Byproduct Formation, Isolation and Structure Elucidation

From the crude reaction mixtures following the phosphonamidation reactions of the monoethyl benzylphosphonic acid 171, two minor by-products were consistently observed by $^{31}$P-NMR measurements (Figure 3.4). The by-products were observed after the aminolysis step and appeared at approximately 36.2 and 25.6 ppm, and were obtained on average in 1-4% conversion.

Figure 3.4 – A representative $^{31}$P-NMR spectra of the crude reaction mixtures obtained after the COMU mediated phosphonamidation reaction between benzylamine and monoethyl benzylphosphonic acid 171.

The first by-product at 25.6 ppm were isolated and identified as the diethyl benzylphosphonate 170 from comparison of spectral data of previously synthesised material. The lack of formation of this product from the PyBOP mediated reaction, suggested that the EtOH needed for the reaction, originated from COMU and/or Oxyma, and not from impurities found in the reaction solvent, base or amine. Thus, we propose that the diethyl benzylphosphonate 170 is formed from alcoholysis of the activated phosphonates 176a-b and 177 by ethanol that has been displaced from the ethyl ester of Oxyma/COMU (Scheme 3.5). The stability of Oxyma has been evaluated by the inventors in their seminal paper which introduced Oxyma as an additive in amidation reactions.[20] Ethoxide displacement of the ester group of Oxyma by the amine coupling partner was described, and could explain the origin of the ethanol.

Peaks with similar shift values in $^{31}$P-NMR were also found for the monomethyl- and monoisopropyl benzylphosphonic acids, but these by-products were not isolated and structure elucidated. Following a similar line of thought it is expected that these products correspond to mixed phosphonates formed via a similar process to that proposed in Scheme 3.5. By extension we propose that the degradation of Oxyma is independent of the identity of the phosphonic acid. Previous reports undertaken with PyBOP have shown that
alcoholysis is faster than aminolysis of activated phosphonates,\textsuperscript{[12]} thus it is expected that the ethanol produced \textit{in situ} is consumed rapidly into phosphonates.

Scheme 3.5 – The proposed degradation of Oxyma which explains the phosphonate generation observed in the COMU mediated phosphonamidation.

Clues regarding the second by-product were obtained during the phosphonamidation reaction with diethylamine. Mixed fractions containing the product and the by-product following the column chromatography were separated by means of Kügelrohr distillation, which allowed 7 mg of relatively pure by-product to be obtained. Analysis of the isolated compound by NMR spectroscopy and MS provided us with the following proposed structure elucidation (Compound 195, Scheme 3.6).

Scheme 3.6 – Proposed structure of the by-product obtained from phosphonamidation of phosphonic acid 171 with diethylamine.

The proposed structure of the by-product resembles an iminophosphorane which is an important reactive intermediate in Staudinger reactions.\textsuperscript{[21, 22]} Staudinger reactions involves reactions between organic azides and and trivalent phosphorous species (phosphines, phosphites and phosphorous triamides),\textsuperscript{[23, 24, 25]} however, iminophosphoranes with the following substitution pattern around the phosphorous atom have not been prepared previously. The mechanism leading to the proposed structure has not been investigated in
any detail but a possibility could be that the by-product is formed from a reaction of the target product with a degradation product of Oxyma (Scheme 3.6). The exact reactive species required to form the by-product are not known but the idealised ions (*synthons*) responsible for our suggestion are depicted in Scheme 3.6. The degradation of Oxyma was not investigated further, but similar reactions where oxims rearrange into amides are known as the Beckmann rearrangement.[26, 27]
3.6 - Attempted Synthesis of Short Peptides of Aminophosphonates

Having established a method to prepare phosphonamidates mediated by coupling agents we could return to one of the original goals of this project, namely the synthesis of peptides containing aminophosphonic acids exclusively. The following section covers our brief attempt to prepare dipeptides between α-aminophosphonates and appropriately protected α-aminophosphonic acids. The following part was undertaken in co-operation with Hui-Chung Wen, during her Erasmus studies as part of a Bachelor’s project.

3.7 - Preparation of Starting Materials

To initiate the project, two different α-aminophosphonates 197 and 199 were prepared; which in turn could be used to access two N-Boc-protected monoethyl α-aminophosphonic acids 198 and 200 (Figure 3.5). These starting materials were used to target four different dipeptides 201 - 204.

![Chemical structures](image)

**Figure 3.5** - From the four building blocks 197 - 200, the four dipeptides 201 - 204 were targeted.

The α-aminophosphonate 199 could be obtained in two steps from the Kabachnik-Fields reaction between acetone, benzylamine and diethylphosphite followed by hydrogenation of the N-benzyl α-aminophosphonate 205 over Pd/C (Scheme 3.7). The α-aminophosphonate 197 had to be prepared in one extra step compared to 199 due to the greater electrophilicity of formaldehyde compared to acetone which effected the Kabachnik-Fields reaction (Scheme 3.7). This required the imine to be generated by a slow dropwise addition of the formaldehyde to an ice-cooled solution of benzylamine in toluene. The imine was used immediately in the next step which involved a nucleophilic attack by diethylphosphite in toluene to afford the N-benzyl α-aminophosphonate 208. Both of the N-benzylated α-aminophosphonates 205 and 208 were readily converted to their respective α-aminophosphonates 197 and 199 after hydrogenation over Pd/C. Boc-protection of both...
α-aminophosphonates was achieved with Boc-anhydride in H₂O:acetone (95:5) which afforded the products 206 and 209 in decent yields (60 - 65%).[28] The excess Boc anhydride was removed by treating the crude reaction mixture with imidazole and a catalytic amount of DMAP followed by an aqueous acidic work-up.[29] This provided a chromatography free route to the N-Boc-protected α-aminophosphonates 206 and 209.

Scheme 3.7 – The chromatography free synthesis of the α-aminophosphonates 197 and 199 and N-Boc-protected α-aminophosphonic acids 198 and 200.

To obtain the N-Boc-protected α-aminophosphonic acids 198 and 200, a mono-dealkylation reaction of the appropriate phosphonate was undertaken in acetonitrile using NaI to afford
the sodium salt of the phosphonic acid. The product was isolated as the free acid by extracting the acidified aqueous phase by CHCl₃ during the work-up.

Unlike acidic hydrolysis of phosphonates, neutral and basic hydrolysis affords the mono-dealkylation as the major product. The build-up of negative charge in near proximity of the second phosphonate ester is thought to prevent the second dealkylation step by repulsion of the negatively charged base or nucleophile. With the procedures depicted in Scheme 3.7, the building blocks required to prepare the dipeptides 201 - 204 were available. No hydrolysis of the phosphonate group was detected with LiOH in THF:H₂O (2:1). Mono-dealkylation of the phosphonate group was observed with LiBr in acetonitrile however, the LiBr promoted a N-Boc-deprotection simultaneously. LiBr has been shown to promote a mono-deprotection of N,N'-diBoc-protected amines into N-Boc-amines.[30] The authors suggested that a chelation between the lithium cation and the two Boc-carbonyls promote the decarboxylation by weakening the t-BuC-O bond (Scheme 3.8). Following the same line of thought, a possible explanation for the observed Boc-deprotection could be that the phosphonate group and the Boc-carbonyl assist the chelation with the lithium ion, thus promoting the Boc-deprotection (Scheme 3.8).

Scheme 3.8 - Proposed mechanism for the LiBr promoted Boc-deprotection of the α-aminophosphonate 206.
3.8 - Attempted Phosphonamidation of \(\alpha\)-Aminophosphonic Acids

The \(N\)-Boc-protected \(\alpha\)-aminophosphonic acids 197 - 200 were initially tested in a phosphonamidation reaction with benzylamine in order to evaluate which coupling agent to use. As in the previous studies (see Table 3.3), PyBOP did not require any lengthy preactivation period or special considerations to afford the product in near-quantitative conversion. The phosphonamidation reaction was also attempted using COMU with added Oxyma employing the methods described in earlier sections. \(^{31}\text{P-NMR}\) of the crude reaction mixtures revealed that the use of PyBOP resulted in full conversion to product, while COMU with added Oxyma afforded the product in 65% conversion. Consequently, PyBOP was considered the most practical coupling agent when targeting the dipeptides, even though the Kitamura/Ishibashi paper discourages the use of PyBOP since was unable to generate their product (see their supporting information\(^{[11]}\)).

For all of the attempted phosphonamidation reactions with the starting materials found in Figure 3.5, we were unable to isolate and verify the existence of the targeted dipeptides based on structure elucidation of purified material. The reason being that the products, especially those synthesised from phosphonic acid 198, appeared to undergo rapid degradation during aqueous work-up and column chromatography (Scheme 3.9). This conclusion was reached after observing several new peaks in \(^{31}\text{P-NMR}\) and a reduction of the peak believed to be the product. Evidence supporting the existence of compound 202 and 204 was obtained by MS (ESI\(^{+}\)) measurements of the crude reaction mixture before the attempted purification. Changing the coupling agent to COMU or DIC together with Oxyma did not improve the preparation of the dipeptides by simplifying the isolation of the products.

**Scheme 3.9** - Attempted synthesis of dipeptides of sufficiently protected \(\alpha\)-aminophosphorous analogues.
Scheme 3.10 - Attempted synthesis of dipeptides between sufficiently protected α-aminophosphorous analogues.

It was decided to synthesise the phosphonamidates using exclusively the more stable phosphonic acid 200 in order to familiarise ourselves with this class of compounds. Four amines were tested in the phosphonamidation reaction. The compounds were structure elucidated after purification by column chromatography. Common for all of the synthesised phosphonamidates in Table 3.6 was that full conversion to product was observed but the challenging purification eroded most the isolated yield of the purified products (Table 3.6). Due to time limitations, additional attempts to prepare and isolate the dipeptides 201 - 204 were not undertaken.
Table 3.6 – PyBOP mediated phosphoamidation of α-aminophosphonic acid 200 with various amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conversion [%][a]</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Amine 1" /></td>
<td>&gt;95</td>
<td>211</td>
<td>Not measured</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Amine 2" /></td>
<td>&gt;95</td>
<td>212</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Amine 3" /></td>
<td>&gt;95</td>
<td>213</td>
<td>23</td>
</tr>
<tr>
<td>4[b]</td>
<td><img src="image4" alt="Amine 4" /></td>
<td>&gt;95</td>
<td>214</td>
<td>18</td>
</tr>
</tbody>
</table>

[a] Conversion was measured by $^{31}$P-NMR analysis of the crude reaction mixtures. [b] 3.5 eq. of Et$_3$N was used.

Method used: PyBOP was added to a mixture of the phosphonic acid 200, Et$_3$N (2 eq.) amine (2.5 eq.) and CH$_2$Cl$_2$. 

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3.9 - Summary and Conclusion

In this work, several coupling agents (see Figure 3.1) were evaluated in the phosphonamidation reaction between monoesters of phosphonic acids and amines. The reactions were first attempted using standard reaction conditions that are typically used for carboxylic acids. This resulted in poor performances for all coupling agents, except PyBOP (see Table 3.2). It was found that the original reaction conditions promoted an irreversible side-reaction between the amine and the coupling agent, with the formation of guanidinium salts. The solution to this problem was to introduce a preactivation period without the coupling amine in order to obtain activated phosphonates (see Table 3.3). This led us to investigate the reactive species responsible for the product formation and how they affected the outcome of the reaction. This was achieved by individually synthesising and characterising the activated phosphonates and eventually evaluating their reactivity using similar reaction conditions to what was used in the amidation experiments. This insight led to further improvements to the reaction conditions, which provided a further increase in the conversion to product (see Table 3.4). Several amines were screened in the phosphonamidation reaction using COMU as a step to evaluate the robustness of the new methods. Primary amines gave good conversions to product while secondary amines performed poorly, affording significantly reduced conversions. The reduced conversion was found to occur during the aminolysis step via an unknown reaction pathway that was not investigated further.

Other by-products obtained from the COMU mediated phosphonamidation reaction were purified and their structure was attempted to be elucidated. Among these by-products was the diethyl benzylphosphonate 170, which is likely to have been formed from alcoholysis of the activated phosphonates by ethanol released after the hydrolysis of the ethylester of Oxyma. The other by-product is most likely an iminophosphorane, 195. The mechanism explaining its formation is unknown, but it is likely to originate from the targeted product and a degradation product of Oxyma (see Chapter 3.5).

In an attempt to cover one of the original aims of the study, an attempted solution-phase synthesis of dipeptides of aminophosphonic acids were initiated. The intrinsic instability of the dipeptides 201 - 204 led to a difficult isolation of the products. As a result none of the targeted dipeptides were isolated and consequently structure elucidated.

To conclude, the work has indicated that a majority of coupling agents are not effective in the phosphonamidation reaction without necessary precautions such as a preactivation period. A possible solution could be to develop new coupling agents that are specifically developed towards amidation of phosphonic acids or otherwise prevent the pyrophosphonate formation and/or side-reaction between the amine and coupling agent. A strategy or the latter is covered in Chapter 5.
3.10 - References


CHAPTER 4 – SYNTHESIS AND EVALUATION OF CHIRAL COUPLING AGENTS IN ENANTIOSELECTIVE PHOSPHONAMIDATION REACTIONS

4.1 - Stereoselective Preparation Methods of Phosphonamidates

During the investigation of the phosphonamidation reaction it became evident that few of the existing methods are able to exercise control over the stereochemistry of the phosphonamidate functional group. Unlike the carboxamide functionality, which is pseudo-planar and achiral; the phosphonamidate functional group is tetrahedral and contain a stereogenic centre (Figure 4.1).

![Figure 4.1](comparison.png)

Figure 4.1 – A comparison between carboxamides and phosphonamidates.

At the time of writing this thesis, few papers were available detailing stereoselective approaches used to obtain chiral phosphorous compounds with controllable stereochemistry of the phosphorous atom, such as phosphinamides, phosphinoxides and other functional groups. These methods focused primarily on the use of the chiral phosphinates 215 and 216 (Figure 4.2), which serve as chemically modifiable, chiral building blocks.

![Figure 4.2](building_blocks.png)

Figure 4.2 – Chiral phosphinates 215 and 216 used to prepare P-stereogenic compounds.

The enatiopure phosphinate 215 was obtained by purification using a chiral semi-preparative HPLC column, while compound 216 was obtained through repeated recrystallization of the diastereomeric mixture originating from its preparation. Both phosphinates were used to generate phosphonamidates through the Atherton-Todd reaction (Scheme 4.1).
Scheme 4.1 – An overview of the Atherton-Todd reaction, including the reactive intermediates.

In context of preparing enantioenriched phosphonamidates by the Atherton-Todd reaction, the lack of a general preparation method of the enantioenriched phosphinates currently restricts a broad application of this method. As such, employing post-modifications to the phosphonamidates obtained from the Atherton-Todd reaction by modifying the O-alkyl and/or the alkyl group may be challenging (R₁ and R₂ in Scheme 4.1). With this in mind, we were curious to investigate a different strategy which involves the use of an enantioselective phosphonamidation reaction by the utilisation of chiral coupling agents. If successful, this bottom-up strategy would allow chiral phosphonamidates to be constructed with complete control of the different substituents of the phosphonamidate functional group (R₁ – R₃ in Figure 4.1, R₁ – R₄ in Scheme 4.1). However, a common limitation in the currently employed phosphonamidation methods is that they were never designed to distinguish between enantiomers. As such, the commercially available coupling agents that are used today are achiral and designed to solve problems experienced in traditional peptide chemistry. These problems normally include decreasing racemisation/epimerisation rates of neighbouring stereogenic centres and to increase the coupling efficiency of difficult substrates. As a consequence, phosphonamidates prepared using these methods are obtained as racemates and sometimes as diastereomeric product mixtures. This constitutes a significant weakness in the current methodologies and should be addressed in order to obtain reliable and trustworthy results from biological testing of these compounds. An example detailing this issue can be found in the hexameric phosphonamidate 217 prepared by Kitamura and Ishibashi using an SPPS-methodology (Figure 4.3).

Figure 4.3 – A hexameric peptide synthesised by an SPPS-method developed by Kitamura and Ishibashi.
Even though this methodology provided a straightforward route to prepare peptides of different sizes, the reagents used don’t exert any control of the stereochemical outcome of the reaction. The consequence of this is apparent from the increasing amount of stereoisomers formed after each successful coupling of an α-aminophosphonic acid segment. Thus, applying a stereoselective method would be valuable if a specific stereoisomer were targeted. For the articles targeting synthesis of phosphonamidates,[9, 10, 11, 12, 13] ours included,[14] the concept of stereoselectivity has mostly been ignored, favouring instead to develop and/or discover new reagents that generate the phosphonamidate functionality.

We wanted to investigate the possibility of synthesising phosphonamidates stereoselectively in order to address the problems inherent in the current methods. Inspiration to achieve this was found in the work reported by Kaminski and co-workers,[15, 16] Their study demonstrated how chiral dimethoxytriazine-ammonium (DMT-ammonium) coupling agents could be used to selectively amidate one enantiomer out of a racemic mixture of CBz-protected alanine (220) (Scheme 4.2). The best results were obtained when strychnine and brucine were used as the chiral scaffold for the coupling agents, which led to compounds 218a and 219a.

Scheme 4.2 - Preparation of a chiral triazine-based coupling agent and its use in a racemic mixture of CBz-protected alanine (±220).
4.2 - Initial Testing of Chiral Coupling Agents in the Phosphonamidation Reaction

We envisioned that the application of a chiral coupling agent could differentiate the rate in which the prochiral phosphonic acid is activated to either the \((R)\)- or \((S)\)-DMT-phosphonate (Scheme 4.3). In order to obtain an enantioriched product mixture, a stereoselective activation of the prochiral phosphonic acid is required. To the best of our knowledge, no reports have been presented on the activation of monoalkyl phosphonic acids using DMT-ammonium-type coupling agents. An experiment was conducted to investigate whether the coupling agent could generate the activated phosphonates **176a-b** and **225** that could subsequently undergo aminolysis (Scheme 4.4).

Scheme 4.3 – An envisioned stereoselective phosphonamidation reaction using the strychnine-DMT-BF₄ **219a** coupling agent.

The coupling agent, base and monoethyl benzylphosphonic acid **171** were preactivated for 24 hours, using a commercially available DMT-ammonium-type coupling agent DMTMM (153). ³¹P-NMR analysis of the crude reaction mixture revealed that pyrophosphonates **176a-b** where exclusively generated with no measurable quantity of the expected DMT-phosphonate **225** (Scheme 4.4). Aminolysis of the activated phosphonates afforded the product in 25% conversion as was measured from ³¹P-NMR of the crude reaction mixture. The increased duration of the preactivation period (24 hours compared to 1 hour) was necessary as the activation step was slower than the other coupling agents that were tested previously (Table 3.2, Chapter 3). The absence of a preactivation period gave no product formation even though the coupling agent was consumed. This outcome was not unexpected considering our previous endeavours with the phosphonamidation reaction (Chapter 3, Table 3.2). Subsequently we propose that the favoured reaction pathway is the irreversible side-reaction between the coupling agent and the amine, affording the proposed by-product **224**. No efforts were undertaken in order to isolate and elucidate the structure.
of the by-product. A purified racemate of the product 185 was analysed on a chiral HPLC-column to establish the conditions required for the separation of the enantiomers of compound 185.

Scheme 4.4 – Initial testing of the commercially available DMTMM coupling agent 153 in the phosphonamidation reaction.

The exclusive generation of pyrophosphonates measured after the preactivation period was regarded as problematic since the pyrophosphonates obtained consists of equal amounts of the chiral 176a and the achiral (meso) 176b pyrophosphonate (Figure 4.4). Even if one enantiomer of the chiral pyrophosphonate 176a (S,S or R,R) is generated with complete enantioselectivity, the enantiomeric excess of the product is limited to roughly 50% ee, since roughly 50% of the product is made from the achiral pyrophosphonates 176b. Thus, it was decided to test the coupling agent described by the Kaminsky-group since it provided a fast route to a chiral coupling agent (Scheme 4.5).

Figure 4.4 – The different pyrophosphonates that are generated during the preactivation.
From the chemicals that were available to us, it was decided to prepare the brucine-DMT-Cl 218b followed by an anion exchange to the brucine-DMT-BF₄ using AgBF₄. The synthesis of the brucine-DMT-Cl 218b has previously been described by the Kaminsky group (Scheme 4.5, Method B). However, in our hands, degradation of the intermediate compound brucine-DMT-Cl 218b occurred within minutes after it was generated. The extent of the degradation could be monitored by following the crude reaction mixture by ¹H-NMR over several minutes (NMR-experiment is located in the Supporting Information).

Scheme 4.5 – Synthesis of triazine-type coupling agents.
The thermal instability of DMT-ammonium-Cl salts is described in the Kaminski paper, but the rate in which the products undergo degradation was not specified. The degradation is believed to occur as a consequence of a nucleophilic attack of the chloride anion on one of the three adjacent α-alkyl carbons of the ammonium group. A chloride addition product was observed from a MS (ESI+) measurement of our crude reaction mixture which supports their claim. The general procedure for the generation of the ammonium-DMT-Cl salts, provided by the Kaminsky group, requires 30 min of stirring in addition to the time required for the purification and isolation. Since degradation occurred immediately after the product had been prepared it was thought necessary to change the procedure. The degradation of the coupling agent could be avoided altogether with a minor modification to the original procedure, which was practical on a small scale (see “Method C” in Scheme 4.5).

The inherent toxicity of brucine (142) prompted us to undertake the experiments in a small scale (<1 mmol) to afford the BF₄-salts which is in gross contrast to the scale undertaken by the Kaminsky group (100 mmol scale, Scheme 4.5). Addition of chloro-dimethoxytriazine (CDMT) (228) to a solution containing both the brucine and AgBF₄ resulted in an immediate anion replacement of the in situ generated brucine-DMT-Cl 218b to the more stable brucine-DMT-BF₄ salt 218a (Scheme 4.5). This was evident by the instantaneous observation of AgCl precipitate when combining the reagents together. This modification afforded a quantitative conversion to brucine-DMT-BF₄ 218a in less than 5 min, which was stable in CDCl₃ solution for prolonged periods of time (Evident by ¹H-NMR analysis).

Brucine-DMT-BF₄ 218a was tested in the phosphonamidation reaction, and like the achiral DMTMM 153 coupling agent, brucine-DMT-BF₄ 218a gave pyrophosphonates exclusively as the activated species, and not the wanted triazine-phosphonate 225 even after 21 hours of preactivation. Subsequent aminolysis of the activated phosphonates afforded the product in 25% conversion as a racemate, which was determined after HPLC-analysis of the purified material.

![Scheme 4.6](image)

**Scheme 4.6** – Testing the chiral brucine-DMT-BF₄ 218a coupling agent in the phosphonamidation reaction of the phosphonic acid 171.
Since the triazine-type coupling agents 218a and 153 were slow to activate the phosphonic acid 171, and only afforded pyrophosphonates as the activated species, it was decided to develop a chiral chiral coupling agent based on the structural motif of COMU instead.

4.3 - Different Strategies to Afford Chiral COMU Derivatives

It was envisaged that COMU could be modified in two different positions in order to contain a chiral enantiodifferentiating group; either replacing the \(N,N\)-dimethyl morpholin uronium group (Strategy 1, Scheme 4.7) or by replacing the ethylester of Oxyma with a chiral ester or amide functionality (Strategy 2, Scheme 4.7).

![Scheme 4.7](image)

Scheme 4.7 - Different strategies envisioned in order to obtain chiral derivatives of COMU following the general procedure developed by the inventors.\(^{[17]}\)
4.4 - Development of Chiral COMU Derivatives via a Modification of the Uronium Group

According to the procedure presented by Albericio and co-workers, COMU derivatives can be obtained in 3 steps from \( N,N,N,N \)-tetraalkyl ureas and commercially available K-Oxyma (Scheme 4.7, Strategy 1).\(^{[17]}\) We hypothesised initially that it would be preferable to introduce a chiral modification to the uronium rather than the ester group since the uronium group participates directly in the first step in the proposed mechanism for the COMU activated amidations (see Table 3.1, Entry 3 or Scheme 4.11). Three chiral ureas 233, 235 and 238 were prepared from commercially available amines 232 and 234, and suitable urea precursors 231 and 236 (Scheme 4.8).
The C2-symmetric ureas 238 and 240 were prepared using 1,1'-carbonyldiimidazole (CDI) (236) as the carbonyl source. CDI was used instead of phosgene since it is considered a safer alternative.[18] Our attempts to prepare ureas containing the bis[[(R)-1-phenylethyl]amine (241) scaffold were unsuccessful, presumably due to the low nucleophilicity of the amine.

For the ureas 233, 235 and 238, the corresponding PF₆-chlorouronium-salts could be obtained after treatment with oxaly chloride followed by an anion exchange from chloride to hexafluorophosphate using AgPF₆ (Scheme 4.9). The driving force behind the anion exchange is the precipitation of solid AgCl which is poorly soluble in most solvents. The PF₆-uronium-salts 245, 248 and 251 could then be treated with K-Oxyma to complete the synthesis of the chiral coupling agents 246, 249 and 252 (Scheme 4.9). Of the completed chiral derivatives of COMU, compound 246 was easily obtained since it was sufficiently crystalline. Compound 249 was obtained as an oil, and did not crystallise in ether or any other low polarity solvent. While stored in a refrigerator, some crystal formation was observed. These crystals were used to characterise the compound. Due to time restrictions, the synthesis of compound 252 was attempted only once, which resulted in a crude reaction mixture that proved too difficult to purify. Thus, coupling agent 246 was used as our model substrate for the attempted chiral coupling reactions.

![Scheme 4.9 - Preparation of chiral COMU derivatives from chiral ureas.](image-url)
The chiral COMU derivative 246 was then evaluated on its ability to exercise control of the stereoselectivity in the phosphonamidation reaction between the monoethyl benzylphosphonic acid 171 and benzylamine (Scheme 4.10). The initial reaction with the chiral coupling agent 246 was undertaken under reduced temperature (0 °C) following the method explained in Chapter 3 (Table 3.4, Method A). This method provided no product formation as was evident after an analysis of the crude product mixture by 31P-NMR. When the reaction was performed at room temperature, product formation was achieved in 37% conversion, suggesting that a slower activation of the phosphonic acid is achieved with 246 as compared to COMU. Analysis of the purified material on a chiral HPLC-column revealed that the product had been obtained as a racemate.

Scheme 4.10 – Attempted enantioselective phosphonamidation reaction using the chiral COMU derivative 246.

The low conversion to product was problematic since a significant portion of the material is lost during the chromatographic step. This made the task of detecting the product in the collected fractions challenging (and time consuming) since 1H- and 31P-NMR analysis of the individual fractions was the most practical way of evaluating the content, and by extension the purity of the product containing fractions. Efforts were put into employing TLC-analysis in combination with UV-light and different TLC staining solutions to detect the products but these techniques were not accurate enough. To obtain sufficiently pure product in order to obtain reliable HPLC chromatograms, the conditions used in the chromatographic step had to be changed from what was used initially (see the Supporting Information). Before the alternative purification method was reached, the achiral benzylamine was replaced with (S)-1-phenylethylamine. The chiral induction obtained from the catalyst was envisioned to be evaluated from the diastereometric ratio of the products, observable by NMR, and not by HPLC-analysis (see Section 4.6).
4.5 - Mechanism of the Phosphonamidation Revisited – Implications for the Enantioselective Phosphonamidation Reaction

As neither the chiral triazine- nor the chiral COMU-derivative coupling agents provided products with a measurable enantiomeric excess, it appeared necessary to re-evaluate the mechanism in more detail. During this process important questions regarding the mechanism that have profound implication to the outcome of the reaction were clarified.

- Do the individual steps occur with retention or inversion of stereochemistry?
- Is there an equilibrium between the activated phosphonates, and if so, how does it affect the outcome of the reaction?

The following section is dedicated to evaluate the implications of each of these questions and how it is likely to affect the enantioselectivity in the strategies explained in previous sections. For the COMU-derived coupling agent 246, the enantiodiscrimination of the pro-chiral phosphonic acid 171 could be achieved in the first activation step (Scheme 4.11, Step 1, Phase 1). During this phase, two high-energy intermediates 253 and 254 are expected to form which may either revert to the starting materials or react via an irreversible pathway to the more stable pyrophosphonates 176a-b (Step 2, reaction pathway A and C, Phase 2) or the Oxyma-phosphonate 177 (Step 2, reaction pathway B, Phase 2).

Had the high-energy intermediates 253 and 254 been measurable by 31P-NMR, the stereoselectivity of the first step could have been determined. After the second step, the chiral uronium-salt is transferred to a chiral urea 255 that cannot activate the remaining starting material or otherwise influence the reaction via any reasonable pathways. Its role for the remainder of the reaction is that of a spectator. During this phase of the preactivation (Phase 2, Scheme 4.11), reaction pathways that cause racemisation of the activated phosphonates will erode the enantiomeric excess measured of the product. This is a severe limitation to the strategies focusing on a chiral activation group that cannot influence the other activated-phosphonates directly after the initial activation (Phase 2).

Since the Oxyma-derived coupling agents (COMU, PyOxim and 246) requires a preactivation period in order to form the product during the aminolysis step, it is crucial to identify mechanisms which could facilitate racemisation during this period. During our initial investigation of the phosphonamidation reaction, we found evidence of an equilibrium between the pyrophosphonates 176a-b and the Oxyma-phosphonate 177.[14] Chemical equilibria are obtained when the rate of the backward reaction is equal to the forward reaction.
Scheme 4.11 – The proposed mechanism of the phosphonamidation reaction
An equilibrium between the activated phosphonates would then be expected to cause racemisation over time since pyrophosphonate 176b is an achiral meso compound. Thus, the rate of racemisation would be equal to the rate in which the two chiral activated phosphonates are transformed to the achiral meso compound 176b. On the other hand, if a chiral additive such as a chiral Oxyma derivative were used, one could expect the equilibrium to be forced towards the chiral Oxyma-phosphonate.

An additional mechanistic feature that could influence both the stereochemistry and the enantiomeric excess of the final product is related to whether the nucleophilic substitution reactions undergo inversion or retention of configuration at the phosphorous atom. It should be stressed, that if steps 2, 3 and 4 do not undergo strict inversion or retention of stereochemistry, an additional erosion of the stereoselectivity will occur.

From previous aminolysis studies of phosphonochloridates it has been shown that the tetrahedral phosphonochloridates undergo stereo inversion at the phosphorous atom. Nucleophilic substitution reactions of similar compounds are commonly accepted to go through a trigonal bipyramidal transition state. The nucleophile promotes either stereo-inversion or stereo-retention depending on the relative position of the nucleophile and the leaving group prior to the decomposition of the pentacoordinated intermediate (Figure 4.4). If both the nucleophile and the leaving group are in the apical plane (From an “in line” attack), stereo-inversion is obtained, while stereo-retention is explained when the nucleophile is in the equatorial plane (“adjacent” attack) and the leaving group is in the apical plane (Figure 4.4). From studies regarding nucleophilic substitution reactions of phosphonochloridates, the nucleophile prefers an apical entry which would result in an inversion of configuration at the phosphorous atom. Retention of configuration is believed to occur from a ligand reorganisation of the intermediate formed by an apical entry of the nucleophile. Retention of configuration has been found in nucleophilic substitution reaction of five-membered ring chlorophosphates, and for the chlorination step of the Atherton-Todd reaction and other reactions.
In order to evaluate if steps 2, 3 and 4 in Scheme 4.11 undergo inversion or retention of configuration, the probability of the nucleophile and the leaving group positioning themselves according to Figure 4.4 has to be investigated. At present there are no papers discussing this, but from the work presented on aminolysis of phosphonochloridates and on chlorophosphates, inversion of configuration appears to be the most probable outcome.\textsuperscript{[19]} It has been stated that the pathways leading to retention or inversion are a function on several parameters such as the identity of the nucleophile, leaving group and on the substituents on the phosphorus atom. A possible solution to how these problems can be fixed and how the time consuming preactivation period can be reduced is described in the future works part of this thesis.

\textbf{Figure 4.4} – Proposed trigonal bipyramidal intermediates responsible for inversion or retention of configuration of the phosphonamidation using COMU derivatives.
4.6 - Chiral Phosphonamidation using a Chiral Amine

As mentioned in the previous section, before the new conditions to the chromatographic step were established, we envisioned that we could obtain the corresponding diastereomeric ratio (d.r.) from the reaction by replacing benzylamine with (S)-1-phenylethylamine. Our assumption was that the enantiomeric excess of the activated phosphonates obtained after phase 1 of the reaction (Scheme 4.11), would be preserved during the aminolysis. The chiral phosphoamidation study was initiated by investigating the amidation of monoethyl benzylphosphonic acid 171 promoted by the chiral COMU derivative 246 (Scheme 4.12). As in previous studies, the crude reaction mixtures were analysed by $^{31}$P-NMR. Two overlapping product peaks were observed, which were assigned to the two diastereomers 258 and 259, which combined accounted for a 43% conversion from the starting material. The two diastereomers were obtained in a ratio of approximately 2:1 (Scheme 4.12, Method A). However, a similar result was obtained when achiral COMU was used as the coupling agent (Scheme 4.12, Method B), thus it is unlikely that the d.r. that was obtained may be explained by the enantiodifferentiation ability of 246. Interestingly, the chlorophosphonate provided both diastereomers in equal quantities, indicating a significant difference between the methods (Scheme 4.12, Method C).

Scheme 4.12 - A Phosphonamidation reaction using a chiral amine.

The difference observed from the phosphonamidation reaction obtained through the use of coupling agents and chlorinated intermediates were also found to be significant for other phosphonic acids as well (Table 4.1). In this limited study, the chlorophosphonates provided an equal distribution of the diastereomers (Table 4.1, entries 3, 6 and 9), while COMU and 246 appeared to favour one diastereomer over the other (Table 4.1, entries 1, 2, 4, 5, 7, 8, 10 and 11). No efforts were undertaken to figure out which diasteriomer that is favoured for each substrate. The Boc-protected phosphoAIB derivative 200 decomposed when mixed with the chlorinating reagent. However, compound 200 gave an uneven distribution of the diastereomers with both COMU and 246. Interestingly, the difference between the diastereomers was consistently larger for 246 than for COMU (Table 4.1 entries 1 and 2, 4 and 5, 7 and 8 and 10 and 11). However no solid evidence was found supporting
that these differences originated from the chiral activator group in the chiral coupling agent 246.

Table 4.1 – Aminolysis study of activated phosphonates using (S)-1-phenylethylamine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁, R₂</th>
<th>Method</th>
<th>D.r.</th>
<th>Product</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-Bn, -Et 171</td>
<td>A</td>
<td>1.00 : 0.57</td>
<td>256 and 257</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>-Bn, -Et 171</td>
<td>B</td>
<td>1.00 : 0.62</td>
<td>256 and 257</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>-Bn, -Et 171</td>
<td>C</td>
<td>1 : 1</td>
<td>256 and 257</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>-Bn, -Me 180</td>
<td>A</td>
<td>1.00 : 0.46</td>
<td>258 and 259</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>-Bn, -Me 180</td>
<td>B</td>
<td>1.00 : 0.58</td>
<td>258 and 259</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>-Bn, -Me 180</td>
<td>C</td>
<td>1 : 1</td>
<td>258 and 259</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>-Bn, -i-Pr 181</td>
<td>A</td>
<td>1.00 : 0.38</td>
<td>260 and 261</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>-Bn, -i-Pr 181</td>
<td>B</td>
<td>1.00 : 0.44</td>
<td>260 and 261</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>-Bn, -i-Pr 181</td>
<td>C</td>
<td>1 : 1</td>
<td>260 and 261</td>
<td>&gt;95</td>
</tr>
<tr>
<td>10</td>
<td>Boc-NH-C(Me)₂, -Et 200</td>
<td>A</td>
<td>1.00 : 0.68</td>
<td>262 and 263</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>Boc-NH-C(Me)₂, -Et 200</td>
<td>B</td>
<td>1.00 : 0.74</td>
<td>262 and 263</td>
<td>65</td>
</tr>
<tr>
<td>12[a]</td>
<td>Boc-NH-C(Me)₂, -Et 200</td>
<td>C</td>
<td>-</td>
<td>262 and 263</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Degradation of the starting material was observed.

An investigation was undertaken to check if an in situ generation of a chiral guanidinium salt 264 could explain the results.

Figure 4.5 – A chiral guanidinium-salt 264 that could form in a reaction between the amine and 246.
As in previous studies, the activated phosphonates 176a-b and 177 were generated from the phosphonochloridate 178. The Oxyma-phosphonate:pyrophosphonate ratio was ca 4:1 and provided the two product diastereomers 256 and 257 in a ratio of 2:1, in 42% yield after the aminolysis step (Scheme 4.13). This experiment demonstrates that the similar diastereomeric ratio between 256 and 257 is possible, even in systems were chiral compounds such as 264 and the alike are not present. This indicates that the diastereomeric ratio is dependent on the identity of the activated phosphonates and possibly by the ratio between them.

Scheme 4.13 – An experiment was conducted to evaluate if the d.r. obtained in Table 4.1 could occur from a chiral guanidinium salt 264 or from the identity of the activated phosphonates. The same phosphonomidation reaction was attempted with DIC and PyBOP coupling agent (Scheme 4.14). A set of two experiments were undertaken with DIC, one with 0.5 eq. and one with 1.5 eq. of coupling agent. 0.5 eq. of DIC would generate the pyrophosphonates 176a-b exclusively without any leftover DIC coupling agent during the aminolysis step which could form a chiral guanidinium salt. In both experiments the diastereomers were
obtained with approximately the same ratio of 2.5:1, which made it difficult to tell if the presence of a chiral guanidinium salt actually does impact the outcome of the reaction. Both experiments gave a poor yield of the reaction, and the product mixture was obtained in 12 and 6% conversion after 20 hours of stirring. The lower yield obtained from the experiment with 1.5 eq. of DIC may suggest that more of the amine is removed from the reaction by the formation of guanidinium salts. With PyBOP, the ratio between the diastereomers (1.00:0.86) was lower than for DIC, but the conversion to products was higher (38% yield compared to 12 and 6%). This slow rate of aminolysis of the pyrophosphonate compared to the other activated phosphonate suggests that the majority of the product is obtained by aminolysis of the Oxyma or HOBt-phosphonates.

**Scheme 4.14** – DIC and PyBOP mediated phosphonamidation using the chiral amine, (S)-1-phenylethylamine during the aminolysis step.

Thus it appears that the results provided in Table 4.1, can be related to the identity and the relative amount of the activated phosphonates.
4.7 - Summary and Conclusions

As a continuation of our previous phosphonamidation work (Chapter 3), we have attempted to promote an enantioselective phosphonamidation reaction by employing chiral coupling agents. The coupling agents used were the brucine-triazine-BF$_4^-$ \(218\text{b}\), developed by Kaminski and co-workers, and a chiral derivative of COMU \(246\). No conclusive evidence was found supporting that the coupling agents were able to differentiate between the pro-S and the pro-R side of the achiral phosphonic acids. The triazine-type coupling agents tested in this study were generally slow to react and provided only the pyrophosphonates \(176\text{a-b}\) as the only activated species. This is not optimal since pyrophosphonate \(176\text{b}\) is achiral.

After a re-evaluation of the proposed mechanism (Scheme 4.11) and how it may affect the different strategies, we propose that strategies focusing on a chiral activator group (Definitions in Table 3.1) are not beneficial for liquid-phase phosphonamidations. In relation to chiral phosphonamidations employing coupling agents with a chiral activator group, we propose that the reaction go through two phases. The chiral induction occurs in phase 1 while racemisations occur in phase 2 (Scheme 4.10). Common for these strategies are that the chiral breakdown products of the coupling agents are thought to not be able to affect the enantioselectivites in phase 2 of the reaction. Subsequently, any pathway that causes racemisation in phase 2 of the reaction will permanently reduce the enantiomeric excess of the product. A possible solution to avoid this problem is discussed in Chapter 5.

For phosphonamidations using a chiral coupling agents derived from COMU and (S)-1-phenylethylamine, it was found that the type of activated phosphonate formed were crucial for the outcome of the reaction. Phosphonochloridates provided an equal distribution of diastereomers while the activated phosphonates \(175\), \(176\text{a-b}\), and \(177\) provided an unequal distribution (Table 4.1 and Scheme 4.14).
4.8 - References

CHAPTER 5 – FUTURE PROSPECTS

5.1 – Free P-Terminal Polymer Supported Phosphonamidation

During our exploration of the phosphonamidation reaction, a considerable effort was undertaken to manipulate the reaction conditions to favour product formation over unproductive reaction pathways. The unproductive pathways were predominant when procedures designed for carboxylic acids were employed. Central in our exploration were the identification and characterisation of the main reactive species 175 – 177. Additionally, an observation was made suggesting there is an equilibrium between the reactive species formed during the preactivation period. From experiments and from the evaluation of the proposed reaction mechanism it became evident that controlling the number of activated phosphonates and the relative ratio between them were important. From experiments it was found that minimising the concentration of the pyrophosphonates were beneficial in order to obtain a high conversion to product. From evaluation of the proposed mechanism it is believed that the generation of pyrophosphonates will affect the enantioselective amidation reactions negatively. Consequently, being able to significantly reduce or prevent the generation of pyrophosphonates altogether would improve the existing methods drastically. One way this could be achieved is to develop new coupling agents, where the activation steps does not allow or minimise the likelihood of generating the pyrophosphonates. What the structure of a coupling agent with these characteristics entails is not yet obvious. More obvious is the realisation that pyrophosphonate formation can be avoided altogether by physically “anchoring” the phosphonic acid to a heterogeneous polymeric support with sufficient spacing between the anchors. If the distance between each phosphonic acid is sufficiently large pyrophosphonate generation is not possible. An obvious limitation with this methodology is that it is limited to compounds containing a suitable functional group that can be used to attach the phosphonic acid to the polymeric support.

In the case of preparing short peptides of α-aminophosphonic acids, the amine functional group can act as an anchor point for the polymeric support. To anchor the amine rather than the acid functional group to the polymeric support is the opposite of what is normally undertaken in traditional SPPS-methodologies. The growing peptide would then be elongated from the acid terminal (Free P-terminal, usually denoted C-terminal for regular peptides) and not from the N-terminal. The work undertaken by Kitamura and Ishibashi describes the traditional method were the phosphonic acid is anchored to the polymeric support and were each segment is coupled to the N-terminal of the growing peptide.
Related to our attempted liquid-phase strategy to obtain peptides of \(\alpha\)-aminophosphonic acid 200, we envisioned that the amine could be used to anchor the to the \(\alpha\)-aminophosphonic acid to the polymeric support by the formation of a carbamate group. The carbamate generation can be obtained from the reaction between the amine group of the \(\alpha\)-aminophosphonic acid and a suitable carbamate precursor. The carbamate precursor envisioned for this project is the commercially available polymer bound \(p\)-nitrophenyl carbonate 265 (Scheme 5.1). A nucleophilic attack of an amine on the carbonate carbonyl displaces the \(p\)-nitrophenolate forming a carbamate. Aminolysis of \(p\)-nitrophenyl carbonates has been accomplished on several occasions, both on polymer-supported analogues,[1, 2, 3] and non-polymer supported analogues.[4, 5, 6, 7] The carbamates that are formed from aminolysis of the carbonate 265 are structurally similar to the CBz-protection group. The polymer bound \(\alpha\)-aminophosphonate can then be transformed to the phosphonic acid 264 after a selective mono-dealkylation of the phosphonate group. The polymer bound phosphonic acid 266 can then undergo activation from a coupling agent and subsequently undergo aminolysis, alcoholysis or thiolysis.

The finished polymer bound product 269 needs to be released from the polymeric support in order to isolate the product. It is assumed that the polymer bound CBz group reacts similarly to homogeneous and solubilised CBz-protected amines. CBz-deprotection is normally undertaken by hydrogenation over Pd/C.[8] This method is not suitable for polymer supported CBz-amines since the heterogeneous Pd/C source is less likely to react with the CBz-protected amines located inside the polymer beads. An alternative would be to use the Me₃SiI in MeCN which has been reported to effectively remove the CBz-group. Me₃SiI does not hydrolyse the phosphonate group as it was tested for this specific purpose on an earlier occasion. Hydrolyses of phosphonates using Me₃Si-halides are known in literature, especially for dimethylphosphonates.
Scheme 5.1 – Suggestion for a solid-phase CBz-protected aminophosphonic acid using a p-nitrophenyl carbonate functionalised polymer support.
5.2 – Liquid-Phase Phosphonamidation with a Chiral Additive

In Chapter 4.5 during the discussion of the mechanism of the phosphonamidation using coupling agents with a chiral activator group, phase two of the reaction was mentioned as a problem. With coupling agents designed with a chiral activator group rather than a chiral leaving group is employed, racemisation will occur since there are numerous racemisation pathways available. Additionally the activator group is converted into a urea or phosphoramidate, which depends on choice of coupling agent. It is not obvious how these compounds can inflict any meaningful impact on the stereoselectivity during this phase, and they should probably be treated as spectator molecules. However, if the leaving group of the coupling agent or a chiral additive were added, then phase two of the reaction could be affected. Examples could include chiral derivatives of Oxyma or HOBt. In Chapter 4.3 chiral derivatives of Oxyma was suggested (Figure 5.2).

\[\text{Figure 5.2} \quad \text{– Examples of chiral derivatives of Oxyma.}\]

Practically, if any enantiodifferentiation occurs during phase two with the chiral additive, then this may be measured by NMR-analysis of the preactivated reaction mixture. For the COMU mediated phosphonamidation reactions we have shown that the activated phosphonates can be shifted primarily towards the Oxyma-phosphonate if the preactivation is done appropriately.

\[\text{Figure 5.3} \quad \text{– Examples of a diastereomeric pair of an activated phosphonate that can be obtained using the chiral Oxyma-derivative 272.}\]

This method could be important for phosphonic acids that are not applicable for the SPPS-methodology discussed in section 5.1.
5.3 - Enantioselective Synthesis of Mixed Phosphonates and Thiophosphonates

An obvious continuation of the project may also be directed towards an enantioselective synthesis of mixed phosphonates. Both of the methods explained in section 5.1-2 are independent with regards to the nucleophile that undergoes nucleophilic substitution of the activated phosphonates. The enantiomeric excess of the target molecule would then originate from the enantiodifferentiation step obtained during the preactivation step. This step is independent of the nucleophile if a preactivation is undertaken. Subsequently, if the aminolysis, alcoholysis or thiolysis of the activated phosphonate undergo with strict inversion or retention of stereochemistry a similar enantiomeric excess of the products should be obtained.

Scheme 5.2 – Examples of an aminolysis, alcoholysis and thiolysis of a polymer supported Oxyma-phosphonate.
5.4 - References


SUPPORTING INFORMATION

General Information

Reagents were obtained from commercial suppliers (Sigma Aldrich, Fluka, Fluorochem) and used without further purification unless stated otherwise.

Column chromatography was performed by manual flash chromatography and by Flash chromatography (Type: CombiFlash Companion) using silica gel as the packing material (0.04-0.063 mm from Merck). Room temperature is approximately 20-22 °C.

Solvents

Dry and unstabilised solvents were obtained from a MBraun solvent purifying system (SPS) 800 instrument. These solvents include CH₂Cl₂, Et₂O, THF, MeCN and DMF. CH₂Cl₂ (GPR Rectapur with 0.2% EtOH as stabilizer) and MeOH (HiPerSolv Chromanorm) was used for the column chromatography. The catalytic amount of DMF used in the phosphochloridate formation was obtain from a stock solution, initially obtained from the solvent purifying machine, which were covered in Al-foil and added mol. sieves (4 Å).

Microwave reactor

The microwave reactions were carried out in an Anton Parr Monowave 300 microwave synthesis reactor. The reaction mixtures prepared for the microwave synthesis reactor was thoroughly degassed with Ar (g) before use.

Mass spectrometry instrumentation

Mass spectra under electron impact (EI) conditions were recorded on a VG Prospec instrument at 70 eV ionizing voltage. Mass spectra under electron-spray (ESI) condition were recorded on a Bruker Maxis II ETD or a Micromass Q-Tof-2 instrument. All mass spectra are presented as m/z. HRMS-EI and HRMS-ESI were performed with the instruments mentioned above. MeCN (HiPerSolv Chromanorm) was used to prepare the samples in approx. 1-2 mg dissolved compound per mL solvent.

HPLC-analysis

The HPLC-analysis was split between two different instruments. The evaluation of the PT-catalysed enantioselective alkylation reactions of phosphoglycine Schiff bases (see Chapter 2) were done on an instrument containing; an Spectrasystem P200, Spectrasystem UV300 and Spectrasystem SN4000. The visualisation of the chromatograms was undertaken by using the program “ChromQuest”.

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The evaluation of the experiments targeting chiral phosphonamidations (see chapter 4) were undertaken on a Agilent technologies 1260 Infinity instrument.

Solvents used were HiPerSolv CHROMANORM iso-hexane and 2-propanol in a ratio specified where it is relevant in the Supporting Information. Columns used were the Chiralpak type As-H and AD-H.

NMR instrumentation, structure characterisation and reporting of NMR data

Instrumentation

Nuclear magnetic resonance (NMR) spectroscopy was performed on various instruments; including a Bruker DPX 200 and 300, AVII 400 AVII HD 400, DRX500 AV600 and AVII600 spectrometers operating at 200, 300, 400, 500 and 600 MHz respectively for $^1$H.

$^{13}$C NMR was mainly recorded on the AVII (HD) 400 and AV600 spectrometer operating at 101 and 151 MHz. All carbon spectra are proton decoupled during the acquisition period ($^{13}$C-CPD). $^1$H and $^{13}$C NMR spectra were calibrated against residual CHCl$_3$ ($\delta$H = 7.24 ppm, $\delta$C = 77.0 ppm). $^{31}$P-NMR spectra were recorded on the DPX 200, DPX 300 and AVII (HD) 400 spectrometers operating at 81, 121 and 162 MHz, and the calibration of the spectra was undertaken using a sealed capillary containing 50 wt% D$_3$PO$_4$ dissolved in D$_2$O. All phosphorous spectra are proton decoupled during the acquisition period ($^{31}$P-CPD).

Resonance multiplicities are denoted s, d, t, q, m and br, for singlet, doublet, triplet, quartet, multiplet and broad, respectively.

The NMR data presented in the thesis are processed using MestReNova v8.0.1-10878, © Mestrelab Research S.L. COSY spectra are processed using MestReNova’s “symmetrise, $\rightarrow$COSY-like”-function to reduce $t_1$-noise from the spectrum. Certain HMBC spectra have been processed using the “Reduce $t_1$ Noise”-function to clean up the spectra.

Processing tools such as linear prediction and zero-filling has also been utilised to enhance the visuals of the spectra.
A COSY-spectrum before employing MestReNovas symmetrise function

A COSY-spectrum after employing MestReNovas symmetrise function

**Figure SI-1** - An example of applying the symmetrise function to a COSY-spectrum
A HMBC-spectrum before employing MestReNovas “Reduce t1-Noise”-function

A HMBC-spectrum after employing MestReNovas “Reduce t1-Noise”-function

**Figure SI-2** - An example of applying the “Reduce t1-Noise”-function.
Reporting NMR-spectra containing higher-order splitting pattern relevant for this thesis

During the acquisition of NMR-spectra, certain spin-active nuclei that are coupled to each other through chemical bonds may give rise to higher-order splitting patterns. Spin active nuclei that are affected by higher-order splitting may be affected in two principal ways, both affecting their appearance in the Fourier-transformed spectra. Before these changes are briefly introduced, it may be beneficial to recap how these effects may originate in a spectrum. Higher-order splitting patterns may arise if the difference in chemical shift between the spin active nuclei ($\Delta v$) and to the magnitude of the coupling constant ($J$) between them approaches each other. This can be visualised as:

$$\frac{\Delta v}{J}$$ (1)

First-order spectra, may be obtained for systems where the ratio of $\Delta v / J$ is greater than 10. If the ratio described by (1) is lower than 10, second-order splitting patterns may be observed. Sign of second-order effects in the NMR-spectrum may be observed as the intensities of peaks does not confirm to the expected integer ratios, which may be observed as “leaning”. Peaks may additionally appear as more complex by the additional splitting of peaks. Below are two examples from compounds relevant for this thesis, which demonstrate how these effects may appear.

Figure SI-3 - In a mixture of two diastereomers, one diastereomer appears to be a doublet of doublets (dd) (blue dots), while the other show second-order splitting (red dots)
A consequence of having second-order peaks in the NMR-spectrum is that additional analysis is required in order to obtain the real chemical shift and coupling constants. For an organic chemist without specialisation in NMR spectroscopy, these calculations quickly become time-consuming and difficult to undertake, especially if overlap with other peaks are observed.

As the focus of this thesis is primarily that of organic chemistry and catalysis, these calculations have been omitted. For compounds where this phenomenon has been observed the peaks have been treated as multiplets, or calculated as if they were genuine first-order spectra. For the assignment of peaks that are suspected of having second order effects or splitting patterns that do not appear right is highlighted with the abbreviation “app.*”.

**Figure SI-4** – Leaning of peaks are a sign of second-order effects.
Synthesis of dibromo m-xylene (118)

A RBF was loaded with N-bromosuccinimide (Recrystallised, 28.929 g, 162.54 mmol, ca 2.2 eq.), dibenzoyl peroxide (0.109 g, 0.45 mmol), m-xylene (7.849 g, 73.92 mmol) and PhCl (100 mL), forming an heterogeneous mixture. The resulting reaction mixture was heated to 80 °C where it was maintained for 6 hours. The solution turned orange during the course of the reaction. The crude reaction mixture was washed with aqueous Na$_2$S$_2$O$_2$ (Sat., 2 × 20 mL), water (4 × 20 mL), and then saturated NaCl (Sat., 20 mL). The organic phase was then dried over anhydrous MgSO$_4$, filtered and then concentrated under reduced pressure to afford an oil.

The resulting product mixture was immersed with petroleum ether (20 mL, 60 - 80 °C boiling range) and set aside in the refrigerator up to 10 hours. The product precipitated, forming colourless crystals that were collected by filtration of the heterogeneous mixture through a Büchner funnel. The product was dried in a desiccator by storing it over P$_2$O$_5$ under reduced pressure for 12 hours.

This procedure afforded the product as a colourless crystalline compound (6.377 g, 30.7% yield).

\[ \text{Br} \begin{array}{c} \text{Br} \\ 118 \end{array} \]

$^1$H-NMR (400 MHz, Chloroform-d) $\delta = 7.41$ (s, 1H), 7.31 (d, $J = 1.3$ Hz, 3H), 4.46 (s, 4H).

$^{13}$C-NMR (101 MHz, Chloroform-d) $\delta = 138.38, 129.53, 129.26, 129.02, 32.80$.

MS (ESI+, m/z): Unable to obtain product peak.

MS (EI+, m/z): Unable to obtain product peak.

HRMS (ESI+, m/z): Unable to obtain product peak.
$^1$H- and $^{13}$C-NMR spectrum of compound **118** recorded in CDCl$_3$
**Synthesis of trans-4-hydroxy-L-proline ethyl ester·HCl (119)**

trans-4-Hydroxy-L-proline (115) (15.717 g, 119.85 mmol) was suspended in EtOH (abs., 150 mL) and the resulting solution was cooled down by an ice-H₂O bath. The heterogeneous mixture was carefully added SOCl₂ (13 mL, 178.22 mmol) via an addition funnel over 20 min, in which gas evolution was observed (SO₂). The reaction mixture was brought to reflux where it was maintained for 3 hours affording a clear and colourless solution. The crude reaction mixture was cooled down by an ice-H₂O bath, which caused the product to precipitate. The crystals were collected by vacuum-filtration of the heterogeneous mixture through a Büchner funnel. Additional product was obtained by first removing half of the EtOH of the mother-liquor under reduced pressure followed by the addition of ice-cooled Et₂O (50 mL). The crystals were obtained by vacuum-filtration of the heterogeneous mixture through a Büchner funnel. The crystals were dried under open atmosphere for 24 hours (22.926 g, 98%).

![Chemical Structure](image)

**¹H-NMR (400 MHz, Methanol-d₄)** δ = 4.65 – 4.51 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.48 – 3.37 (m, 1H), 3.34 – 3.27 (m, 2H), 2.52 – 2.34 (m, 1H), 2.19 (ddd, J = 14.1, 10.7, 4.1 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H).

**¹³C-NMR (101 MHz, Methanol-d₄)** δ = 170.22, 70.63, 64.02, 59.51, 55.04, 38.68, 14.30.

**MS (ESI⁺ m/z):** 160 [M-H]⁺

**MS (EI⁺, m/z):** Not obtained

**HRMS (ESI⁺, m/z):** for C₇H₁₄O₃⁺[M-H]⁺, observed 160.0967, calculated 160.0968
1H- and 13C-NMR spectrum of compound 119 recorded in MeOD-d₃
Preparation of the Grignard reagent, PhMgBr

An oven-dried 3-necked RBF fitted with a water condenser and CaCl₂ drying tube, was loaded with Mg-twinings (13.000 g, 536 mmol), dried Et₂O (30 mL) and degassed with N₂-gass. An addition funnel containing a solution of PhBr (65 mL, 536 mmol) in dried Et₂O (330 mL) was attached to the RBF. The reaction was initiated by adding a small portion of the PhBr-solution into the RBF (approximately 20 mL). After a few minutes the reaction started as evidenced by the solution changing colour (colourless to dark red colour) and by the observation of boiling Et₂O, caused by the exothermic reaction. The remaining PhBr-solution was added dropwise into the refluxing solution to maintain a steady reflux (1.5 hours). The resulting solution was stirred for an additional 30 min then diluted with dried Et₂O (70 mL). The entire PhMgBr-solution was used immediately in the subsequent reaction to afford compound 120.

Synthesis of compound 120

The freshly prepared Grignard reagent was cooled down to room temperature, and solid trans-4-hydroxy-L-prolineate×HCl (15.002 g, 76.6 mmol) was added in small portions. The resulting solution was diluted with dried Et₂O (70 mL) and left to stir for approximately 14 hours, which afforded a light brown and heterogeneous mixture. The excess Grignard reagent was quenched by a careful addition of water (cooled to approx. 0 °C) to the crude reaction mixture that was cooled down by an ice-H₂O bath. Aqueous HCl (1 M) was added until a biphasic solution was formed (Clear organic phase, slurry of the aqueous phase). The phases were separated by decantation of the top ether layer and the water phase was washed once, using Et₂O (120 mL). The water phase was then neutralised by the addition of solid NaHCO₃, which promoted additional precipitation. The slurry was filtrated through a Büchner funnel, and washed using water (500 mL) then Et₂O (300 mL). The crude was then dissolved in MeOH (120 mL) and TFA (6 mL), and then vacuum filtered. The solution was TFA salt was removed aqueous NaOH solution which promoted precipitation of the product. The product was collected on a Büchner funnel and washed using MeOH (100 mL), water (100 mL) and THF (200 mL). The filter cake was thoroughly dried in a desiccator containing a drying agent. This afforded the pure compound (9.306 g, 45% yield)
\(^{1}H\)-NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 7.64 – 7.57 \text{ (m, 2H)}, 7.46 \text{ (d, } J = 8.5 \text{ Hz, 2H)}, 7.34 – 7.22 \text{ (m, 4H)}, 7.22 – 7.12 \text{ (m, 2H)}, 5.78 \text{ (Broad s, 2H)}, 4.86 \text{ (s, 1H)}, 4.68 \text{ (dd, } J = 9.7, 6.8 \text{ Hz, 1H)}, 4.31 – 4.06 \text{ (m, 1H)}, 3.33 \text{ (s, 1H)}, 3.04 \text{ (dd, } J = 11.3, 4.3 \text{ Hz, 1H)}, 2.95 – 2.72 \text{ (m, 1H)}, 1.76 \text{ (ddd, } J = 14.4, 9.8, 5.1 \text{ Hz, 1H)}, 1.38 \text{ (dd, } J = 13.1, 6.8 \text{ Hz, 1H}).

\(^{13}C\)-NMR (101 MHz, DMSO-\(d_6\)) \(\delta = 146.71, 145.92, 127.91, 127.84, 126.42, 126.25, 125.30, 77.11, 70.03, 63.24, 54.89, 36.01\).

**MS (ESI+, m/z):** 270 [M-H]^+

MS (EI+, m/z) Not observed [M]^+, 182, 86

**HRMS (ESI+, M/Z):** for C\(_{14}\)H\(_{25}\)O\(_4\)P\(_1\)^+, [M-H]^+, observed 270.1488, calculated 270.1489
$^1$H- and $^{13}$C-NMR spectrum of compound 120 recorded in DMSO-d$_6$.
Synthesis of compound 111

Dibromo m-xylene 118 (1.280 g, 4.8 mmol) and trans-4-hydroxydiphenyl-l-prolinol 120 (2.8073 g, 10.42 mmol) were dissolved in dried DMF (55 mL). The resulting reaction mixture was stirred for 24 hours at room temperature. The crude reaction mixture was added Et₂O (100 mL) and aqueous NaHCO₃ (Sat., 50 mL, CO₂ (g) observed). The phases were separated and the aqueous phase was extracted once with Et₂O (40 mL). The combined organic phase was washed with aqueous NaCl (Sat., 7 × 30 mL), then dried over anhydrous Na₂SO₄, filtered and then concentrated under reduced pressure. The crude product mixture was recrystallized from EtOH affording the product (2.52 g, 83% yield).

\[ \text{[1H-NMR (600 MHz, Chloroform-d)} ] \delta = 7.77 \text{ (d, } J = 8.2 \text{ Hz, 2H, Ar-H), 7.59 \text{ (d, } J = 8.1 \text{ Hz, 2H, Ar-H), 7.31 - 7.25 \text{ (m, 8H, Ar-H), 7.18 - 7.12 \text{ (m, 2H, Ar-H), 7.11 - 7.08 \text{ (m, 2H, Ar-H), 7.08 - 7.05 \text{ (m, 1H, H_C), 6.83 \text{ (d, } J = 7.5 \text{ Hz, 2H, H_B}, 6.71 \text{ (s, 1H, H_A), 4.43 - 4.34 \text{ (m, 2H, possibly dd, } J = 7.82 \text{ Hz, H_d), 4.29 - 4.21 \text{ (m, 2H, H_p), 3.25 and 3.23}\text{ (ABq, 4H, } J_{AB} = 12.77 \text{ Hz, H_d), 3.02 \text{ (dd, } J = 11.2, 4.5 \text{ Hz, 2H, H_d), 2.47 \text{ (dd, } J = 11.2, 3.2 \text{ Hz, 2H, H_E), 1.95 - 1.78 \text{ (m, 4H, H_G).}}] \]

\[ \text{[13C-NMR (151 MHz, Chloroform-d)} ] \delta = 147.70 \text{ (Ar-C), 145.99 \text{ (Ar-C), 139.47 \text{ (C_A), 128.64 \text{ (C_A), 128.28 \text{ (Ar-C), 128.11 \text{ (Ar-C), 127.19 \text{ (C_A), 126.58 \text{ (Ar-C), 126.40 \text{ (Ar-C), 125.66 \text{ (Ar-C), 125.41 \text{ (Ar-C, 70.92 \text{ (C_E), 70.40 \text{ (C_A), 62.08 \text{ (C_E), 61.07 \text{ (C_D), 38.76 \text{ (C_G).}}] \]

MS (ESI+ m/z): 641 [M-H]+, 321 [M-2×H]+

MS (EI+, m/z) Not observed [M]+, 182, 105, 77

HRMS (ESI+, m/z): for C₄₂H₄₄N₂O₄ [M-H]+, observed 641.3364, calculated 641.3374
$^1$H- and $^{13}$C-NMR spectrum of compound 111 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 111 recorded in CDCl₃
HMBC (\(^1\)H detected) and COLOC (\(^{13}\)C detected) NMR spectrum of compound 111 recorded in CDCl\(_3\)
HETCOR (\(^{13}\text{C}\) detected) NMR spectrum of compound 111 recorded in CDCl\(_3\)
The protocol used for the attempted synthesis of crown ether 112

Compound 111 was dissolved in [solvent] (0.01 or 0.5 M). The resulting solution was added a [base] (3 eq.) and was left stirring for 1 hour. A solution of the [electrophile] (1 eq.) in the [solvent] was added dropwise to the reaction mixture. The resulting reaction mixture was heated to reflux where it was maintained for [time].

The crude reaction mixture was quenched with water, and then extracted with EtOAc. The crude reaction mixture was analysed by TLC and 1H-NMR analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp. [°C]</th>
<th>X</th>
<th>Solvent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KO-t-bu</td>
<td>20</td>
<td>O-Ts</td>
<td>THF</td>
<td>1 day</td>
</tr>
<tr>
<td>2</td>
<td>KO-t-bu</td>
<td>80</td>
<td>O-Ts</td>
<td>DMF</td>
<td>2 days</td>
</tr>
<tr>
<td>3</td>
<td>K-HMDS</td>
<td>80</td>
<td>O-Ts</td>
<td>THF</td>
<td>2 days</td>
</tr>
<tr>
<td>4[a]</td>
<td>NaH</td>
<td>80</td>
<td>Cl</td>
<td>THF</td>
<td>2 days</td>
</tr>
<tr>
<td>5[b]</td>
<td>NaH</td>
<td>80</td>
<td>Cl</td>
<td>DMF</td>
<td>2 days</td>
</tr>
<tr>
<td>6[b]</td>
<td>NaH</td>
<td>80</td>
<td>O-Ts</td>
<td>PhMe</td>
<td>3 days</td>
</tr>
</tbody>
</table>

[a] TBAI as additive (1 eq.) [b] 0.5 M dilution
THREE-STEP SYNTHESIS OF THE IMINOPHOSPHONATE 133

Step 1 - Synthesis of compound 133

An round–bottom flask (RBF) fitted with a Dean-Stark trap fitted with a condenser and CaCl₂ drying tube, was added the α-aminodiphenylmethane (6.726 g, 36.754 mmol), PhMe (60 mL) and then aqueous formaldehyde (37 wt%, 4 mL, 53.773 mmol) forming a cloudy biphasic solution. The reaction mixture was heated to reflux where it was maintained for 3 hours until no more water was collected in the Dean-Stark trap. The crude product solution was cooled down on an ice-H₂O bath which caused the product to precipitate. The product was collected by filtration of the heterogeneous mixture through a Büchner funnel. Additional product was obtained by concentrating the mother liquor under reduced pressure and followed by recrystallisation of the resulting solid with a minimal amount of boiling PhMe. This afforded the product as a white crystalline compound. Both batches were collected (6.575 g, 92% yield)

\[ \text{1H-NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.32 – 7.23 (m, 12H, Ar-H), 7.12 – 6.97 (m, 18H Ar-H), 4.70 (s, 3H, HB), 3.31 (br s, 6H, HA). \]

\[ \text{13C-NMR (101 MHz, Chloroform-}d\text{)} \delta = 142.31(C_c), 128.19 (Ar-C), 127.49 (Ar-C), 126.57 (Ar-C), 71.79 (C_b), 69.92 (C_a). \]

\[ \text{MS (ESI+ m/z): 608 [M-Na]+} \]

\[ \text{MS (EI+, m/z): Not observed [M]+} \]

\[ \text{HRMS (ESI+, m/z): for the trimer: C_{42}H_{36}N_3Na, [M-Na]+, observed 608.3035, calculated 608.3036,} \]

\[ \text{for the monomer: C}_{14}H_{14}N, [M-H]+, \text{observed 196.1121, calculated 196.1121} \]
$^1$H- and $^{13}$C-NMR spectrum of compound 133 recorded in CDCl$_3$
**Step 2 - Synthesis of aminophosphonates 134**

The imine 133 (0.683 g, 1.16 mmol) was dissolved in PhMe (8 mL) and then added diethyl phosphite (0.500 g, 3.62 mmol) forming a clear and colourless homogeneous solution. The reaction mixture was heated to reflux where it was maintained for 5 hours. The crude product mixture was concentrated under reduced pressure to afford the product (1.039 g, 89% yield).

![Chemical Structure](image)

**1H-NMR (400 MHz, Chloroform-d)** \(\delta = 7.40 - 7.34 \text{ (m, 5H, Ar-H), 7.31 - 7.24 \text{ (m, 4H, Ar-H), 7.23 - 7.15 \text{ (m, 3H, Ar-H), 4.86 \text{ (s, 1H, H}\_e\text{), 4.21 - 4.05 \text{ (m, 4H, H}\_b\text{), 2.92 \text{ (d, J = 13.0 Hz, 2H, Hc), 1.32 \text{ (t, J = 7.1 Hz, 6H, H}_a\text{).}}\)

**13C-NMR (101 MHz, Chloroform-d)** \(\delta = 142.92 \text{ (C}\_f\text{), 128.52 \text{ (Ar-C), 127.28 \text{ (Ar-C), 127.26 \text{ (Ar-C), 68.21 \text{ (d, J = 17.0 Hz, C}_e\text{), 62.11 \text{ (d, J = 6.5 Hz, C}_b\text{), 43.28 \text{ (d, J = 153.8 Hz, C}_c\text{), 16.49 \text{ (d, J = 5.9 Hz, C}_a\text{).}}\)

**MS (ESI+, m/z):** 334 [M-H]+, 356 [M-Na]+

**MS (EI+, m/z):** Not found [M]+

**HRMS (ESI+, m/z):** for C\textsubscript{18}H\textsubscript{25}N\textsubscript{1}O\textsubscript{3}P\textsubscript{1}, [M-H]+, observed 334.1569, calculated 334.1567
$^1$H- and $^{13}$C-NMR spectrum of compound 134 recorded in CDCl$_3$
Step 3 - Synthesis of compound 104

The aminophosphonate 134 (0.826 g, 2.47 mmol), PhMe (7 mL, stored over mol. sieves 4 Å) and mol. sieves (1.002 g, 4 Å, activated) was added to an oven dried RBF. The resulting solution was degassed with Ar (g) before solid DDQ (0.696 g, 3.066 mmol, 1.2 eq.) was added in one portion, immediately affording a dark red solution. The reaction mixture was heated to 60 °C where it was maintained for 4 hours. During this period the solution turned light orange and a precipitate was observed. The conversion of the reaction was obtained from analysis of the crude reaction mixture by $^{31}$P- and $^1$H-NMR spectroscopy.

The crude reaction mixture was cooled down to room temperature, filtered through a celite pad (Celite 503, $\varnothing \times h$, 2.5 × 4 cm). The celite pad was washed with Et$_2$O (40 mL) and before the product mixture was concentrated under reduced pressure to afford a dark red residue.

The crude product mixture was purified by column chromatography on silica gel ($\varnothing \times h$, 2.5 × 10 cm). The column was eluted with the following program, CH$_2$Cl$_2$ (20 mL/min, 5 min), then CH$_2$Cl$_2$:MeOH (100:0, 20 mL/min, to 95:5 over 10 min) then CH$_2$Cl$_2$:MeOH (95:5, 20 mL/min until the product is obtained). The product was afforded as a slightly red oil (0.570 g, 70% yield)

![Image of compound 104]

$^1$H-NMR (400 MHz, Chloroform-d) $\delta$ 7.64 – 7.58 (m, 2H, Ar-H), 7.48 – 7.33 (m, 4H, Ar-H), 7.33 – 7.26 (m, 2H, Ar-H), 7.22 – 7.16 (m, 2H, Ar-H), 4.23 – 4.09 (m, 4H, H$_B$), 3.91 (d, $J$ = 17.5 Hz, 2H, H$_C$), 1.31 (t, $J$ = 7.1 Hz, 6H, H$_A$).

$^{13}$C-NMR (101 MHz, Chloroform-d) $\delta$ 171.77 (d, $J$ = 18.4 Hz, C$_E$), 139.21 (d, $J$ = 3.4 Hz, C$_D$), 135.45 (d, $J$ = 2.4 Hz, Ar-C), 130.29 (Ar-C), 128.73 (Ar-C), 128.60 (Ar-C), 127.96 (Ar-C), 127.90 (d, $J$ = 1.5 Hz, Ar-C), 62.30 (d, $J$ = 6.6 Hz, C$_B$), 51.43 (d, $J$ = 160.0 Hz, C$_C$), 16.45 (d, $J$ = 5.9 Hz, C$_A$).

MS (ESI+ m/z): 332 [M-H]+, 354 [M-Na]+

MS (EI+, m/z): Not found [M]+. Signal found for breakdown product benzophenone, 182

HRMS (ESI+, m/z): for C$_{18}$H$_{22}$N$_2$O$_3$P$_1$Na$_1$, [M-Na]+, observed 354.1228, calculated 354.1230
$^{1}$H- and $^{13}$C-NMR spectrum of compound 104 recorded in CDCl$_3$
General procedure for asymmetric alkylation reactions

A reaction vial was loaded with the imonophosphoglycine 104 (60 mg, 0.18 mmol), [PT-catalyst] (5 or 20 mol%), [solvent] (1 mL), and KOH (50 wt% aq., 0.3 mL). The resulting solution was placed under sufficient stirring (600-800 rpm) and brought to the temperature in which the asymmetric alkylation reaction was to take place (-15, 0 or 20 °C). Benzyl bromide (0.1 mL, 0.84 mmol) was then added with a syringe and the solution was left to stir for the required amount of time (Table 2.3, see the next page).

The conversion of the experiment was obtained by 1H- or 31P-NMR analysis of small portion of the crude reaction mixture. The reaction mixture was diluted with H2O (5 mL), and EtOAc (x mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phase was dried over anhydrous Na2SO4, filtered and then concentrated under reduced pressure.

The crude product mixture was purified by column chromatography on silica gel (φ × h, 2.5 × 8 cm). The column was eluted with the following program, CH2Cl2 (20 mL/min, 3 min), then CH2Cl2:MeOH (100:0, 20 mL/min, to 95:5 over 15 min) then CH2Cl2:MeOH (95:5, 20 mL/min until the product was obtained).

The enantiomeric excess was measured from HPLC analysis using a chiral AS(-H) column (1 ml/min, i-Hex:i-PrOH/95:5, Rf=7.9 and 16.0 min)

\[\text{1H-NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.61 – 7.55 (m, 2H), 7.46 – 7.25 (m, 4H), 7.24 – 7.14 (m, 3H), 7.04 – 6.98 (m, 2H), 4.31 – 4.09 (m, 4H), 4.04 – 3.95 (m, 1H), 3.28 – 3.22 (m, 2H), 1.42 – 1.31 (m, 7H).

\[\text{13C-NMR (101 MHz, Chloroform-}d\text{)} \delta = 170.92 (d, J=16.8, Hz), 139.35 (d, J=3.5), 138.32 (d, J=17.5), 135.58 (d, J=2.5), 130.10 , 129.93 , 128.64 (d, J=1.2), 128.14 , 128.08 , 127.93 , 127.91 , 127.76 (d, J=1.7), 126.24 , 63.59 (d, J=158.2), 62.68 (d, J=7.1), 62.52 (d, J=6.8), 37.37 (d), 16.66 – 16.48 (m).

MS (ESI+ m/z): 444 [M-Na]+

MS (EI+, m/z): [M]+ not found, 330, 284, 256, 165.

HRMS (ESI+, m/z): for C25H28N1O3P1Na1, [M-Na]+, observed 444.1699, calculated 444.1699
Table 2.3 – Evaluation of chiral PT-catalysts and their performance in the alkylation reaction of phosphoglycine Schiff base 104.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp. [°C]</th>
<th>Conv. [%]a</th>
<th>% ee²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAB (20 mol%)</td>
<td>CHCl₃-PhMe (30:70)</td>
<td>5h</td>
<td>20</td>
<td>&gt;95</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>137/141 (5 mol%)</td>
<td>CHCl₃-PhMe (30:70)</td>
<td>5h</td>
<td>-10</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>137/141 (20 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>7 days</td>
<td>20</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>138 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>48h</td>
<td>0</td>
<td>&gt;95</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>138 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>48h</td>
<td>-15</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>138 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>48h</td>
<td>20</td>
<td>&gt;95</td>
<td>8</td>
</tr>
<tr>
<td>7⁷</td>
<td>80 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>24h</td>
<td>0</td>
<td>16</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>80 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>24h</td>
<td>20</td>
<td>18</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>80 (20 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>7 days</td>
<td>20</td>
<td>20</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>136 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>24h</td>
<td>20</td>
<td>30</td>
<td>0</td>
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<tr>
<td>11</td>
<td>136 (5 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>24h</td>
<td>0</td>
<td>Trace</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>143 (20 mol%)</td>
<td>CH₂Cl₂:PhMe (20:80)</td>
<td>3 days</td>
<td>20</td>
<td>&gt;95</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Measured by ¹H- and ³¹P-NMR of the crude reaction mixtures. [b] Measured from HPLC analysis of the purified material. [c] CsOH (5 eq.) was used as the base.
Figure SI-5 – The catalysts used for the asymmetric alkylation reaction.
SPECTROSCOPIC DATA FOR THE SYNTHESISED PT-CATALYSTS

Spectroscopic data for compound 137

\[ \text{\textsuperscript{1}H-NMR (600 MHz, DMSO-\textit{d\textsubscript{6}}) } \delta \ 9.00 (d, J = 4.4 Hz, 2H), 8.36 (d, J = 8.5 Hz, 2H), 8.14 (s, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 7.89 - 7.83 (m, 5H), 7.80 - 7.72 (m, 3H), 6.76 (d, J = 4.3 Hz, 2H), 6.62 - 6.57 (m, 2H), 5.70 (ddd, J = 17.1, 10.6, 6.4 Hz, 2H), 5.31 (d, J = 12.5 Hz, 2H), 5.20 (s, 2H), 5.19 - 5.16 (m, 2H), 4.96 (d, J = 10.5 Hz, 2H), 4.36 - 4.27 (m, 2H), 4.01 - 3.93 (m, 2H), 3.85 - 3.78 (m, 2H), 3.62 - 3.54 (m, 2H), 3.40 - 3.36 (m, 2H, overlapping with water in the d\textsubscript{6}-DMSO), 2.78 - 2.73 (m, 2H), 2.17 - 2.10 (m, 2H), 2.09 - 1.99 (m, 4H), 1.88 - 1.80 (m, 2H), 1.35 - 1.26 (m, 2H).

\[ \text{\textsuperscript{13}C-NMR (151 MHz, DMSO-\textit{d\textsubscript{6}}) } \delta 150.17, 147.61, 145.17, 138.84, 138.13, 135.26, 129.89, 129.52, 129.45, 128.61, 127.29, 124.29, 123.64, 120.13, 116.33, 67.69, 64.20, 62.26, 59.18, 50.59, 36.86, 25.83, 24.19, 21.06.

\[ \text{MS (ESI\textsuperscript{+} m/z): } 346 \ [M, \pm 2\times \text{Br}]^{2+}

\[ \text{MS (EI\textsuperscript{+}, m/z): } \text{Not recorded}

\[ \text{HRMS (ESI\textsuperscript{+}, m/z): } \text{for C}_{46}\text{H}_{52}\text{N}_{4}\text{O}_{2}\text{^{2+}}, [M, \pm 2\times \text{Br}]^{2+} \text{ observed } 346.2031, \text{ calculated } 346.2040

135
$^1$H- and $^{13}$C-NMR spectrum of compound 137 recorded in DMSO-d$_6$. 
Spectroscopic data for compound 138

1H-NMR (600 MHz, DMSO-\textit{d}_6) \( \delta \) 9.02 (d, \( J = 4.4 \) Hz, 2H), 8.32 (d, \( J = 8.5 \) Hz, 2H), 8.15 (d, \( J = 8.3 \) Hz, 2H), 8.10 (s, 1H), 7.95 (d, \( J = 7.7 \) Hz, 2H), 7.90 – 7.86 (m, 2H), 7.82 – 7.76 (m, 3H), 7.72 (d, \( J = 4.4 \) Hz, 2H), 6.21 – 6.14 (m, 2H), 5.73 (ddd, \( J = 17.2, 10.5, 6.6 \) Hz, 2H), 5.51 – 5.46 (m, 2H), 5.34 (d, \( J = 12.4 \) Hz, 2H), 5.31 – 5.26 (m, 2H), 5.16 (d, \( J = 17.3 \) Hz, 2H), 5.10 (d, \( J = 12.3 \) Hz, 2H), 4.99 (d, \( J = 10.5 \) Hz, 2H), 4.44 (dd, \( J = 12.6, 5.2 \) Hz, 2H), 4.09 – 3.99 (m, 6H), 3.79 – 3.73 (m, 2H), 3.67 – 3.60 (m, 2H), 3.47 – 3.38 (m, 2H), 2.81 – 2.75 (m, 2H), 2.36 – 2.29 (m, 2H), 2.16 – 2.08 (m, 2H), 2.08 – 2.03 (m, 2H), 1.92 – 1.83 (m, 2H), 1.54 – 1.44 (m, 2H).

13C-NMR (151 MHz, DMSO-\textit{d}_6) \( \delta \) 150.26, 148.03, 141.26, 138.82, 137.89, 135.54, 134.25, 129.99, 129.68, 129.58, 128.44, 127.52, 125.01, 123.61, 119.63, 117.60, 116.54, 71.89, 67.93, 63.04, 58.89, 50.86, 36.84, 25.95, 24.20, 20.79.

MS (ESI+ m/z): 386 [M, +2×Br]^2^+

MS (EI+, m/z): Not recorded

HRMS (ESI+, m/z): for C\(_{52}\)H\(_{60}\)N\(_4\)O\(_2\)^2^+, [M, +2×Br]^2^+; observed 386.2344, calculated 386.2353
$^1$H- and $^{13}$C-NMR spectrum of compound 138 recorded in DMSO-d$_6$
Spectroscopic data for compound 135

**$^1$H-NMR (500 MHz, Chloroform-$d$)** $\delta$ 8.83 (d, $J$ = 4.5 Hz, 1H), 8.33 (d, $J$ = 8.4 Hz, 1H), 8.09 (d, $J$ = 8.4 Hz, 1H), 7.96 – 7.81 (m, 1H), 7.73 – 7.63 (m, 1H), 7.63 – 7.56 (m, 1H), 7.54 – 7.40 (m, 2H), 7.20 – 7.06 (m, 2H), 6.87 (d, $J$ = 5.9 Hz, 1H), 5.73 (ddd, $J$ = 17.5, 10.3, 7.4 Hz, 1H), 4.97 – 4.87 (m, 2H), 3.51 – 3.34 (m, 1H), 3.32 – 3.18 (m, 1H), 3.05 (dd, $J$ = 13.8, 10.1 Hz, 1H), 2.72 – 2.60 (m, 2H), 2.30 – 2.22 (m, 1H), 1.90 – 1.81 (m, 2H), 1.81 – 1.71 (m, 2H), 1.61 – 1.42 (m, 1H).

**$^{13}$C-NMR (126 MHz, Chloroform-$d$)** $\delta$ 163.26 (d, $J$ = 3.7 Hz), 161.82 (d, $J$ = 259.9 Hz), 149.79, 148.39, 144.69, 141.02, 134.98 (d, $J$ = 9.1 Hz), 132.29, 130.26, 129.13, 126.92, 125.52, 124.10 (d, $J$ = 3.7 Hz), 123.20, 118.2, 117.74 (d, $J$ = 10.0 Hz), 116.97 (d, $J$ = 22.6 Hz), 114.63, 74.75, 59.59, 56.40, 42.47, 39.23, 27.39, 27.06, 23.44.

**MS (ESI+ m/z):** 403 [M+Cl]$^+$

**MS (EI+, m/z):** Not recorded

**HRMS (ESI+, m/z):** for C$_{26}$H$_{28}$F$_1$N$_2$O$_1^+$, [M+Cl]$^+$, observed 403.2181, calculated 403.2180
$^1$H- and $^{13}$C-NMR spectrum of compound 135 recorded in DMSO-d$_6$. 
Spectroscopic data for compound 136

\[ \text{H-NMR (600 MHz, Acetone-} d_6) \delta = 8.98 \text{ (d, } J = 4.4 \text{ Hz, 1H), 8.93 (dd, } J = 8.19, 1.31 \text{ Hz, 1H), 8.65 – 8.59 (m, 1H), 8.09 (d, } J = 7.9, 1H), 7.86 – 7.73 (m, 3H), 7.67 – 7.56 (m, 1H), 7.40 – 7.25 (m, 2H), 6.51 (s, 1H), 6.37 (d, } J = 12.2 \text{ Hz, 1H), 6.29 – 6.19 (m, 1H), 5.77 (ddd, } J = 17.0, 10.7, 6.0 \text{ Hz, 1H), 5.59 – 5.47 (m, 2H), 5.36 – 5.31 (m, 1H), 5.23 (d, } J = 12.2 \text{ Hz, 1H), 5.06 – 4.99 (m, 1H), 4.91 (d, } J = 10.7 \text{ Hz, 1H), 4.73 – 4.62 (m, 1H), 4.53 – 4.44 (m, 2H), 4.31 – 4.21 (m, 1H), 3.54 – 3.46 (m, 1H), 3.43 – 3.36 (m, 1H), 2.81 (s, 1H), 2.34 – 2.27 (m, 1H), 2.28 – 2.19 (m, 1H), 2.17 – 2.11 (m, 1H), 2.10 – 1.96 (m, 1H), 1.45 – 1.37 (m, 1H). \]

\[ \text{C-NMR (151 MHz, Acetone-} d_6) \delta 163.31 \text{ (d, } J = 248.5 \text{ Hz), 150.72, 149.53, 141.61, 138.42, 137.64, 134.62, 133.75 (d, } J = 8.8 \text{ Hz), 130.72, 130.28, 128.97, 126.39, 126.19, 125.68 (d, } J = 3.3 \text{ Hz), 120.61, 118.64, 117.56, 116.92 (d, } J = 13.3 \text{ Hz), 116.62 (d, } J = 22.3 \text{ Hz), 74.88, 70.84, 67.37, 59.83, 56.02, 52.66, 38.50, 27.52, 25.70, 23.09. \]

\[ \text{MS (ESI+ m/z): 443 [M+Br]^+} \]

\[ \text{MS (EI+, m/z): Not recorded} \]

\[ \text{HRMS (ESI+, m/z): for C}_{29}\text{H}_{32}\text{F}_{1}\text{N}_{2}\text{O}_{1}^+, [M+Br]^+, \text{ observed 443.2492, calculated 443.2180} \]
$^1$H- and $^{13}$C-NMR spectrum of compound 136 recorded in acetone-d$_6$
Spectroscopic data for compound 79

\[
\begin{align*}
{^1}H-NMR \ (600 \text{ MHz, DMSO-}d_6) \ & \delta = 9.04 \ (d, \ J = 4.4 \text{ Hz, 1H}), 8.96 \ (s, 1H), 8.96 - 8.92 \ (m, 2H), \\
& 8.68 \ (d, \ J = 8.3 \text{ Hz, 1H}), 8.27 \ (d, \ J = 3.5 \text{ Hz, 1H}), 8.26 \ (d, \ J = 3.6 \text{ Hz, 1H}), 8.16 \ (d, \ J = 8.3 \text{ Hz, 1H}), \\
& 7.94 \ (d, \ J = 4.4 \text{ Hz, 1H}), 7.92 - 7.87 \ (m, 1H), 7.85 - 7.81 \ (m, 1H), 7.79 - 7.74 \ (m, 2H), \\
& 7.70 - 7.63 \ (m, 3H), 7.03 \ (d, \ J = 4.1 \text{ Hz, 1H}), 6.52 \ (d, \ J = 14.1 \text{ Hz, 1H}), 5.91 \ (d, \ J = 14.0 \text{ Hz, 1H}), \\
& 5.70 \ (ddd, \ J = 17.4, 10.5, 7.0 \text{ Hz, 1H}), 5.01 \ (d, \ J = 17.3 \text{ Hz, 1H}), 4.95 \ (d, \ J = 10.5 \text{ Hz, 1H}), \\
& 4.65 - 4.53 \ (m, 2H), 3.94 - 3.84 \ (m, 1H), 3.07 - 2.99 \ (m, 1H), 2.82 - 2.71 \ (m, 1H), 2.44 - 2.35 \ (m, 1H), 2.25 - 2.18 \ (m, 1H), 2.12 - 2.01 \ (m, 1H), 1.90 - 1.83 \ (m, 1H), 1.59 - 1.49 \ (m, 1H), \\
& 1.44 - 1.34 \ (m, 1H).
\end{align*}
\]

\[
\begin{align*}
{^{13}}C-NMR \ (151 \text{ MHz, DMSO-}d_6) \ & \delta = 150.16, 147.73, 145.94, 138.04, 133.12, 133.07, 131.91, \\
& 131.11, 131.04, 129.76, 129.55, 129.44, 129.40, 127.64, 127.47, 127.11, 125.43, 125.36, \\
& 124.62, 124.34, 120.35, 119.23, 116.52, 68.36, 64.39, 60.10, 55.46, 51.29, 37.45, 25.31, \\
& 24.61, 21.25.
\end{align*}
\]

\[
\begin{align*}
\text{MS \ (ESI}^+ \ m/z) & : \ 485 \ [M^+Cl]^+ \\
\text{MS \ (EI}^+, \ m/z) & : \ \text{Not recorded} \\
\text{HRMS (ESI}^+, \ m/z) & : \ \text{for C}_{34}H_{33}N_2O_1^+, \ [M^+Cl]^+, \ \text{observed 485.2588, calculated 485.2587}
\end{align*}
\]
\(^1\)H and \(^{13}\)C-NMR spectrum of compound 79 recorded in DMSO-d\(_6\).
Spectroscopic data for compound 80

\[ \text{1H-NMR (600 MHz, DMSO-}d_6) \delta = 9.08 \text{ (d, } J = 4.4 \text{ Hz, 1H), 9.01 \text{ (s, 1H), 8.91 \text{ (d, } J = 9.1 \text{ Hz, 1H), 8.56 \text{ (d, } J = 8.2 \text{ Hz, 1H), 8.48 \text{ (d, } J = 9.0 \text{ Hz, 1H), 8.33 – 8.27 \text{ (m, 2H), 8.20 \text{ (d, } J = 8.2 \text{ Hz, 1H), 7.93 \text{ (app. } * \text{ t, } J = 7.6 \text{ Hz, 1H), 7.88 \text{ (app. } * \text{ t, } J = 7.3 \text{ Hz, 1H), 7.82 \text{ (d, } J = 4.5 \text{ Hz, 1H), 7.81 – 7.78 \text{ (m, 1H), 7.77 – 7.73 \text{ (m, 1H), 7.70 – 7.65 \text{ (m, 2H), 7.01 \text{ (s, 1H), 6.46 \text{ (d, } J = 13.9 \text{ Hz, 1H), 6.36 – 6.28 \text{ (m, 1H), 5.81 \text{ (d, } J = 14.1 \text{ Hz, 1H), 5.69 \text{ (dd, } J = 17.4, 10.5, 7.0 \text{ Hz, 1H), 5.62 \text{ (dd, } J = 17.3, 1.5 \text{ Hz, 2H), 5.51 – 5.44 \text{ (m, 2H), 5.04 – 4.93 \text{ (m, 2H), 4.66 – 4.53 \text{ (m, 3H), 4.31 – 4.24 \text{ (m, 1H), 4.22 \text{ (dd, } J = 13.1, 4.7 \text{ Hz, 1H), 3.92 – 3.83 \text{ (m, 1H), 3.18 – 3.08 \text{ (m, 1H), 2.85 – 2.76 \text{ (m, 1H), 2.45 – 2.35 \text{ (m, 1H), 2.13 – 1.97 \text{ (m, 0H), 1.93 – 1.89 \text{ (m, 1H), 1.62 – 1.54 \text{ (m, 1H), 1.52 – 1.41 \text{ (m, 1H).}}) \]

\[ \text{13C-NMR (151 MHz, DMSO-}d_6) \delta = 150.72, 148.65, 141.47, 138.37, 134.57, 133.68, 133.35, 132.68, 131.62, 131.58, 130.42, 130.27, 130.24, 130.17, 128.17, 128.03, 127.84, 125.96, 125.91, 125.74, 125.45, 124.83, 124.54, 120.49, 119.19, 117.87, 117.18, 69.79, 68.15, 60.71, 55.97, 51.99, 37.73, 25.70, 25.14, 21.72. \]

\[ \text{MS (ESI}^+ \text{ m/z): 525 [M}+\text{Br}^+ \]

\[ \text{MS (EI}^+, \text{ m/z): Not recorded} \]

\[ \text{HRMS (ESI}^+ \text{, m/z): for C}_{37}\text{H}_{37}\text{N}_2\text{O}_1^+, \text{ [M}+\text{Br}^+, \text{ observed 525.2897, calculated 525.2900} \]
$^1$H and $^{13}$C-NMR spectrum of compound 80 recorded in DMSO-d$_6$
Synthesis and spectroscopic data for compound 143

**Warning!** As brucine is highly toxic, extra measures should be undertaken to ensure a safe handling of the chemical. Lab coat, double long-sleeved nitrile gloves and a respiratory mask was used at all times during the handling of the chemical. Any equipment and glassware that were in contact with the compound where thoroughly washed.

A RBF was loaded with brucine (143) (205 mg, 0.52 mmol) and added MeCN (dried, 3 mL). The heterogeneous brucine-mixture required some heat (using an heating gun) to dissolve. The solution was allowed to cool down to room temperature before adding BnBr (77 μL, 0.65 mmol) in equal portions over 1 min. A precipitate was observed before the BnBr addition was completed. The resulting heterogeneous solution was allowed to stir for 1 hour. Et₂O (3 mL) was added to the heterogeneous solution which was then filtered through sintered glass funnel. The precipitate was washed with additional Et₂O (3 mL). The product was obtained as a colourless precipitate that was dried in open atmosphere for 16 hours, (264 mg, 90% yield).

\[ \text{1H NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.99 – 7.89 (m, 2H), 7.67 (s, 1H), 7.46 – 7.36 (m, 3H), 6.67 (s, 1H), 6.34 – 6.22 (m, 1H), 5.74 (d, J=12.5 Hz, 1H), 5.65 (d, J=12.6 Hz, 1H), 4.90 – 4.82 (m, 1H), 4.66 (s, 1H), 4.35 – 4.22 (m, 2H, overlapping), 4.18 – 4.08 (m, 2H, overlapping), 3.96 (dd, J=14.0, 5.6 Hz, 1H), 3.86 (s, 3H), 3.85 – 3.81 (m, 4H, overlapping), 3.58 – 3.45 (m, 1H), 3.35 – 3.20 (m, 2H), 3.06 (dd, J=17.9, 8.4 Hz, 1H), 2.59 (dd, J=17.9, 2.6 Hz, 1H), 1.88 – 1.69 (m, 2H, overlapping with Acetone-d₆), 1.66 – 1.54 (m, 1H), 1.35 – 1.24 (m, 1H).

\[ \text{13C NMR (101 MHz, Chloroform-}d\text{)} \delta = 168.36, 150.27, 146.73, 136.43, 135.41, 133.71, 132.93, 130.81, 129.32, 128.61, 118.60, 105.34, 100.85, 77.20, 70.78, 68.41, 64.14, 63.80, 59.24, 57.88, 57.05, 56.26, 52.63, 47.09, 41.97, 39.95, 30.07, 25.64.

\[ \text{MS (ESI+ m/z): 485 [M+Br]+} \]

\[ \text{MS (EI+, m/z): Not found [M]+, 394 [100%), 379.} \]

\[ \text{HRMS (ESI+, m/z): for C₃₀H₃₃N₂O₄, [M+Br]+, observed 485.2433, calculated 485.2435} \]
$^1$H and $^{13}$C-NMR spectrum of compound 143 recorded in CDCl$_3$
COSY- and HSQC NMR spectrum of compound 143 recorded in CDCl₃
HMBC NMR spectrum of compound 143 recorded in CDCl₃
SUPPORTING INFORMATION FOR CHAPTER 3

Spectroscopic data and synthetic procedures for the following compounds can be found in the supporting information of the published material.

<table>
<thead>
<tr>
<th>Phosphonates and monosilyl phosphonic acids</th>
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<td><img src="image1.png" alt="Phosphonate 1" /></td>
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<tr>
<td><img src="image2.png" alt="Phosphonate 2" /></td>
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<tr>
<td><img src="image3.png" alt="Phosphonate 3" /></td>
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<th>Activated phosphonates</th>
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<tr>
<td><img src="image5.png" alt="Activated Phosphonate 2" /></td>
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<td><img src="image6.png" alt="Activated Phosphonate 3" /></td>
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<th>Phosphonamidates</th>
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<td><img src="image8.png" alt="Phosphonamide 2" /></td>
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<td><img src="image9.png" alt="Phosphonamide 3" /></td>
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<td><img src="image12.png" alt="Phosphonamide 6" /></td>
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<td><img src="image13.png" alt="Phosphonamide 7" /></td>
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<tr>
<td><img src="image14.png" alt="Phosphonamide 8" /></td>
</tr>
</tbody>
</table>
Isolated by-product from the phosphonamidation reaction

Proposed structure of the by-product 195 obtained from the phosphonamidation of the phosphonic acid 171 with diethylamine.

![Proposed structure of the by-product](image)

$^1$H-NMR (600 MHz, Chloroform-$d$) $\delta$ = 7.28 - 7.22 (m, 4H), 7.22 - 7.17 (m, 1H), 4.14 - 4.04 (m, 2H), 3.64 - 3.51 (m, 2H), 3.49 - 3.37 (m, 2H), 3.21 (d, $J$=20.6, 2H, $H_6$), 1.27 (t, $J$=7.0, 3H), 1.24 - 1.20 (m, 7H), 1.05 (t, $J$=7.1, 3H).

$^{13}$C-NMR (151 MHz, Chloroform-$d$) $\delta$ = 136.66, 132.81 (d, $J$=8.8), 129.97 (d, $J$=6.2), 128.31 (d, $J$=3.1), 126.53, 108.49 (d, $J$=11.6, $C_M$), 61.93 (d, $J$=6.6), 45.38, 42.13, 36.60 (d, $J$=128.5, $C_3$), 29.69, 16.30 (d, $J$=6.2), 14.37, 11.60.

MS (EI+, m/z, rel%): 307 [0.25, M]$^+$, 253, 239, 216, 188 [100%]

HRMS (ESI+, m/z): for C$_{14}$H$_{25}$O$_4$P$_1$, [M-H]$^+$, observed 307.1457, calculated 307.1449
$^1\text{H}$- and $^{13}\text{C}$-NMR spectrum of compound 195 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 195 recorded in CDCl$_3$
HMBC-NMR spectrum of compound 195 recorded in CDCl₃
**Synthesis compound 205**

A single-necked RBF (100 mL) fitted with a condenser was added PhMe (40 mL), BnNH₂ (9.6 mL, 87.9 mmol), acetone (6.8 mL, 92.61 mmol), diethyl phosphite (11.32 mL, 87.87 mmol) and p-TsOH (44.8 mg, 0.26 mmol) in the following order. The resulting solution was stirred at room temperature for 70 minutes, before heating the reaction mixture to 80 °C. The reaction solution was maintained at 80 °C for 24 hours before allowing the solution to cool down to room temperature.

The volatiles were removed under reduced pressure and the crude was re-dissolved in diethyl ether (60 mL) and transferred to a separatory funnel where the organic-phase was washed with H₂O (3 x 30 mL). The washed organic-phase was dried over anhydrous Na₂SO₄, filtered then concentrated under reduced pressure. This afforded the product as green oil (15.93 g, 60.3% yield)

\[ \text{1H-NMR (400 MHz, Chloroform-} d \text{) } \delta \ 7.36 – 7.26 \text{ (m, 4H, Ar-H), 7.23 – 7.18 \text{ (m, 1H, Ar-H), 4.23 – 4.09 \text{ (m, 4H, H₆}, 3.92 – 3.87 \text{ (s, 2H, H₅), 1.35 \text{ (d, } J = 15.3 \text{ Hz 6H, H₃ overlapping with H₄), 1.35 – 1.28 (app.}^* \text{ t, } J = 7.09 \text{ Hz 9H, H₅ overlapping with H₆}} \]

\[ \text{13C-NMR (101 MHz, Chloroform-} d \text{) } \delta \ 141.03 \text{ (C₇), 128.33 (Ar-C), 128.15 (Ar-C), 126.83 (Ar-C), 62.07 (d, } J = 7.6 \text{ Hz, C₆}, 53.56 (d, } J = 145.5 \text{ Hz, C₅), 47.55 (d, } J = 5.0 \text{ Hz, C₄), 23.20 (d, } J = 3.4 \text{ Hz, C₃), 16.64 (d, } J = 5.5 \text{ Hz, C₂}} \]

**MS (ESI⁺ m/z):** 286.1 [M-H]⁺

**MS (EI⁺, m/z, rel %):** 285.1 [0.01, M⁺], 147.1 [27.99], 91.0 [10.00], 65.0 [19.83], 45.0 [5.72], 29.0 [6.15]

**HRMS (ESI⁺, m/z):** for C₁₄H₂₅O₄P₁, [M-H]⁺, observed 286.1571, calculated 286.1572
$^1$H- and $^{13}$C-NMR spectrum of compound 205 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 205 recorded in CDCl₃
HMBC-NMR spectrum of compound 205 recorded in CDCl$_3$
Synthesis of compound 199

A single-necked RBF (250 mL) was added 10 wt% Pd/C (0.8149 g) and was placed under a gentle stream of Ar (g) for 15 min. MeOH (100 mL, degassed for 15 min using Ar (g)) was added carefully to the Pd/c. Compound 205 (3.43 g, 13.33 mmol) was then transferred to the reaction flask using MeOH (50 mL, degassed for 15 min using Ar (g)). The reaction flask was then fitted with a 3-way tap, connected to both a H₂-ballon and to a double-manifold set-up. The system was placed under reduced pressure, using a water-aspirator until boiling of MeOH was observed, and then the system was backfilled using Ar (g). This process was repeated four times. The resulting system was again placed under reduced pressure, using a water-aspirator until boiling of MeOH was observed, then the system was backfilled using H₂ (g) from a balloon. This process was repeated 4 times. The resulting heterogeneous mixture was kept under a balloon pressure of H₂-gass for 20 hours, 40 min.

The 3-way tap was removed and the reaction mixture was degassed using Ar (g) for 15 minutes. The heterogeneous solution was filtered through a Celite-plug (Celite 503, 5 × 5 cm) and subsequently rinsed with additional MeOH. The volatiles were then removed under reduced pressure, affording the product as a colourless oil (2.02 g, 90.5% yield).

In some cases, a black precipitate was observed after the crude had been filtered through the celite-pad. This could be removed via a filtration through a filter paper using CH₂Cl₂ as the solvent.

$^1$H-NMR (400 MHz, Chloroform-d) δ 4.12 (p, J = 7.2 Hz, 4H, H₄), 1.34 – 1.24 (m, 12H, H₃ and H₅, two peaks overlapping. One app.*, triplet at approximately 1.31 ppm J = 6.90 Hz, H₃, and one doublet at approximately 1.27 ppm, J = 15.4 Hz, H₅).

$^{13}$C-NMR (101 MHz, Chloroform-d) δ 62.26 (d, J = 7.7 Hz, C₄), 49.02 (d, J = 147.8 Hz, C₃), 25.02 (d, J = 3.5 Hz, C₂), 16.59 (d, J = 5.5 Hz, C₁).


MS (EI⁺, m/z): 195.1 [0.02, M⁺]

HRMS (ESI⁺, m/z): for C₇H₁₈O₃P₁Na₁, [M-Na]^+, observed 218.0924, calculated 218.0922
$^{1}H$- and $^{13}C$-NMR spectrum of compound 199 recorded in CDCl₃
HSQC-NMR spectrum of compound 199 recorded in CDCl₃
Synthesis of compound 206

A single-necked RBF (25 mL) was added compound 199 (0.4013 g, 2.056 mmol) and H₂O (4 mL), (Boc)₂O (0.6109 g, 2.799 mmol), K₂CO₃ (0.5811 g, 4.205 mmol), and THF (4 mL) were then added in the following order. A sleeve stopper was fixed on the top of the flask and a syringe needle was inserted through the rubber to relieve the system of CO₂(g), originating from the consumption of K₂CO₃ and (Boc)₂O during the reaction. The resulting solution was stirred at room temperature for 22 hours.

The volatiles were removed under reduced pressure and the crude was re-dissolved in CHCl₃ (4 mL), H₂O (2 mL), and aqueous NaCl solution (Sat., 2 mL). The solution was transferred to a separatory funnel were the organic-phase was washed with H₂O (5 × 4 mL). The washed organic-phase was dried over anhydrous Na₂SO₄, filtered and then concentrated under reduced pressure. This afforded a crude consisting of both product and residual (Boc)₂O. The crude was re-dissolved in methanol (4 mL) in a single-necked RBF (25 mL) together with imidazole (0.0565 g, 0.83 mmol) and DMAP (10 mol%). The amount of imidazole added to the reaction is the difference, measured in mole, between the (Boc)₂O and the amine. The resulting solution was stirred at room temperature for 1 hour and later aqueous HCl (1 M, 1 mL) and aqueous NaCl (Sat., 4 mL) was added into the same flask. White precipitation was observed when the acid was added. The solution was stirred for 5 minutes and transferred into a separatory funnel were the product was extracted using CHCl₃ (4 × 4 mL). The combined organic-phase was dried over Na₂SO₄, filtered, and then concentrated under reduced pressure. This afforded the pure product as a clear oil (365 mg, 60.1 %. yield)

\[
{^1}H\text{-NMR (400 MHz, Chloroform-}d{)} \delta \ 4.78 \ (d, \ J = 5.1 \ Hz, \ 1H, \ H_{E}), \ 4.21 - 4.02 \ (m, \ 4H, \ H_{B}), \ 1.53 \ (d, \ J = 15.9 \ Hz, \ 6H, \ H_{C}), \ 1.39 \ (s, \ 9H, \ H_{H}), \ 1.30 \ (t, \ J = 7.0 \ Hz, \ 6H, \ H_{A}).
\]

\[
{^{13}}C\text{-NMR (101 MHz, Chloroform-}d{)} \delta \ 154.38 \ (d, \ J = 11.0 \ Hz, \ C_{f}), \ 79.40 \ (C_{o}), \ 62.72 \ (d, \ J = 7.3 \ Hz, \ C_{i}), \ 51.84 \ (d, \ J = 157.0 \ Hz, \ C_{d}), \ 28.308 \ (C_{ii}), \ 22.82 \ (C_{c}), \ 16.48 \ (d, \ J = 5.5 \ Hz, \ C_{a}).
\]

MS (ESI\textsuperscript{+} m/z): 318.2 [M-Na]\textsuperscript{+}, 613.4 [2×M-Na]\textsuperscript{+}

MS (EI\textsuperscript{+}, m/z, rel\%): 295.1 [0.36, M\textsuperscript{+}], 194.1 [5.10], 158.1 [24.87]

HRMS (ESI\textsuperscript{+}, m/z): for C\textsubscript{12}H\textsubscript{26}N\textsubscript{1}O\textsubscript{5}P\textsubscript{1}Na\textsubscript{1}, [M-Na]\textsuperscript{+}, observed 318.1454, calculated 318.1446
$^1$H- and $^{13}$C-NMR of compound 206 spectrum recorded in CDCl$_3$. 

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COSY- and HSQC-NMR spectrum of compound 206 recorded in CDCl₃
HMBC-NMR spectrum of compound 206 recorded in CDCl₃
**Synthesis of compound 200**

Compound **206** (3.66 g, 12.39 mmol), MeCN (25 mL) and NaI (17.016 g, 113.5 mmol) was added in the following order into a single-necked RBF (50 mL) fitted with a condenser attached to a CaCl₂ drying tube. The resulting heterogeneous mixture was heated to 80 °C where it was maintained for 8 days. A yellow precipitate was observed after 1 hour. During the course of the reaction the solution turned red.

The volatiles were removed under reduced pressure and the crude was dissolved with H₂O (40 mL) and CH₂Cl₂ (40 mL) and transferred into a separatory funnel. The CH₂Cl₂-phase was removed and the pH of the aqueous-phase was adjusted to pH=3 by carefully adding aqueous HCl (35 wt%, 1.5 mL). The aqueous-phase (dark yellow in colour) was extracted with CHCl₃ (4 × 40 mL). The combined organic-phase was dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure. This afforded the product as a slightly yellow oil (2.81 g, 84.89% yield) that precipitated under storage.

Traces of compound **171**, was observed in the CH₂Cl₂-layer.

*CH₂Cl₂ was not a good choice for the extraction of the product for two main reasons. Often it was difficult to obtain a phase-separation due to similar densities of the aqueous- and organic-phase. Additionally, lower yields were obtained when using CH₂Cl₂ instead of CHCl₃.

![Diagram](image)

**1H-NMR (400 MHz, Chloroform-d)** δ 9.66 (s, 1H, H₁), 4.98 (s, 1H, H₂), 4.20 - 2.08 (m, J = 7.1 Hz, 2H, H₃), 1.52 (d, J = 15.0 Hz, 6H, H₄), 1.42 (s, 9H, H₅), 1.31 (app. *t*, J = 7.1 Hz, 3H, H₆).

**13C-NMR (101 MHz, Chloroform-d)** δ 156.21 (d, J = 6.1 Hz, C₆), 81.07 (C₇), 62.43 (d, J = 7.5 Hz, C₈), 51.45 (d, J = 152.0 Hz, C₉), 28.26 (C₁₀), 23.00 (C₁₁), 16.52 (d, J = 5.6 Hz, C₁₂).

**MS (ESI+ m/z):** 557.3 [2×M-Na]+, 290.1 [M-Na]+

**MS (EI+, m/z, rel%):** 267.1 [0.04, M⁺], 158.1 [30.16], 166.0 [8.16], 194.0 [13.00]

**HRMS (ESI+, m/z):** for C₁₀H₂₂N₁O₅P₁Na₁, [M-Na]+, observed 290.1131, calculated 290.1133
$^1$H- and $^{13}$C-NMR spectrum of compound 200 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 200 recorded in CDCl₃
HMBC-NMR spectrum of compound 200 recorded in CDCl₃
Two-step synthesis of compound 208

Step one, synthesis of compound 207.

An open Erlenmeyer flask (250 mL) was charged with BnNH₂ (6.475 g, 60.42 mmol), EtOAc (60 mL) and H₂O (60 mL). The resulting biphasic solution was cooled to 0 °C by an ice-H₂O bath and then slowly added the aqueous formalin solution (37 wt%, 2.0165 g, 67.15 mmol) using a automated syringe pump (13 mL/h addition rate). The internal temperature was kept below 5 °C during the addition of the formalin solution. The resulting reaction mixture was stirred for an additional 2.5 hours at to 0 °C. The crude reaction mixture was then transferred to a separatory funnel where the aqueous-phase was removed. The organic-phase was washed once with H₂O (60 mL) then dried over anhydrous Na₂SO₄, filtered, then concentrated under reduced pressure to give a colourless oil (7.3 g, >100% yield, 100% = 7.22 g). The oil could be stored in the fridge (-18 to 0 °C).

Step two, synthesis of compound 208.

Compound 207 (6.77 g, 18.93 mmol) was diluted with PhMe (100 mL) and heated to 65 °C. The diethylphosphite (10 mL, 77.624 mmol) was added using an automated syringe pump (4 mL / hour). The resulting reaction mixture was then heated to 85 °C where it was maintained for 22 hours. The crude reaction mixture was transferred to a separatory funnel and the organic-phase was washed with H₂O (100 mL), aqueous NaOH (0.5 M, 100 mL), then H₂O (100 mL) then aqueous HCl (0.5 M, 50 mL). The resulting organic-phase was then dried over anhydrous Na₂SO₄, filtered then concentrated under reduced pressure to afford the product (3.600 g, 74% yield).

³¹H-NMR (400 MHz, Chloroform-d) δ = 7.34 – 7.26 (m, 4H), 7.27 – 7.21 (m, 1H), 4.20 – 4.05 (m, 4H), 3.84 (s, 2H), 2.93 (d, J = 12.6, 2H), 1.31 (app.† t, J = 7.1, 6H).

³¹C-NMR (101 MHz, Chloroform-d) δ = 139.17, 128.42, 128.19, 127.19, 62.07 (d, J = 6.6), 54.76 (d, J = 16.3), 44.09 (d, J = 154.5), 16.48 (d, J = 5.8).


MS (EI+, m/z): 257 [M]+, 120, 106, 91 [100%]

HRMS (ESI+, m/z): for C₁₂H₂₀N₁O₃P₁, [M]+, observed 257.1183, calculated 257.1180
$^1$H- and $^{13}$C-NMR spectrum of compound 208 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 208 recorded in CDCl₃
HMBC-NMR spectrum of compound 208 recorded in CDCl₃
Synthesis of compound 197

Similar to the procedure utilised for the synthesis of compound 206.

Amounts: Compound 170 (2.00 g, 7.77 mmol), Pd/C (10%, 446 mg), MeOH (110 mL)
Product obtained in 1.238 g, 95% yield.

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (400 MHz, Chloroform-d) } & \delta = 4.23 - 4.03 \text{ (m, 4H, } H_a) , 3.02 \text{ (d, } J = 10.5 \text{ Hz, 2H, } H_c), \\
& 2.49 \text{ (s, 2H, } H_b), 1.31 \text{ (app.}^* \text{t, } J = 7.1, 6H, H_\alpha).
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{13}C-NMR (101 MHz, Chloroform-d) } & \delta = 62.14 \text{ (d, } J = 6.8, C_B), 37.46 \text{ (d, } J = 149.7, C_C), \\
& 16.47 \text{ (d, } J = 5.7, C_A).
\end{align*}
\]

MS (ESI+ m/z): 168 [M-H]+, 190 [M-Na]+

MS (EI+, m/z): 167 [M]+, 138, 30 [100%]

HRMS (ESI+, m/z): for C_{5}H_{14}N_{1}O_{3}P_{1}Na_{1}, [M-Na]+, observed 190.0616, calculated 190.0609
$^1$H- and $^{13}$C-NMR spectrum of compound 197 recorded in CDCl$_3$. 
HSQC-NMR spectrum of compound 197 recorded in CDCl₃
Synthesis of compound 209

Similar to the procedure utilised for the synthesis of compound 206.

Amounts: Compound 197 (0.5900 g, 3.52 mmol), H₂O-Acetone (5:95, 3.5 mL), Boc₂O (0.9342 g, 4.27 mmol), imidazole (50.39 mg, 0.74 mmol) and DMAP (10 mol%).

Compound was afforded as an oil (0.665 g, 65 %)

\[
\text{1H-NMR (400 MHz, Chloroform-}d\text{)} \delta = 4.77 \text{ (s, 1H, } H_0\text{), 4.19} - 4.03 \text{ (m, 4H, } H_B\text{), 3.53 (dd, } J = 11.1, 6.0, 2H, H_C\text{), 1.42 (s, 9H, } H_G\text{), 1.31 (app.*t, } J = 7.1, 6H, H_A\text{).}
\]

\[
\text{13C-NMR (101 MHz, Chloroform-}d\text{)} \delta = 155.44 \text{ (d, } J = 6.9, C_E\text{), 80.12 (C_F\text{), 62.45 (d, } J = 6.5, C_B\text{), 36.06 (d, } J = 156.9, C_C\text{), 28.25 (C_D\text{), 16.37 (d, } J = 5.96, C_A\text{).}
\]

**MS (ESI+ m/z):** 290 [M-Na]^+

**MS (EI+, m/z):** Not found [M]^+, 194, 166, 41.2 [100%]

**HRMS (ESI+, m/z):** for C₁₀H₂₂N₁O₅P₁Na₁, [M-H]^+, observed 290.1128, calculated 290.1128
$^1$H- and $^{13}$C-NMR spectrum of compound 209 recorded in CDCl$_3$. 
COSY- and HSQC-NMR spectrum of compound 209 recorded in CDCl₃
HMBC-NMR spectrum of compound 209 recorded in CDCl₃
Synthesis of compound 198

Compound 209 (1.000 g, 3.740 mmol), anhydrous NaI (5.500 g, 36.91 mmol) and MeCN (5 mL) was placed in an RBF fitted with a condenser. The resulting heterogeneous mixture was heated to reflux where it was maintained for 5 days. The crude reaction mixture was concentrated under reduced pressure before was transferred it to a separatory funnel by the addition of H₂O (15 mL) and CH₂Cl₂ (10 mL). The organic-phase was removed, and the aqueous-phase was added CHCl₃ (10 mL) and aqueous HCl (35 wt%, 0.9 mL, dropwise while the biphasic solution was swirled). The organic-phase was collected and the water-phase was extracted using CHCl₃ (4 × 10 mL). The combined organic-phase was dried over anhydrous Na₂SO₄, filtered and then concentrated under reduced pressure in which the product was obtained (370 mg, 41.3% yield).

$$\text{1H-NMR (400 MHz, Chloroform-d) } \delta = 10.61 \text{ (br s, 1H, } H_D) , 5.18 \text{ (br s, 1H, } H_H) , 4.15 - 3.99 \text{ (m, 2H, } H_B) , 3.52 \text{ (app.}^* \text{d, } J = 11.1, 2H, H_C) , 1.40 \text{ (s, 9H, } H_G) , 1.28 \text{ (app.}^* \text{t, } J = 7.0, 3H, H_A) .$$

$$\text{13C-NMR (101 MHz, Chloroform-d) } \delta = 155.67 \text{ (d, } J = 6.4 \text{ Hz, } C_E) , 80.06 \text{ (C_F) , 62.45 (d, } J = 6.0 \text{ Hz, } C_B) , 36.36 \text{ (d, } J = 157.4 \text{ Hz, } C_C) , 28.23 \text{ (C_G) , 16.24 (d, } J = 6.2 \text{ Hz, } C_A) .$$

MS (ESI⁺ m/z): 262 [M-Na]⁺, 284 [M⁺H, +2×Na]⁺

MS (EI⁺, m/z): No product ions or fragments were observed.

HRMS (ESI⁺, m/z): for C₈H₁₈N₁O₅P₁Na₁, [M-Na]⁺, observed 262.0811, calculated 262.0815
$^1$H- and $^{13}$C-NMR spectrum of compound 198 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 198 recorded in CDCl₃
HMBC-NMR spectrum of compound \textbf{198} recorded in CDCl$_3$
The general procedure employed for the phosphonamidation of phosphonic acid 200

The phosphonic acid 200 (0.1057 g, 0.467 mmol) was dissolved in CH₂Cl₂ (1 mL) and then added the amine (0.900 mmol) and Et₃N (0.16 mL, 1.15 mmol). After 5 minutes solid PyBOP was added. The resulting reaction mixture stirred for 20 hours at room temperature, after in which the conversion was measured by ³¹P-NMR analysis of the crude reaction mixture. The crude reaction mixture was transferred to a separatory funnel where the organic-phase was diluted with additional CH₂Cl₂ (2 mL). The organic-phase was then washed with H₂O (2 × 2.5 mL), dried over Na₂SO₄, filtered, and then concentrated under reduced pressure.

The crude product mixture was purified by column chromatography on silica gel (φ × h,4 × 6.5 cm). The column was eluted with the following program, CH₂Cl₂ (20 mL/min, 5 min), then CH₂Cl₂:MeOH (100:0, 20 mL/min, to 95:5 over 10 min) then CH₂Cl₂:MeOH (95:5, 20 mL/min until the product is obtained). The product was detected by NMR analysis of individual fractions that were collected. TLC analysis by the use of TLC staining solutions or UV-light did not provide a clear picture of the content of the collected fractions or the purity of it.

Table 3.6 – PyBOP mediated phosphoamidation of α-aminophosphonic acid 200 with various amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conversion [%][a]</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Amine" /></td>
<td>&gt;95</td>
<td>211</td>
<td>Not measured</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Amine" /></td>
<td>&gt;95</td>
<td>212</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Amine" /></td>
<td>&gt;95</td>
<td>213</td>
<td>23</td>
</tr>
<tr>
<td>4[b]</td>
<td><img src="image4" alt="Amine" /></td>
<td>&gt;95</td>
<td>214</td>
<td>18</td>
</tr>
</tbody>
</table>

[a] Conversion was measured by ³¹P-NMR analysis of the crude reaction mixtures. [b] 3.5 eq. of Et₃N was used.
Compound 211

\[ \text{\textsuperscript{1}H-NMR (400 MHz, Chloroform-} \text{d}) \delta 7.37 - 7.28 (m, 4H, Ar-H), 7.25 - 7.20 (m, 1H, overlapping with CDCl}_3, \text{Ar-H} \), 4.73 (d, \text{J} = 5.0 \text{ Hz}, 1H, \text{H}_d), 4.37 - 4.26 (m, 1H, \text{H}_d), 4.23 - 4.11 (m, 1H, \text{H}_d), 4.12 - 3.92 (m, 2H, \text{H}_b), 3.80 (s, 1H, \text{H}_n), 1.52 (d, \text{J} = 15.0 \text{ Hz}, 3H, \text{H}_c \text{ or H}_c', \text{overlapping peaks}), 1.50 (d, \text{J}=14.3, 3H, \text{H}_c \text{ or H}_c', \text{overlapping peaks}), 1.39 (s, 9H, \text{H}_o), 1.23 (\text{app.}^* \text{t, J} = 7.1 \text{ Hz}, 3H, \text{H}_a). \]

\[ \text{\textsuperscript{13}C-NMR (101 MHz, Chloroform-} \text{d}) \delta 155.17 (d, \text{J} = 3.8 \text{ Hz}, \text{C}_e), 140.79 (d, \text{J} = 5.3 \text{ Hz}, \text{C}_i), 128.44 (\text{C-Ar} \text{, 127.38 (C-Ar) , 127.01 (C-Ar) , 79.80 (C}_f \text{, 60.71 (d, J = 7.5 Hz, C}_b \text{, 52.52 (d, J = 141.2 Hz, C}_b \text{, 45.19 (C}_b \text{, 28.32 (C}_o \text{, 24.23 (C}_c \text{ or C}_c \text{), 23.12 (d, J = 4.4 Hz, C}_c \text{ or C}_c \text{), 16.51 (d, J = 5.8 Hz, C}_a).} \]

\[ \text{MS (ESI+ m/z)}: \text{379.2 [M-Na]}^+ \]

\[ \text{MS (EI+, m/z, rel%)}: 356.2 \text{ [1.09, M}^+], 198.1 \text{ [25.38], 158.1 [28.64], 106.0 [57.60], 77.0 [5.11]} \]

\[ \text{HRMS (ESI+, m/z)}: \text{for C}_{17}\text{H}_{29}\text{N}_2\text{O}_4\text{P}_1\text{Na}_1, [M-Na]}^+, \text{observed 379.1768, calculated 379.1762} \]
$^{1}$H- and $^{13}$C-NMR spectrum of compound 211 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 211 recorded in CDCl₃
HMBC-NMR spectrum of compound 211 recorded in CDCl₃
Compound 212

$^{1}$H-NMR (400 MHz, Chloroform-$d$) δ 4.80 (app.$^*$ d, $J = 5.3$ Hz, 1H, $H_6$), 4.11 – 3.95 (m, 2H, $H_a$), 3.48 (s, 1H, $H_i$), 3.41 (t, $J = 10.5$ Hz, 2H, $H_j$), 3.32 (s, 3H, $H_d$), 3.28 – 3.10 (m, 2H, $H_b$), 1.48 (d, $J=15.2$ Hz, 3H, $H_c$ or $H_c'$), 1.46 (d, $J = 14.6$ Hz, 3H, $H_c$ or $H_c'$), 1.38 (s, 9H, $H_o$), 1.26 (app.$^*$ t, $J = 7.1$ Hz, 3H, $H_a$).

$^{13}$C-NMR (101 MHz, Chloroform-$d$) δ 155.00 (d, $J = 6.2$ Hz, C$_8$), 79.55 (C$_9$), 73.53 (d, $J = 4.6$ Hz, C$_8$), 60.41 (d, $J = 7.5$ Hz, C$_8$), 58.62 (C$_j$), 52.45 (d, $J = 142.7$ Hz, C$_9$), 41.03 (C$_a$), 28.30 (C$_g$), 23.77 (C$_c$ or C$_c'$), 22.83 (d, $J = 3.2$ Hz, C$_c$ or C$_c'$), 16.45 (d, $J = 5.9$ Hz, C$_a$).

MS (ESI$^+$ m/z): 671.4 [2×M-Na]$^+$, 347.2 [M-Na]$^+$

MS (EI$, \ m/z$): 324.1(0.68, M$^+$), 251.1(7.00), 166.0(6.23), 158.1(25.01)

HRMS (ESI$^+$, m/z): for C$_{13}$H$_{29}$N$_2$O$_5$P$_1$, observed 324.1815, calculated 324.1814
$^1$H- and $^{13}$C-NMR spectrum of compound 212 recorded in CDCl$_3$. 
COSY- and HSQC-NMR spectrum compound 212 recorded in CDCl₃
HMBC-NMR spectrum compound **212** recorded in CDCl₃
Compound 213

\(^1\)H-NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 4.73 (d, \(J = 3.5\) Hz, 1H, \(H_M\)), 4.19 – 4.11 (m, 1H, \(H_B\)), 3.97 – 3.88 (m, 1H, \(H_B\)), 3.46 – 3.28 (m, 4H, ambiguous signals belonging to \(H_H\), \(H_H'\), \(H_I\), \(H_I'\)), 3.28 – 3.20 (m, 2H, ambiguous signals belonging to \(H_H\), \(H_H'\), \(H_I\), \(H_I'\)), 3.11 – 2.99 (m, 2H, ambiguous signals belonging to \(H_H\), \(H_H'\), \(H_I\), \(H_I'\)), 1.50 (d, \(J = 15.1\), 3H, \(H_C\) or \(H_C'\)), 1.46 (d, \(J = 15.3\), 3H, \(H_C\) or \(H_C'\)) 1.41 (s, 9H, \(H_G\) or \(H_L\)), 1.38 (s, 9H, \(H_G\) or \(H_L\)), 1.30 (app.\(^*\)t, \(J = 7.1\) Hz, 3H, \(H_A\)).

\(^{13}\)C-NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 154.58 (\(C_J\)), 154.27 (d, \(J = 6.9\) Hz, \(C_E\)), 79.92 (\(C_F\) or \(C_K\)), 79.35 (\(C_F\) or \(C_K\)), 60.45 (d, \(J = 7.6\) Hz, \(C_G\)), 53.66 (d, \(J = 145.0\) Hz, \(C_D\)), 45.00 – 44.57 (m, ambiguous signals \(C_H\), \(C_H'\), \(C_I\), \(C_I'\)), 28.43 – 28.24 (m, ambiguous signals, probably two singlets, 28.37 ppm and 28.34 ppm, \(C_G\) and \(C_L\)), 23.96 (\(C_C\) or \(C_C'\)), 22.88 (\(C_C\) or \(C_C'\)), 16.32 (d, \(J = 6.0\) Hz, \(C_A\)).

\[\text{MS (ESI+ m/z): 893.5 [2M+Na], 458.2 [M+Na]^+}\]
\[\text{MS (EI+, m/z): 435.2 (0.36, M^+), 205.0(10.9), 158.1(20.23), 57.0(100.0)}\]
\[\text{HRMS (ESI+, M/Z): for C}_{19}\text{H}_{38}\text{N}_3\text{O}_6\text{P}_1, \text{observed 435.2492, calculated 435.2498}}\]
\textsuperscript{1}H- and \textsuperscript{13}C-NMR spectrum of compound 213 recorded in CDCl\textsubscript{3}
COSY- and HSQC-NMR spectrum of compound 213 recorded in CDCl₃
HMBC-NMR spectrum of compound 213 recorded in CDCl₃
Compound 214

$^1$H-NMR (600 MHz, Chloroform-d) $\delta$ 4.77 (d, $J = 4.3$ Hz, 1H, $H_L$), 4.57 (s, 1H, $H_M$), 4.14 – 4.02 (m, 2H, $H_A$), 3.72 (s, 3H, $H_O$), 1.57 (s, 3H, $H_i$ or $H_{i'}$), 1.53 (s, 3H, $H_i$ or $H_{i'}$), 1.51 (d, $J = 14.9$ Hz, 3H, $H_C$ or $H_C'$), 1.47 (d, $J = 14.3$ Hz, 3H, $H_C$ or $H_C'$), 1.42 (s, 9H, $H_G$), 1.27 (t, $J = 7.1$ Hz, 3H, $H_A$).

$^{13}$C-NMR (151 MHz, Chloroform-d) $\delta$ 176.37 (d, $J = 6.2$ Hz, $C_{d}$), 155.29 (d, $J = 4.2$ Hz, $C_{d}$), 79.88 (C_{d}), 61.33 (d, $J = 7.5$ Hz, $C_{d}$), 57.10 (d, $J = 2.0$ Hz, $C_{d}$), 52.46 (d, $J = 141.8$ Hz, $C_{d}$), 52.44 (C_{d}), 28.36 (C_{d}), 28.10 (d, $J = 4.2$ Hz, C_{d} or C_{d}), 27.81 (d, $J = 2.9$ Hz, C_{d} or C_{d}), 23.91 (C_{d} or C_{d}), 23.00 (d, $J = 4.0$ Hz, C_{d} or C_{d}), 16.47 (d, $J = 6.3$ Hz, C_{d}).

MS (ESI+ m/z): 755.52 [2M+Na], 389.2 [M-Na]

MS (EI+, m/z): 366.2 (0.55, M$^+), 293.1(5.37), 208.1(9.81), 158.1(13.70)

HRMS (ESI+, M/Z): for C_{15}H_{31}N_{2}O_{6}P_{1}, observed 366.1915, calculated 366.1920
$^1$H- and $^{13}$C-NMR spectrum of compound **214** recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 214 recorded in CDCl₃
HMBC-NMR spectrum of compound 214 recorded in CDCl₃
NMR-study of the stability of Brucine-DMT-Cl (Compound 218b)

**Warning!** Handling of brucine should be undertaken with care! See synthesis of compound 143 on page 142.

A NMR tube was charged with a MeCN-d$_3$ (0.5 mL) and brucine (142) (19.3 mg, 0.048 mmol). A reference spectre of brucine was obtained (Spectrum 1). The solution was then added 1-chloro-4,6-dimethoxy-1,3,5-triazine (228) (9.2 mg, 0.052 mmol) and stirred vigorously with a vortex mixer for 1 min. The resulting reaction mixture was analysed by $^1$H-NMR (Spectrum 2). The crude reaction mixture indicated primarily product formation. Two additional NMR spectrum was recorded 7 and 14 min after the first spectrum of the reaction product was recorded (Spectrum 3 and 4). Both spectrum indicated product degradation as can be observed from the emerging peaks between 7.4 and 5.5 ppm.

![Figure S4.1 - NMR study of the stability of brucine-DMT-Cl.](image)

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203
NMR-scale synthesis of Brucine-DMT-BF₄ (Compound 218a)

A test vial was charged with a MeCN-d₃ (0.5 mL) AgBF₄ (11 mg, 0.56 mmol) and brucine (20.3 mg, 0.051 mmol). The resulting solution was then added a solution of MeCN-d₃ (0.5 mL) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (228) (10.3 mg, 0.058 mmol), which immediately formed a white precipitate (AgCl (s)). The heterogeneous mixture was filtered through a glass-pipette fitted with cotton-wool and the filtrated solution was transferred to a NMR tube and analysed by ¹H-NMR (Spectrum 2). A reference spectrum was recorded 20 min later and showed no signals indicative of product degradation.

Figure S4.2 - NMR study of the stability of brucine-DMT-BF₄ 218a.
**NMR-scale visualisation of the activation of phosphonic acid**

Monoethyl benzylphosphonic acid (11 mg, 0.055 mmol) and brucine (7 mg, 0.017 mmol) as a catalytic base was added to the NMR-tube. A NMR experiment was undertaken immediately, showing 2 peaks in $^{31}$P-NMR, corresponding to the protonated and deprotonated phosphonic acid (Spectrum 1). After 1 hour of preactivation with occasional stirring using the vortex mixer (1 min each 15 min) pyrophosphonate was observed (Spectrum 2). The NMR tube was left for 14 hours and then analysed again by $^{31}$P-NMR showing additional conversion to the pyrophosphonate (Spectrum 3).

**Figure S4.3** - NMR study of the activation of monoethyl benzylphosphonic acid with brucine-DMT-BF$_4$.
Synthesis of compound 218a using a modificaton to the Kaminski Paper

An RBF was loaded with brucine (142) (195, mg, 0.494 mmol), AgBF₄ (105 mg, 0.53 mmol) was added dried MeCN (3.5 mL). The resulting heterogeneous mixture was added solid 2-chloro-4,6-dimethoxy-1,3,5-triazine (228) (87.51 mg, 0.5 mmol). Precipitation of solid AgCl was immediately observed. The resulting reaction mixture was stirred for 10 min before being filtered through a celite pad (Celite 503, 1 cm high in a glass pipette stuffed with cotton-plug). The celite pad was rinsed with additional MeCN (2 mL). The product mixture was concentrated under reduced pressure to afford the compound 184 (349 mg, >100% yield, 100% = 306.94 mg). The crude product were analysed by ¹H-NMR and matched the reference reported by Kaminski and co-workers.

The coupling agent was evaluated as sufficiently pure to be evaluated in the enantioselective phosphonamidation reaction.
Spectroscopic data for compound 218a


$^1$H-NMR (200 MHz, Acetonitrile-$d_3$) $\delta$ = 7.74 (s, 1H), 6.89 (s, 1H), 6.58 – 6.41 (m, 1H), 5.11 – 5.02 (m, 1H), 4.98 – 4.78 (m, 2H), 4.41 (dt, $J$=8.1, 3.2 Hz, 1H), 4.30 – 4.10 (m, 9H), 3.96 (d, $J$=2.0 Hz, 1H), 3.52 – 3.41 (m, 1H), 3.03 (dd, $J$=17.5, 8.3 Hz, 1H), 2.80 (dt, $J$=15.8, 4.1 Hz, 1H), 2.65 (dd, $J$=17.5 Hz, 3.1 Hz, 1H), 2.38 – 2.23 (m, 2H), 1.86 (d, $J$=15.9 Hz, 1H), 1.54 (dt, $J$=10.7 Hz, 2.9, 1H).

$^1$H-NMR spectrum of compound 218a recorded in MeCN-$d_3$
Attempted Enantioselective Phosphonamidation Reaction of Monoethyl Benzylphosphonic Acid using Compound 218a

A reaction vial was loaded with compound 218a (149 mg, 0.23 mmol), MeCN (1.5 mL), brucine (142) (21.6 mg, 0.054 mmol) and monoethyl benzylphosphonic acid (171) (44 mg, 0.22 mmol). The resulting solution was stirred for 18 hours to afford the preactivated crude required for the aminolysis step.

The preactivation crude was analysed by $^{31}$P-NMR revealing unconsumed starting material and pyrophosphonates. Starting material:pyrophosphonate ratio were 0.24:1.00.

A solution consisting of BnNH$_2$ (50 μL, 48.56 mmol), Et$_3$N (30 μL, 23 mmol) and MeCN (1 mL) was added to the preactivated solution in one portion. The solution became homogeneous immediately and became red. The reaction mixture was stirred for 24 hours.

NMR of the crude reaction mixture showed: Product (ca. 30 ppm), anion of the starting material (ca. 21 ppm) and traces of pyrophosphonates (ca 20 ppm). The crude product mixture was filtrated through a cotton plug and diluted with Et$_2$O (5 mL). The organic-phase was washed with H$_2$O (2 x 5 mL), aqueous NH$_4$Cl (Sat., 2 x 5 mL) then H$_2$O (5 mL). The organic-phase was dried over anhydrous Na$_2$SO$_4$, filtered, and then concentrated under reduced pressure to afford the crude product. The product was purified by column chromatography (SiO$_2$, φ x h, 2.5 x 17 cm) using CH$_2$Cl$_2$:MeOH 100:2, (700 mL) as the eluent. The yield was not documented.

Spectrum analysis of a pure fraction matched that of previously synthesised material.

The sample was analysed by HPLC analysis using a chiral AD-H column. Eluent $i$-Hex:$i$-PrOH (97:3). The product was obtained as a racemate.

The HPLC conditions were found from a racemate prepared from the phosphonochloridate.
Figure S4.4 - $^{31}$P-NMR showing the crude reaction mixture of the preactivation when using brucine-DMT-BF$_4$ (218a) (Spectrum 1) as the coupling agent and the subsequent product mixture obtained after the aminolysis step with benzylamine (Spectrum 2).
Synthesis of compound 235

Morpholinecarbonyl chloride (231) (1.0 mL, 8.88 mmol) was added dropwise into a thoroughly stirred CH$_2$Cl$_2$-solution (18 mL) containing (S)-(-)-N,α-dimethylbenzylamine (234) (1.035 g, 7.4 mmol) and Et$_3$N (0.9090 g, 8.88 mmol) over 5 min. Precipitation was observed 25 min after the addition. The resulting heterogeneous solution was stirred for 21 hours.

An aqueous NaOH-solution (0.5 M, 10 mL) was added to the crude reaction mixture, forming a homogeneous mixture after 15 min. The solution was transferred into a separatory funnel and extracted using CH$_2$Cl$_2$ (30 mL). The organic phase was then washed with aqueous HCl-solution (0.5 M, 2 × 30 mL). The resulting organic phase was dried over anhydrous Na$_2$SO$_4$, filtered, and then concentrated under reduced pressure to give the product as a colourless oil (1.7953 g, 97% yield).

1H-NMR (400 MHz, Chloroform-d) $\delta$ = 7.36 – 7.26 (m, 4H, Ar-H), 7.26 – 7.19 (m, 1H, Ar-H), 5.26 (q, $J = 7.0$ Hz, 1H, H$_E$), 3.70 – 3.65 (m, 4H, H$_A$ and H$_A'$), 3.24 – 3.19 (m, 4H, H$_B$ and H$_B'$), 2.56 (s, 3H, H$_D$), 1.52 (d, $J = 7.0$, 3H, H$_F$).

13C-NMR (101 MHz, Chloroform-d) $\delta$ = 164.70 (C$_C$), 141.03 (C$_D$), 128.40 (Ar-C), 127.10 (Ar-C), 66.64 (C$_A$ and C$_A'$), 54.32 (C$_B$), 47.51 (C$_B$ and C$_B'$), 30.90 (C$_D$), 16.13 (C$_F$).

**MS (ESI+ m/z)**: 249 [M-H]$^+$, 271, [M-Na]$^+$, 519 [2×M-Na]$^+$

**MS (EI+, m/z)**: 248 [M]$^+$, 233.1, 134, 114, 105

**HRMS (ESI+, m/z)**: for C$_{14}$H$_{20}$N$_2$O$_2$, [M-H]$^+$, observed 249.1595, calculated 249.1598
\(^1\)H- and \(^{13}\)C-NMR spectrum of compound 235 recorded in CDCl\(_3\)
COSY- and HSQC-NMR spectrum of compound \textbf{235} recorded in CDCl$_3$
HMBC-NMR spectrum of compound 235 recorded in CDCl₃
Synthesis of compound 233

Morpholinecarbonyl chloride (231) (1.2 mL, 10.284 mmol) was added dropwise into a thoroughly stirred CH₂Cl₂-solution (10 mL) containing (S)-(+)-2-(methoxymethyl)pyrrolidine (232) (1.0107 mg, 8.68 mmol) and Et₃N (1.0451 mg, 10.42 mmol) over 5 min. Precipitation was observed almost immediately after the morpholinecarbonyl chloride solution was added. The resulting heterogeneous solution was stirred for 18.5 hours.

Aqueous NaOH-solution (0.5 M, 10 mL) was added to the crude reaction mixture, forming a homogeneous mixture after 15 min. The solution was transferred into a separatory funnel and extracted using CH₂Cl₂ (30 mL). The organic phase was then washed with HCl (aq., 0.5 M, 2 × 30 mL). The resulting organic phase was dried over Na₂SO₄, filtered, and then concentrated under reduced pressure to give the product 233 as a colourless oil (1.6783 g, 85% yield).

\[
\text{H-NMR (400 MHz, Chloroform-}d\text{)} \delta = 4.26 - 4.17 (m, 1H, H_F), 3.73 - 3.66 (\text{app.* ddd, } J = 3.04, 6.45, 11.20 \text{ Hz, } 2H, H_A/H_A'), 3.65 - 3.57 (\text{app.* ddd, } J = 3.02, 6.55, 11.29 \text{ Hz, } 2H, H_A/H_A), 3.48 (dd, J = 9.5, 3.7 \text{ Hz, } 1H, H_D), 3.40 - 3.23 (m, 8H, H_B/H_B', H_H, H_C), 3.17 (ddd, J = 13.3, 6.4, 2.9, 1H, H_D), 2.12 - 1.98 (m, 1H, H_B), 1.90 - 1.80 (m, 1H, H_B), 1.77 - 1.61 (m, 2H, H_B and H_B).
\]

\[
\text{C-NMR (101 MHz, Chloroform-}d\text{)} \delta = 162.65 (C_I), 74.08 (C_B), 66.72 (C_A/C_A'), 59.1 (C_B), 57.24 (C_E), 50.75 (C_A), 46.63 (C_B/C_B'), 28.33 (C_E), 25.62 (C_D).
\]


MS (EI⁺, m/z): Not found [M⁺], 142 (100%), 114

HRMS (ESI⁺, m/z): for C₁₁H₂₁N₂O₃, [M-H]⁺, observed 229.1543, calculated 229.1547
$^1$H- and $^{13}$C-NMR spectrum of compound 233 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 233 recorded in CDCl₃
HMBC-NMR spectrum of compound 233 recorded in CDCl₃
Synthesis of compound 239

(S)-(-)-N,α-dimethylbenzylamine (234) (0.270 g, 2 mmol) was dissolved in dried THF (2 mL), and degassed with Ar (g). Solid CDI (236) (0.389 g, 2.40 mmol) was added in one portion. The resulting solution was subsequently heated to 50 °C where it was maintained for 24 hours. This afforded a near colourless solution which was concentrated under reduced pressure, redissolved in CH₂Cl₂ (2 mL) and then transferred to a separatory funnel. The organic phase was washed with water (2 × 2 mL, then 2 × 4 mL), dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure.

This afforded the product as a clear colourless oil (0.453 g, 96% yield).

\[ \text{[\text{Product}] = 7.90 (s, 1H, H_{imidazole}), 7.41 - 7.35 (m, 2H, Ar-H),} \\
7.34 - 7.28 (m, 2H, Ar-H), 7.24 (s, 1H, H_{imidazole}), 7.06 (s, 1H, H_{imidazole}), 5.53 (q, J = 7.0, 1H, \\
H₂), 2.77 (s, 3H, H₂), 1.64 (d, J = 7.0, 3H, H₂). \]

\[ \text{[\text{Product}] = 151.93 (C₉), 138.8 (C₂), 136.96 (C_{imidazole A, B or C}),} \\
129.6 (C_{imidazole A, B or C}), 128.8 (Ar-C), 128.02 (Ar-C), 126.99 (Ar-C), 117.97 (C_{imidazole A, B or C}), \\
55.35 (C₆), 31.35 (C₂), 16.23 (C₆). \]

MS (ESI+ m/z): 230 [M-H]+, 252, [M-Na]+

MS (EI+, m/z): 229 [M]+, 105 [100%]

HRMS (ESI+, m/z): for C₁₃H₁₆N₃O₁, [M-H]+, observed 230.1284, calculated 230.1288
$^1$H- and $^{13}$C-NMR spectrum of compound 239 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 239 recorded in CDCl₃
HMBC-NMR spectrum of compound 239 recorded in CDCl$_3$
Synthesis of Compound 237

(S)-(+)-2-(methoxymethyl)pyrrolidine (232) (0.913 g, 7.93 mmol) was dissolved in dried THF (6 mL), and degassed with Ar (g). Solid CDI (236) (0.788 g, 4.86 mmol) was added in one portion. The resulting solution was subsequently heated to 50 °C where it was maintained for 18 hours. This afforded a colourless solution which was concentrated under reduced pressure, re-dissolved in CH₂Cl₂ (8 mL), then transferred to a separatory funnel. The organic phase was washed with water (2 × 8 mL), then dried over anhydrous Na₂SO₄, filtered and then concentrated under reduced pressure. NMR analysis of the crude reaction mixture indicated product and the dimeric specie.

TLC-analysis of the crude product mixture showed 1 peak that was visualised by UV-light. R_f = 0.1 SiO₂ using CH₂Cl₂:MeOH (97:3).

The crude product mixture was purified by column chromatography on silica gel (φ × h, 2.5 × 7 cm) using the following program. Eluent speed: 20 mL/min, CH₂Cl₂:MeOH (99:1) for 10 min, then CH₂Cl₂:MeOH (97:3) for 5 min, then CH₂Cl₂:MeOH (95:5) for 20 min.

This afforded the product 200 as a clear colourless oil (0.7070 g, 70% yield)

Note: By a mistake an excess of CDI and not of the (S)-(+)-2-(methoxymethyl)pyrrolidine was used for the experiment. The experiment was not repeated.

1H-NMR (400 MHz, Chloroform-d) δ = 8.01 (s, 1H, H₄), 7.35 (s, 1H, H₆), 7.07 (s, 1H, H₅), 4.40 – 4.29 (m, 1H, H₇), 3.70 – 3.55 (m, 3H, H₈, H₁₆), 3.51 (app.* dd, J = 9.7, 3.4, 1H, H₉), 3.35 (s, 3H, H₁₀), 2.18 – 1.97 (m, 3H (Integrates to 4, overlapping with water, H₆ and H₁₀), 1.92 – 1.79 (m, 1H, H₁₁).

13C-NMR (101 MHz, Chloroform-d) δ = 149.83 (C₂), 136.7 (C₃), 129.35 (C₅), 117.68 (C₆), 72.00 (C₁), 59.15 (C₉), 58.69 (C₁₆), 50.48 (C₁₇), 27.51 (C₁₀), 25.06 (C₁₁).

MS (ESI+ m/z): 232 [M-Na]^+

MS (EI+, m/z): 209 [M]^+, 164, 142 [100%], 114

HRMS (ESI+, m/z): for C₁₀H₁₅N₃O₂Na, [M-Na]^+, observed 232.1051, calculated 232.1056
$^{1}$H- and $^{13}$C-NMR spectrum of compound 237 recorded in CDCl$_3$
COSY- and HSQC spectrum of compound 237 recorded in CDCl₃
HMBC-NMR spectrum of compound 237 recorded in CDCl₃
Synthesis of compound 238

Compound 237 and (S)-(+)\text{-}2\text{\text{-}}\text{(methoxymethyl)pyrrolidine (232)} were dissolved in PhMe. The resulting solution was degassed with Ar (g) and cooled down using an ice-H\textsubscript{2}O bath. AlMe\textsubscript{3} (2 M in PhMe, 2.5 mL, 5 mmol) was added dropwise to the cooled solution in which gas was observed. After 30 min the resulting reaction mixture was heated to, and maintained at 100 °C for 20 hours.

The crude reaction mixture was cooled down to 0 °C using an ice-H\textsubscript{2}O bath, then added saturated NaHCO\textsubscript{3} (2 mL) to quench excess AlMe\textsubscript{3}. Quenching resulted in a white sticky precipitate and gas evolution. The heterogeneous mixture was vacuum filtered through a Hirsch funnel affording two clear phases. The phases were separated and the water-phase was extracted using CHCl\textsubscript{3} (2 x 15 mL). The combined organic phase was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and then concentrated under reduced pressure.

The crude was purified by column chromatography (SiO\textsubscript{2}, \(\sigma \times h\), 3 x 8.5 cm) using the following program: 20 mL/min eluent speed, CH\textsubscript{2}Cl\textsubscript{2} (100\%) for 7 min, then CH\textsubscript{2}Cl\textsubscript{2}:MeOH (99:1) for 5 min, then CH\textsubscript{2}Cl\textsubscript{2}:MeOH (98:2) for 5 min, then CH\textsubscript{2}Cl\textsubscript{2}:MeOH (96:4) for 30 min.

This afforded the product as a clear colourless oil (0.3025 g, 68\% yield).

\begin{center}
\includegraphics[width=0.3\textwidth]{238.png}
\end{center}

\textbf{\textsuperscript{1}H-NMR (400 MHz, Chloroform-\textit{d})} \(\delta = 4.25 - 4.12\) (m, 1H, H\textsubscript{C}), 3.49 (dd, \(J = 9.4, 3.6, 1\)H, H\textsubscript{A}), 3.34 - 3.24 (m, 6H, H\textsubscript{A}, H\textsubscript{F}, H\textsubscript{B}), 2.10 - 1.98 (m, 1H, H\textsubscript{D}), 1.90 - 1.80 (m, 1H, H\textsubscript{E}), 1.77 - 1.65 (m, 2H, H\textsubscript{E} and H\textsubscript{D}).

\textbf{\textsuperscript{13}C-NMR (101 MHz, Chloroform-\textit{d})} \(\delta = 161.36\) (C\textsubscript{G}), 74.33 (C\textsubscript{B}), 59.00 (C\textsubscript{A}), 57.02 (C\textsubscript{C}), 49.9 (C\textsubscript{F}), 28.54 (C\textsubscript{D}), 25.25 (C\textsubscript{E}).

\textbf{MS (ESI\textsuperscript{+} m/z)}: 257 [M-H]\textsuperscript{+}, 279, [M-Na]\textsuperscript{+}, 535 [2M-Na]\textsuperscript{+}

\textbf{MS (EI\textsuperscript{+}, m/z)}: 256 [M]\textsuperscript{+}, 211, 142 [100\%], 114

\textbf{HRMS (ESI\textsuperscript{+}, m/z)}: Not obtained.
$^1$H- and $^{13}$C-NMR spectrum of compound 238 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compound 238 recorded in CDCl$_3$
HMBC-NMR spectrum of compound 238 recorded in CDCl₃
Synthesis of chlorouronium-X salts (X = Cl, BF₄ or PF₆) from compound 235

Compound 235 (93.3 mg, 0.376 mmol) was dissolved in CH₂Cl₂ (1.5 mL), degassed with Ar(g), and then added oxalyl chloride (35 μL, 0.413 mmol) by dropwise addition from a Hamilton syringe. Gas evolution observed. The reaction crude was then heated to 36 °C, and the conversion to the chlorouronium species was measured from ¹H-NMR analysis of the crude reaction mixture. Full conversion of the urea 235 to the chlorouronium-Cl⁻ 247 species was obtained after 4 days (Scheme SI-4.1, spectrum 2).

The chlorouronium chloride salt could be converted to the chlorouronium-BF₄⁻ salt (Scheme SI-4.1, spectrum 3) or the analogous PF₆ salt 248 (Scheme SI-4.1, spectrum 4) by an anion exchange reaction using AgBF₄ or AgPF₆.

The chlorouronium-Cl 248 crude was concentrated under reduced pressure using a water aspirator, and then re-dissolved in dried CH₂Cl₂ (1 mL), before concentrating it again under reduced pressure using a vacuum pump. The crude was re-dissolved in dried CH₂Cl₂ (2 mL) in which solid AgBF₄ (0.43 mmol) or AgPF₆ (0.43 mmol) was added under vigorous stirring, which resulted in immediate precipitation (AgCl) and a modest heat generation which caused the solvent to boil. The heterogeneous mixture was filtered by gravity through a cotton plug, and rinsed with dried CH₂Cl₂ (3 mL). The crude product mixture was concentrated under reduced pressure to afford the product.
**Figure S4.5** – The comparison of different $^1$H-NMR spectrum of the chlorouronium salts obtained from the urea 235 with different anions.
Spectroscopic data chlorouronium-BF$_4$ salt of compound 248

$^1$H-NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.45 (d, $J = 7.6$, 3H, Ar-H), 7.39 – 7.26 (m, 2H, Ar-H), 5.08 (q, $J = 7.0$, 1H, H$_{E}$), 3.79 – 3.62 (m, 4H, H$_{A}$ and H$_{A'}$), 3.39 – 3.21 (m, 4H, H$_{B}$ and H$_{B'}$), 2.76 (s, 3H, H$_{D}$), 1.56 (d, $J = 7.1$, 3H, H$_{F}$).

$^{13}$C-NMR (101 MHz, Chloroform-$d$) $\delta$ = 165.30 (C$_{C}$), 141.18 (C$_{D}$), 128.52 (Ar-C), 126.74 (Ar-C), 124.46 (Ar-C), 66.54 (C$_{A}$ and C$_{A'}$), 55.26 (C$_{E}$), 47.17 (C$_{B}$ and C$_{B'}$), 32.73 (C$_{D}$), 17.57 (C$_{F}$).

$^1$H-NMR spectrum of chlorouronium-BF$_4$ salt prepared from 235 recorded in CDCl$_3$
$^{13}$C- and COSY-NMR spectrum of chlorouronium-BF$_4$ salt prepared from 235 recorded in CDCl$_3$
HSQC- and HMBC-NMR spectrum of chlorouronium-BF$_4$ salt prepared from 235 recorded in CDCl$_3$
Spectroscopic data for compound 247

\[
\begin{align*}
\text{\textbf{1H-NMR (300 MHz, Chloroform-}d\text{) } & \delta = 7.52 - 7.28 \text{ (m, 5H), 5.58 (q, } J = 6.8, \text{ 1H), 4.09 - 3.87 (m, 8H), 3.25 (s, 3H), 1.86 (d, } J = 6.9, \text{ 3H).} \\
\end{align*}
\]

\text{\textbf{1H-NMR spectrum of compound 247 recorded in CDCl}_{3}
Spectroscopic data for compound 248

$^1$H-NMR (300 MHz, Chloroform-d) $\delta = 7.55 - 7.30$ (m, 5H), 5.53 (q, $J = 6.6$, 1H), 3.95 – 3.81 (m, 8H), 3.12 (s, 3H), 1.82 (d, $J = 6.8$, 3H).

$^1$H-NMR spectrum of compound 248 recorded in CDCl$_3$
Synthesis of compound 248

Compound 235 (0.500 g, 2.016 mmol) was dissolved in CH$_2$Cl$_2$ (4 mL), degassed with Ar(g), and then added oxalyl chloride (0.5 ml, 5.90 mmol) by dropwise addition from a Hamilton syringe. Gas evolution was observed. The crude reaction mixture was heated to 36 °C, where it was maintained for 24 hours. The conversion to the chlorouronium species was measured from NMR analysis of the crude reaction mixture.

The chlorouronium-Cl$^-$ crude was concentrated under reduced pressure using the water aspirator, and then re-dissolved in dried CH$_2$Cl$_2$ (4 mL), before concentrating it again under reduced pressure using the vacuum pump. The crude was dissolved in dried CH$_2$Cl$_2$ (6 mL) then solid AgPF$_6$ (0.522 g, 2.064 mmol) was added under vigorous stirring, which resulted in immediate precipitation of AgCl and a modest heat generation which caused the solvent to boil. The heterogeneous mixture was filtered by gravity through a cotton plug. The cotton-plug was rinsed with additional dried CH$_2$Cl$_2$ (6 mL). The crude was concentrated under reduced pressure to afford the chlorouronium-PF$_6^-$ salt as a red oil (0.7614 g, 92%). A comparison between the Cl$^-$- and PF$_6^-$-salt was undertaken by $^1$H-NMR (Figure S4.6)

**Figure S4.6** – A comparison of the $^1$H-NMR spectrum of the chlorouronium salts 247 and 248 used to obtain the chiral COMU derivative 249.
The crude product mixture was immediately dissolved in CH₂Cl₂ (10 mL) and cooled down to 0 °C under a gentle stream of Ar (g). Solid K-Oxyma was then added in one portion. The resulting reaction mixture was allowed to warm to room temperature. After 20h the crude product mixture was filtered through a celite plug (Celite 503, ø h, 2 × 3 cm). CH₂Cl₂ (10 mL) was used to elute product from the celite plug.

Attempted precipitation of the product from was unsuccessful. Procedure: The crude reaction mixture was dissolved in CH₂Cl₂ (1 mL) or acetone (1 mL), and then added into a vigorously stirred solution of Et₂O (8 mL).

The crude product mixture was placed in the fridge (-18 °C) in which white crystals were observed after 2 weeks. The crystals were removed by a spatula and analysed by NMR and MS indicated that the right product had been formed.

The yield was not documented.

\[
\begin{align*}
\text{1H-NMR (400 MHz, Acetone-} & \text{d}_6) \delta = 7.65 – 7.56 (m, 2H, Ar-H), 7.51 – 7.32 (m, 2H, Ar-H), 5.52 (q, J = 6.8 Hz, 1H, H_e), 4.49 (q, J = 7.1 Hz, 2H, H_f), 4.00 – 3.76 (m, 8H, H_i, H_j, H_k, H_l, H_m and H_n), 3.26 (s, 3H, H_g), 1.87 (d, J = 6.9 Hz, 3H, H_f), 1.39 (t, J = 7.1 Hz, 3H, H_e).
\end{align*}
\]

\[
\begin{align*}
\text{13C-NMR (101 MHz, Acetone-} & \text{d}_6) \delta = 161.82 (C_e), 156.70 (C_m), 137.83 (C_d), 135.57 (C_l), 129.83 (Ar-C), 129.62 (Ar-C), 128.58 (Ar-C), 107.76 (C_k), 66.70 (C_j and C_j'), 65.32 (C_n), 61.26 (C_g), 51.09 (C_i and C_i'), 35.93 (C_o), 16.75 (C_f), 14.15 (C_o).
\end{align*}
\]

MS (ESI+ m/z): 373 [M+PF₆]⁺

MS (EI+, m/z): Not obtained

HRMS (ESI+, m/z): for C₁₉H₂₅N₄O₄⁺, [M+PF₆]⁺, observed 373.1871, calculated 373.1870
$^{1}$H- and $^{13}$C-NMR spectrum of compound 249 recorded in acetone-d$_6$. 
COSY- and HSQC-NMR spectrum of compound 249 recorded in acetone-d$_6$. 

240
HMBC-NMR spectrum of compound 249 recorded in acetone-d$_6$
Synthesis of compound 208, a chiral COMU derivative

Compound 233 (0.9025 g, 3.95 mmol) was dissolved in CH$_2$Cl$_2$ (6 mL), degassed with Ar(g), and then added Oxalyl chloride (2 mL, 23.63 mmol, 6 eq.) by dropwise addition from a Hamilton syringe. Gas evolution observed. The resulting reaction mixture was then heated to, and maintained at 36°C for 2.5 days, affording a slightly red coloured solution.

The crude was converted to the chlorouronium-PF$_6^-$ salt by an anion exchange reaction. The chlorouronium-Cl$^-$ crude was concentrated under reduced pressure using the water aspirator, and then re-dissolved in dried CH$_2$Cl$_2$ (6 mL), before concentrating it again under reduced pressure using the vacuum pump. $^1$H-NMR spectrum was recorded.

The crude was re-dissolved in dried CH$_2$Cl$_2$ (13 mL) then solid AgPF$_6$ (1.061 g, 4.196 mmol) was added in one portion under vigorous stirring, which resulted in immediate precipitation (AgCl) and a modest heat generation which caused the solvent to boil. The heterogeneous mixture was filtered through a glass Hirsch funnel, and the filtered precipitate was washed with additional dried CH$_2$Cl$_2$ (3 mL). The crude was concentrated under reduced pressure to afford an red oil. The yield was not recorded. $^1$H-NMR spectrum was recorded.

The chlorouronium/PF$_6^-$ salt was dissolved in dried CH$_2$Cl$_2$ (20 mL), cooled to 0°C, under a gentle stream of Ar (g). Solid K-Oxyma (0.722 g, 4.011 mmol) was added in one portion and the resulting solution was slowly heated towards room temperature. After 16 hours the crude was added additional dried CH$_2$Cl$_2$ (4 mL) and dried acetone (4 mL). The heterogeneous mixture was then vacuum filtered and concentrated under reduced pressure to give a red crystalline mass. The crude was dissolved in acetone (4 mL) then added dropwise into dried Et$_2$O (10 mL) under vigorous stirring, affording the product as a white precipitate accompanied by a red coloured solution. The product was collected by Büchner filtration, and dried under reduced pressure to afford the product (1.23 g, 62.5% yield).
$^1$H-NMR (400 MHz, Chloroform-$d$) $\delta = 4.80 - 4.66$ (m, 1H, $H_{ii}$), 4.50 (q, $J = 7.4$, 2H, $H_{ii}$), 4.11 - 3.92 (m, 4H, partially overlapping peaks, $H_{E}$ and $H_{C}/H_{D}/H_{F}/H_{G}$), 3.90 - 3.77 (m, 4H, $H_{C}/H_{C}/H_{D}/H_{D}$), 3.75 - 3.68 (m, 2H, $H_{C}/H_{C}/H_{D}/H_{D}$), 3.61 (app.* dd, $J = 10.3$, 3.7 Hz, 1H, $H_{j}$), 3.46 (app.* dd, $J = 10.2$, 8.3 Hz, 1H, $H_{j}$), 3.31 (s, 3H, $H_{J}$), 2.45 - 2.31 (m, 1H, $H_{G}$), 2.28 - 2.15 (m, 1H, $H_{F}$), 2.12-2.02 (m, $H_{F}$, overlapping with the solvent residual peak for acetone-$d_6$), 1.89 - 1.74 (m, 1H, $H_{6}$), 1.39 (t, $J = 7.1$, 3H, $H_{a}$).

$^{13}$C NMR (101 MHz, Acetone-$d_6$) $\delta = 159.82$ (C$_{N}$), 156.85 (C$_{K}$), 134.71 (C$_{L}$), 107.35 (C$_{M}$), 74.18 (C$_{I}$), 66.68 (C$_{C}/C_{C}/C_{D}/C_{D'}$), 65.26 (C$_{B}$), 62.82 (C$_{H}$), 59.22 (C$_{J}$), 53.05 (C$_{E}$), 50.38 (C$_{C}/C_{C}/C_{D}/C_{D'}$), 27.30 (C$_{G}$), 25.51 (C$_{\beta}$), 14.11 (C$_{\alpha}$).

MS (ESI$^+$, m/z): 353 [M+PF$_6$]$^+$

MS (EI$^+$, m/z): Not obtained

HRMS (ESI$^+$, m/z): for C$_{16}$H$_{25}$N$_4$O$_5$, [M+PF$_6$]$^+$, observed 353.1822, calculated 353.1819
$^1$H- and $^{13}$C-NMR spectrum of compound 246 recorded in acetone-d$_6$. 

244
COSY- and HSQC-NMR spectrum of compound 246 recorded in acetone-d$_6$. 
HMBC- and $^{31}$P-NMR spectrum of compound 246 recorded in acetone-d$_6$. 
Spectroscopic data for compound 244

$\text{H-NMR (300 MHz, Chloroform-}d\text{)} \delta = 4.74 - 4.60 \text{ (m, 1H), 4.33 - 4.20 \text{ (m, 1H), 4.11 - 3.95 \text{ (m, 2H), 3.96 - 3.79 (m, 7H), 3.73 - 3.65 \text{ (m, 1H), 3.62 (dd, } J = 10.4, 3.9, 2\text{H), 3.46 (dd, } J = 10.4, 5.5, 1\text{H), 3.35 (s, 3H), 2.44 - 2.04 \text{ (m, 3H), 2.00 - 1.80 \text{ (m, 1H).}}}$

$\text{H-NMR spectrum of compound 244 recorded in Acetone-d}_6.$
Spectroscopic data for compound 245

\[
\begin{align*}
\text{H-NMR (300 MHz, Chloroform-} &\text{d) } \delta = 4.65 - 4.51 (\text{m, 1H}), 4.00 - 3.65 (\text{m, 12H}), 3.58 (\text{dd, } J = 10.5, 4.1, 1\text{H}), 3.41 (\text{dd, } J = 10.4, 5.8, 1\text{H}), 3.35 (\text{s, 3H}), 2.38 - 2.21 (\text{m, 1H}), 2.17 - 2.02 (\text{m, 2H}), 1.95 - 1.75 (\text{m, 1H}).
\end{align*}
\]

\[^1\text{H-NMR spectrum of compound 245 recorded in CDCl}_3\]
Figure S4.7 – A comparison of different $^1$H-NMR spectrum that was obtained from the chlorouronium salt 244 and 255 from urea 233.
**Phosphonamidation Attempts using Achiral and Chiral Coupling Agents**

Phosphonamidation reactions using an achiral amine, BnNH$_2$

Et$_3$N (50 μL, 0.36 mmol) was added dropwise over 2 min to a colourless heterogeneous solution consisting of monoethyl benzylphosphonic acid (171) (40 mg, 0.2 mmol), chiral COMU derivative (248) (150 mg, 0.3 mmol) and CH$_2$Cl$_2$ (1 mL). Immediately upon the addition of the Et$_3$N, the solution turned yellow (Oxyma anion) and the undissolved coupling agent started to dissolve. The preactivation was carried out at room temperature for 1 hour before a sample of the crude reaction mixture was analysed by $^{31}$P-NMR. BnNH$_2$ (50 μL, 0.359 mol) was added dropwise into the reaction mixture over 1 hour, and the reaction stirred for an additional 14 hours.

The crude reaction mixture was concentrated under reduced pressure and the conversion was found by analysis by $^{31}$P-NMR (37.5%). The crude was then dissolved in Et$_2$O (4 mL) and washed with water (2 × 3 mL) and aqueous NaOH (1M, 3 mL). The product was purified by column chromatography (SiO$_2$, ø × h, 2.5 × 17 cm) using CH$_2$Cl$_2$:MeOH 100:2, (700 mL) as the eluent. This afforded the pure product. Yield was not reported.

The purified product was analysed by Chiral HPLC (Column: AD-H; eluent i-Hex-i-PrOH 97:3, affording the product as a racemate, Rf$_{1}$ = 9.41 min and Rf$_{2}$ = 17.97 min).
Aminolysis Study Using (S)-1-Methyl Benzylamine

Et₃N (60 μL, 0.43 mmol) was added dropwise over 2 min to a colourless heterogeneous solution consisting of monoethyl benzylphosphonic acid (171) (0.2 mmol), [coupling agent] and CH₂Cl₂ (1 mL). The preactivation was carried out at room temperature for 1 hour. (S)-1-methyl benzylamine (60 μL, 0.39 mmol) was then added dropwise into the reaction mixture over 1 min. The resulting reaction mixture was stirred for an additional 2 hours.

The crude reaction mixtures were analysed by ³¹P-NMR (Table SI 4.1).

The crude was then dissolved in Et₂O (4 mL) and washed with water (2 × 3 mL) and aqueous NaOH (1 M, 3 mL, can be omitted for methods using the oxalyl chloride). The product was purified by column chromatography (SiO₂, σ × h, 2.5 × 17 cm) using CH₂Cl₂:MeOH 100:2, (approximately 700 -1000 mL) as the eluent. This afforded the pure product.

Table 4.1 – Aminolysis study of activated phosphonates using (S)-methyl benzylamine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁, R₂</th>
<th>Method</th>
<th>D.r.</th>
<th>Product</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-Bn, -Et 171</td>
<td>A</td>
<td>1.00 : 0.57</td>
<td>256 and 257</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>-Bn, -Et 171</td>
<td>B</td>
<td>1.00 : 0.62</td>
<td>256 and 257</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>-Bn, -Et 171</td>
<td>C</td>
<td>1 : 1</td>
<td>256 and 257</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>-Bn, -Me 180</td>
<td>A</td>
<td>1.00 : 0.46</td>
<td>258 and 259</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>-Bn, -Me 180</td>
<td>B</td>
<td>1.00 : 0.58</td>
<td>258 and 259</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>-Bn, -Me 180</td>
<td>C</td>
<td>1 : 1</td>
<td>258 and 259</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>-Bn, -i-Pr 181</td>
<td>A</td>
<td>1.00 : 0.38</td>
<td>260 and 261</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>-Bn, -i-Pr 181</td>
<td>B</td>
<td>1.00 : 0.44</td>
<td>260 and 261</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>-Bn, -i-Pr 181</td>
<td>C</td>
<td>1 : 1</td>
<td>260 and 261</td>
<td>&gt;95</td>
</tr>
<tr>
<td>10</td>
<td>Boc-NH-C(Me)₂-, -Et 200</td>
<td>A</td>
<td>1.00 : 0.68</td>
<td>262 and 263</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>Boc-NH-C(Me)₂-, -Et 200</td>
<td>B</td>
<td>1.00 : 0.74</td>
<td>262 and 263</td>
<td>65</td>
</tr>
<tr>
<td>12[a]</td>
<td>Boc-NH-C(Me)₂-, -Et 200</td>
<td>C</td>
<td>-</td>
<td>262 and 263</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Degradation of the starting material was observed.
Spectroscopic data for compound 258 and 259

\[ ^1H\text{-NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.40 - 7.07 \text{ (m, 20H, Ar-H), 4.45 - 4.25 (m, 2H, H}_F\text{), 3.57 (d, J=11.1 Hz, 3H, H}_O\text{), 3.40 (d, J=11.1 Hz, 3H, H}_O\text{), 3.25 - 2.80 (m, 6H, H}_E\text{ and H}_L\text{), 1.45 - 1.38 (m, 6H, H}_G\text{).} \]

\[ ^{13}C\text{-NMR (101 MHz, Chloroform-}d\text{)} \delta = 145.37 \text{ (d, J=2.9 Hz, C}_D\text{), 145.25 (d, J=3.3 Hz, C}_0\text{), 132.46 (d, J=8.7 Hz, Ar-C), 132.24 (d, J=8.7 Hz, Ar-C), 129.80 (d, J=6.3 Hz, Ar-C), 128.60 (d, J=3.2 Hz, Ar-C), 128.46 (d, J=2.9 Hz, Ar-C), 128.40 (d, J=2.9 Hz, Ar-C), 127.19 (d, J=0.9 Hz, Ar-C), 126.70 - 126.56 (m, Ar-C), 125.86 (d, J=1.2 Hz, Ar-C), 51.09 (d, J=16.9 Hz, C}_7\text{), 50.69 - 50.44 (m, C}_6\text{), 35.68 (d, J=126.3 Hz, C}_8\text{), 35.50 (d, J=126.3 Hz, C}_8\text{), 25.66 (d, J=5.7 Hz, C}_5\text{), 25.52 (d, J=6.2 Hz, C}_0\text{).} \]

**MS (ESI+, m/z):** 312 [M-Na]^+

**MS (EI+, m/z):** 289 [M]^+, 274, 198, 120 [100%], 105, 91.

**HRMS (ESI+, m/z):** for C_{16}H_{20}N_{1}O_{2}P_{1}Na_{1}, [M-Na]^+, observed 312.1123, calculated 312.1124.
$^1$H- and $^{13}$C-NMR spectrum of compounds 258 and 259 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compounds 258 and 259 recorded in CDCl₃
HMBC- and $^{31}$P-NMR spectrum of compounds 258 and 259 recorded in CDCl$_3$
Spectroscopic data for compound 256 and 257

\[ ^1\text{H-NMR (400 MHz, Chloroform-d)} \delta = 7.30 - 7.01 \text{ (m, 20H, Ar-H)}, 4.38 - 4.17 \text{ (m, 2H, H_d)}, 3.99 - 3.71 \text{ (m, 3H, H_o)}, 3.61 - 3.47 \text{ (m, 1H, H_o)}, 3.15 - 2.80 \text{ (m, 4H, H_e)}, 2.80 - 2.67 \text{ (m, 2H, H_l)}, 1.34 - 1.30 \text{ (m, 5H), 1.16 - 1.12 \text{ (m, 6H, H_c)}, 1.03 - 0.98 \text{ (m, 6H, H_p)}}. \]

\[ ^{13}\text{C-NMR (101 MHz, Chloroform-d)} \delta = 145.45 \text{ (d, J=2.9 Hz, C_H (minor))}, 145.29 \text{ (d, J=3.4 Hz, C_D (major))}, 132.65 \text{ (d, J=8.7 Hz, Ar-C (minor))}, 132.43 \text{ (d, J=8.7 Hz, Ar-C (major))}, 129.82 \text{ (d, J=6.4 Hz, Ar-C (major))}, 128.82 \text{ (d, J=6.3 Hz, Ar-C (minor))}, 128.59 \text{ (Ar-C (major))}, 128.56 \text{ (Ar-C (minor))}, 128.40 \text{ (d, J=3.0 Hz, Ar-C (minor))}, 128.35 \text{ (d, J=2.9 Hz, Ar-C (major))}, 127.15 \text{ (Ar-C, both d.r.)}, 126.58 \text{ (d, J=3.55 Hz, Ar-C (minor))}, 126.54 \text{ (d, J=3.63 Hz, Ar-C (minor))}, 125.85 \text{ (Ar-C (major))}, 125.83 \text{ (Ar-C (minor))}, 59.99 \text{ (d, J=6.9 Hz, C_E, both d.r.)}, 51.17 \text{ (C_F (minor))}, 50.98 \text{ (C_F (major))}, 36.08 \text{ (d, J=126.0 Hz, C_E (major))}, 35.84 \text{ (d, J=125.9 Hz, C_E (minor))}, 25.65 \text{ (d, J=5.6 Hz, C_G (major))}, 25.63 \text{ (d, J=6.2 Hz, C_G (minor))}, 16.32 \text{ (d, J=6.6 Hz, C_P (major))}, 16.09 \text{ (d, J=6.9 Hz, C_P (minor))}. \]

The carbon signals corresponding to the different diastereomer was found by comparing the \[^{13}\text{C-NMR}\] spectrum of the product obtained from the COMU and from the oxalyl chloride mediated phosphonamidation.

**MS (ESI$^+$ m/z):** 326 [M-Na]$^+$

**MS (EI$, m/z):** 288 [M]$^+$, 212, 120 [100%], 105, 91.

**HRMS (ESI$^+$, m/z):** for C$_{17}$H$_{22}$N$_1$O$_2$P$_1$Na$_1$, [M-Na]$^+$, observed 326.1279, calculated 326.1280
$^1$H- and $^{13}$C-NMR spectrum of compounds 256 and 257 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compounds 256 and 257 recorded in CDCl₃
HMBC- and $^{31}$P-NMR spectrum of compounds 256 and 257 recorded in CDCl$_3$. 
Spectroscopic data for compound 260 and 261

\[^{1}H\text{-NMR (400 MHz, Chloroform-}d\text{)}\delta = 7.38 - 7.11 (m, 20H, Ar-H), 4.63 - 4.50 (m, 2H, H\text{O}), 4.48 - 4.34 (m, 2H, H\text{F}), 3.16 - 2.86 (m, 4H, H\text{E}), 2.75 (\text{app.}^*t, J=9.6 \text{ Hz}, 1H, H\text{L (Major)}), 2.66 (\text{app.}^*t, J=9.8 \text{ Hz}, 1H, H\text{L (Minor)}), 1.42 (d, J=6.8 \text{ Hz}, 6H, H\text{P (Minor)}), 1.24 (d, J=6.2 \text{ Hz}, 3H, H\text{P (Major)}), 1.23 - 1.19 (m, 6H, H\text{P (Major)}), 1.02 (d, J=6.2 \text{ Hz}, 3H, H\text{P (Minor)}).

\[^{13}C\text{-NMR (101 MHz, Chloroform-}d\text{)}\delta = 145.48 (d, J=3.3 \text{ Hz}, C\text{H (Minor)}), 145.41 (d, J=3.2 \text{ Hz}, C\text{H (Major)}), 132.89 (d, J=8.8 \text{ Hz}, C\text{D (Minor)}), 132.69 (d, J=8.8 \text{ Hz}, C\text{D (Major)}), 129.84 (d, J=6.4 \text{ Hz}, Ar-C), 129.84 (d, J=6.3 \text{ Hz}, Ar-C), 128.57 (Ar-C (Major)), 128.55 (Ar-C (Minor)), 128.30 (d, J=3.03 \text{ Hz}, Ar-C (Minor)), 128.27 (d, J=3.03 \text{ Hz}, Ar-C (Major)), 127.11 (Ar-C, D.r overlapping), 126.46 (d, J=3.46 \text{ Hz}, Ar-C (Minor)), 126.45 (d, J=3.41 \text{ Hz}, Ar-C (Major)), 125.84 (Ar-C (Major)), 125.82 (Ar-C (Minor)), 69.08 (d, J=7.1 \text{ Hz}, C\text{O (Minor)}), 68.83 (d, J=7.1 \text{ Hz}, C\text{O (Major)}), 51.06 (C\text{F (Minor)}), 50.98 (C\text{F (Major)}), 36.71 (d, J=126.2 \text{ Hz}, C\text{E (Major)}), 36.62 (d, J=125.8 \text{ Hz}, C\text{E (Minor)}), 25.79 (d, J=5.6 \text{ Hz}, C\text{G (Minor)}), 25.69 (d, J=5.8 \text{ Hz}, C\text{G (Major)}), 24.25 (d, J=3.5 \text{ Hz}, C\text{P (Minor)}), 24.17 (d, J=3.8 \text{ Hz}, C\text{P (Major)}), 24.00 (d, J=4.9 \text{ Hz}, C\text{P (Major)}), 23.73 (d, J=5.3 \text{ Hz}, C\text{P (Minor)}).

The carbon signals corresponding to the different diastereomer was found by comparing the \[^{13}C\text{-NMR spectrum of the product obtained from the COMU and from the oxalyl chloride mediated phosphonamidation.}

\text{MS (ESI+ m/z): 340 [M-Na]}^+

\text{MS (EI+, m/z): 317 [M]+, 302, 274, 260 [100\%], 120, 105, 91.}

\text{HRMS (ESI+, m/z): for C}_{18}\text{H}_{24}\text{N}_{1}\text{O}_{2}\text{P}_{1}\text{Na}_{1}, \text{[M-Na]}^+, \text{observed 340.1437, calculated 340.1437}
$^1$H- and $^{13}$C-NMR spectrum of compounds 260 and 261 recorded in CDCl$_3$
COSY- and HSQC-NMR spectrum of compounds 260 and 261 recorded in CDCl₃
HMBC- and $^{31}$P-NMR spectrum of compounds 260 and 261 recorded in CDCl$_3$
Spectroscopic data for compound 262 and 263

Ratio of diastereomers 1.00 : 0.75 as calculated from the $^{31}$P-NMR

$^1$H-NMR (400 MHz, Chloroform-d$_2$) $\delta =$ 7.37 – 7.13 (m, 7.5H, Ar-H, both diastereomers), 4.76 – 4.67 (m, 1.5H, H$_D$ or H$_I$), 4.65 – 4.52 (m, 1.6H, H$_O$ both diastereomers), 4.34 – 4.20 (m, 0.87H, H$_D$ or H$_I$), 4.08 – 3.97 (m, 0.72H, H$_M$, minor diastereomer), 3.97 – 3.83 (m, 1.37H, H$_M$, minor diastereomer), 3.82 – 3.71 (m, 0.94H, H$_M$, major diastereomer), 3.71 – 3.59 (m, 1.08H, H$_M$, major diastereomer), 1.58 – 1.37 (m, 28H, H$_A$, H$_E$, H$_E'$ and H$_H$ minor diastereomer), 1.33 (d, $J$=15.3, 3H, H$_H$, major diastereomer), 1.25 – 1.17 (m, 2.55H, H$_N$, minor diastereomer), 1.06 – 0.99 (m, 2.79H, H$_N$, major diastereomer).

$^{13}$C-NMR (101 MHz, Chloroform-d$_2$) $\delta =$ 155.42 (d, $J$=3.2 Hz, C$_C$, major diastereomer), 155.14 (d, $J$=5.7 Hz, C$_C$, minor diastereomer), 146.35 (d, $J$=3.0 Hz, C$_I$, major diastereomer), 145.67 (d, $J$=4.2 Hz, C$_I$, minor diastereomer), 128.45 (Ar-C, minor diastereomer), 128.37 (Ar-C, major diastereomer), 126.90 (Ar-C, minor diastereomer), 126.73 (Ar-C, major diastereomer), 125.94 (Ar-C, minor diastereomer), 125.88 (Ar-C, major diastereomer), 79.90 (C$_B$, major diastereomer), 79.66 (C$_B$, minor diastereomer), 60.73 (d, $J$=7.5 Hz, C$_M$, both diastereomers), 52.42 (d, $J$=142.0 Hz, C$_O$, both diastereomers), 52.03 (d, $J$=141.5 Hz, C$_O$, minor diastereomer), 51.10 (d, $J$=1.2 Hz, C$_O$, minor diastereomer), 50.50 (d, $J$=1.9 Hz, C$_O$, major diastereomer), 28.43 – 28.23 (m, C$_A$ both diastereomers), 26.26 (d, $J$=4.6 Hz, C$_E$, C$_E'$ or C$_H$, unresolved), 25.85 (d, $J$=6.3 Hz, C$_E$, C$_E'$ or C$_H$, unresolved), 24.26 (C$_E$, C$_E'$ or C$_H$, unresolved), 24.05 (C$_N$, minor diastereomer), 23.03 (d, $J$=4.9 Hz, C$_E$, C$_E'$ or C$_H$, unresolved), 22.78 (d, $J$=4.0 Hz, C$_E$, C$_E'$ or C$_H$, unresolved), 16.49 (d, $J$=5.9 Hz, C$_N$, minor diastereomer), 16.34 (d, $J$=5.9 Hz, C$_N$, major diastereomer).

MS (ESI+ m/z): 393 [M-Na]$^+$

MS (EI+, m/z): Not found [M]$^+$, 297, 269, 212

HRMS (ESI+, m/z): for C$_{18}$H$_{24}$N$_2$O$_4$P$_1$Na$_1$, 393 [M-Na]$^+$, observed 393.1914, calculated 393.1914
$^1$H- and $^{31}$P-NMR spectrum of compounds 262 and 263 recorded in CDCl₃
COSY- and HSQC-NMR spectrum of compounds 262 and 263 recorded in CDCl₃
$^{13}$C-and HMBC-NMR spectrum of compounds 262 and 263 recorded in CDCl$_3$