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DOCTORAL DISSERTATION

Asymmetric synthesis of α-substituted phosphonates and phosphonic acids via hydrophosphonylation of substrates containing carbon-heteroatom bond with TADDOL-derived H-phosphonate

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Abstract

Organophosphorus compounds, especially those with stereogenic carbon atom in the proximity of the phosphorus atom, have found a wide range of applications that emerged from pharmaceutically active compounds in drug discovery to enantioselective catalysis due to their unique physical and chemical properties. However, achieving the synthesis of these chiral molecules, particularly with precise control over the stereochemistry at the chiral carbon atom, remains an exceedingly challenging task. Herein, I developed highly diastereoselective methodologies that employed the use of TADDOL-derived *H*-phosphonate, which serves as a chiral auxiliary in the asymmetric synthesis of substituted phosphonates and phosphonic acids through the nucleophilic addition to the carbon-heteroatom bond of α-amido sulphones, imines, aldehydes, ketones, and hydrazones. Good to excellent yields and high diastereoselectivities were obtained. Remarkably, the choice between the enantiomeric forms of the chiral *H*-phosphonate (*R*, *R* or *S*, *S*) significantly influenced the stereochemistry of the newly generated α-carbon. The subsequent removal of the chiral auxiliary resulted in the formation of enantiomerically pure α-substituted phosphonic acids, maintaining the configuration at the chiral α-carbon center.

Streszczenie

Związki fosforoorganiczne, szczególnie te ze stereogenicznym atomem węgla w pobliżu atomu fosforu, ze względu na swoje unikalne właściwości fizyczne i chemiczne znalazły szerokie zastosowanie, od związków o aktywności biologicznej do zastosowania w katalizie enancjoselektywnej. Jednak asymetryczna syntezy tych związków, a szczególnie precyzyjna kontrola stereochemii chiralnego atomu węgla sąsiadującego z atomem fosforu, pozostaje zadaniem trudnym. W niniejszej dysertacji opisuję wysoce diastereoselektywne procedury, które wykorzystują *H*-fosfonian pochodną TADDOL-u jako chiralny pomocnik w asymetrycznej syntezie fosfonianów i kwasów fosfonowych w reakcji nukleofilowej addycji do podwójnego wiązania węgiel-heteroatom w α-amidosulfonach, iminach, aldehydach, ketonach i hydrazonach. Uzyskałem wydajności finalnych produktów od dobrej do bardzo dobrej i w wielu wypadkach wysoką diastereoselektywność reakcji. Co ciekawe, wybór pomiędzy enancjomerycznymi postaciami stosowanego chiralnego *H*-fosfonianu (*R*,*R* lub *S*,*S*) znacząco wpłynął na stereochemię nowo generowanego centrum asymetrycznego na atomie węgla w pozycji α do atomu fosforu. Późniejsze usunięcie chiralnego pomocnika pozwoliło na otrzymanie enancjomerycznie czystych α-podstawionych kwasów fosfonowych.

Acknowledgments

I humbly express my heartfelt gratitude to all those who have been instrumental in my academic journey and towards the completion of this dissertation. Your support, guidance, and inspiration have played an integral role in this achievement.

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The Doctoral School of Wroclaw University of Science and Technology has provided a conducive academic environment and resources that have significantly contributed to my research and academic growth. I am thankful for their support, and I express sincere gratitude for the support provided by the NAWA STER Program in facilitating my international collaboration.

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I am deeply thankful to my uncle, Philemon S. Gbabele, and his family for their parental support, care, and encouragement throughout my academic pursuit. To my girlfriend, thank you for your valuable support and understanding, it means a lot to me**.**

To my spiritual family at VIJ Church, I extend my heartfelt thanks for your prayers, unwavering support, and spiritual guidance. To the many friends who have been a part of my journey, your encouragement and support have been uplifting, and I am grateful for your presence in my life.

I dedicate this academic achievement to the cherished memory of my late parents, Mr. and Mrs. Daniel Gbubele, and to all the orphans across the globe, who embody the resilience, courage, and unyielding spirit to overcome adversity.

Preface

Chiral organophosphorus compounds constitute a distinct class of molecules known for their exceptional biological activity, which is attributed to their remarkable physical and chemical properties. Their applications are extensive, ranging from medicinal chemistry to enantioselective catalysis. Although these compounds continuously captivate the interest of organic and medicinal chemists, their synthesis remains a challenging endeavor. The precise control of stereochemistry at the chiral carbon atoms attached to the phosphorus presents a particularly intricate aspect of their synthesis, requiring advanced methodologies and strategies to achieve accurate and controlled stereochemical outcomes.

In the ***introductory*** section of this dissertation, a comprehensive overview of the current state of knowledge regarding the synthesis of C- and, in certain instances, P-stereogenic organophosphorus compounds with high stereoselectivity was presented. The discussed synthetic strategy relies on the nucleophilic addition of H-P reagents bearing a chiral alcohol group, such as TADDOL, BINOL, or menthol, acting as a chiral auxiliary attached to the phosphorus atom. This approach is applied to various reaction partners, including alkenes, alkynes, imines, and carbonyl compounds, resulting in a wide array of structurally diverse chiral organophosphorus compounds, some featuring as many as five chiral centers. It's crucial to recognize that the specific chiral alcohol employed significantly influences the stereochemical outcomes in each case. As a result, the content in this section is thoughtfully categorized based on the type of chiral alcohol bound to the phosphorus atom in the H-P species utilized.

Chapter one focused on hydrophosphonylation reaction involving TADDOL-derived *H*-phosphonate to generate α-aminophosphonates and α-aminophosphonic acids from α-amido sulphones. The protocol relied on a base-catalyzed, one-pot strategy for in-situ imine formation from these sulphones. The resulting *in-situ* imines underwent hydrophosphonylation using diverse non chiral *H*-phosphonates, yielding racemic α-aminophosphonates in high yield. Using TADDOL-derived *H*-phosphonate facilitated excellent diastereoselectivity (up to 100% diastereomeric ratio) in the desired α-aminophosphonates. Notably, the choice between the enantiomeric forms of the chiral *H*-phosphonate (*R,R* or *S,S*) markedly impacted the stereochemistry at the newly formed α-carbon. Subsequent cleavage of the chiral auxiliary led to the production of enantiomerically pure α-aminophosphonic acids.

The research detailed in ***chapter two*** aimed to utilize TADDOL-derived *H*-phosphonate as a chiral auxiliary in developing a straightforward, diastereoselective method for

hydrophosphonylation of *N*-substituted imines. The focus was on employing non-chiral imines with varying substituent sizes on the nitrogen atom to explore how their steric hindrance might influence the reaction's diastereoselectivity. Regrettably, despite extensive optimizations and diverse strategies, the results obtained were not as encouraging. Nevertheless, a noteworthy observation occurred during a three-component, one-pot reaction entailing the direct condensation of aldehydes, benzhydrylamine, and TADDOL *H*-phosphonate. Besides the intended aminophosphonate, an undesired hydroxyphosphonate by-product was formed and this result was due to the presence of the two nucleophiles which were competing for a single electrophilic center. Interestingly, the diastereoselectivity of the latter product shows promise for further exploration in hydroxyphosphonate preparation.

The third chapter deals with the hydrophosphonylation of carbonyl compounds with TADDOL-derived *H*-phosphonate. Two robust and straightforward methods for synthesizing optically active α-hydroxyphosphonates have been developed. **Protocol A** involves the base-catalyzed diastereoselective hydrophosphonylation of aldehydes with TADDOL-derived *H*-phosphonate at low temperature, while **protocol B** uses quinine catalysis at room temperature. Both protocols give high yields of up to 92% and diastereomeric ratios of over 99:1. Their advantages include the use of inexpensive chiral auxiliaries, mild reaction conditions, and broad substrate compatibility. Protocol A shows better diastereoselectivity despite a longer reaction time, while Protocol B offers milder conditions. Deprotection of the α-hydroxyphosphonate under mild conditions produces enantiomerically pure α-hydroxyphosphonic acids. A reaction mechanism involving double asymmetric induction was proposed. However, the ketone reaction with TADDOL *H*-phosphonate gives quaternary α-hydroxyphosphonates with moderate conversions and poor diastereoselectivity.

In the ***fourth chapter*** of this dissertation, a copper-mediated cross-coupling reaction was detailed, leading to the creation of products featuring P-C(sp^3) bonds. This process entailed the reductive coupling of *N*-tosylhydrazones with TADDOL-derived *H*-phosphonate in the presence of a copper catalyst, resulting in the production of the corresponding alkylphosphonate with good yield but relatively poor diastereoselectivity. Additionally, the chapter delved into the diastereoselective hydrophosphonylation of *N*-acylhydrazones using TADDOL *H*-phosphonate with *R,R*-cofiguration, yielding hydrazinophosphonates with moderate to high yields and excellent diastereoselectivity after column chromatography. Notably, employing the opposite enantiomer (*S,S*) of the TADDOL-derived *H*-phosphonate in the nucleophilic addition to the hydrazone proceeded without complications.

The above research work is subject to two publications.

1. **Gbubele, J.D**., Misiaszek, T., Siczek, M., Olszewski, T.K. α-Amido sulphones as useful intermediates in the preparation of C-chiral α-aminophosphonates and α-aminophosphonic acids. *Org. Biomol. Chem*, **2023**, *21*, 6180-6191.
2. **Gbubele, J.D**., Olszewski, T.K. Asymmetric synthesis of organophosphorus compounds using H-P reagent derived from chiral alcohols. *Org. Biomol. Chem*, **2021**, *19*, 2823-2846 (a review article).

One patent

3. T.K. Olszewski, **J.D. Gbubele**. Method of synthesizing aminophosphosnates. Application number: PL239643, filled on 20/12/2021.

One patent application

4. Tomasz Olszewski, **Joseph Gbubele**, Tomasz Misiasze, Błażej Dziuk. Asymmetric method of preparing chiral 1-hydroxyphosphonates. Application number: PL446966, filled on 04/12/2023.

The results were presented at six conferences:

I. **Joseph D. Gbubele**, Tomasz Misiaszek, Miłosz Siczek, Tomasz Olszewski „Amidosulfony jako użyteczne substraty w syntezie aminofosfonianów i kwasów fosfonowych", 65th Polish Chemical Society Conference, Toruń, 18-22 September 2023, (poster).

II. **Joseph D. Gbubele**, Tomasz Misiaszek, Miłosz Siczek, Tomasz Olszewski „α-Amido sulphones as useful intermediates in the preparation of C-chiral α-aminophosphonates and α-aminophosphonic acids", XXIV International Symposium "Advances in the Chemistry of Heteroorganic Compounds", Łódz, 24 November 2023, (poster).

III. **J. D. Gbubele**, T. K. Olszewski. The utility of phosphonates derived from TADDOL in the synthesis of chiral aminophosphonic acids. 64. Zjazd Naukowy Polskiego Towarzystwa Chemicznego, Lublin, Poland, 11-16 September 2022 (poster).

IV. **J. D. Gbubele**, T. K. Olszewski Chiral H-P reagents derived from alcohol, an effective tool for the asymmetric synthesis of C-stereogenic organophosphorus compound. Balticum Organicum Syntheticum (BOS), Vilnium, Lithuania, 3-6 July 2022 (online poster).

V. **J. D. Gbubele**, T. K. Olszewski. Application of H-P reagent bearing chiral alcohol moiety in the asymmetric synthesis of organophosphorus compounds. VII Szczecińskie Sympozjum Młodych Chemików, Szczecin, Poland, 23-27 May 2022 (Oral presentaion online).

VI. **J. D. Gbubele**, T. K. Olszewski. Synthesis of organophosphorus compounds via nucleophilic addition of chiral H-P reagents derived from chiral alcohols, 23rd International Conference on Phosphorus Chemistry, Częstochowa 5-9 July 2021 (Poster).

In my third year of my PhD studies, I spent six months at Aarhus University in Denmark, collaborating with Prof. Karl Anker Jørgensen at the Department of Chemistry, focusing on catalysis under the NAWA STER program and the Erasmus mobility program. I participated in a project that successfully led to the formation of chiral norcarane scaffolds with high yields and selectivities through a combination of asymmetric organocatalysis with the (pseudo)-halogen effect. This protocol relies on the reaction of (pseudo)-halogenated 3-vinyl chromones with chiral dienamines generated in situ via inverse electron demand [4+2] cycloaddition and subsequently followed by an intramolecular S_N2 reaction. These obtained scaffolds demonstrated the ability to undergo photoinduced rearrangements or lactonization, producing complex chiral ring structures with quantitative yields and retention of configuration. The obtained results were published.

5. Barløse C. L., Faghtmann J., Bitsch R. S., Gbubele J. D., Jørgensen K. A. Asymmetric Organocatalyzed Cascade Reactions─Merging the pseudo-Halogen and Halogen Effect with Dienamine Catalysis, *Org. Lett.* **2023**, *25*, 1209–1213

In my first year of PhD studies, I had the privilege of undertaking a six-month internship at Sheda Science and Technology Complex (SHESTCO) in Abuja, Nigeria. During this tenure, I actively participated in a project centered on exploring the phytochemical and antimicrobial aspects of medicinal plant extracts. The primary emphasis was on elucidating the potential extraction of valuable secondary metabolites from these plants for subsequent biological studies.

Before embarking on my Ph.D. journey, I graduated with a first-class degree in Industrial Chemistry from Nasarawa State University Keffi, Nigeria, in 2015. During my studies, I authored two publications.

6. Tukura, W. B., **Gbubele, J. D.,** Mamman S. Nutritional qualities assessment of locally processed spaghetti, Int. J. Sci. World, 2017:5(1): 5- 8 5.
7. Uzama D., **Gbubele J. D**., Bwai M. D., Kabir M. G. Phytochemical, Nutritional and Antimicrobial Screening of Hexane, Ethyl Acetate and Ethanolic Extracts of Boswellia Dalzielii Leaves and Bark. American Journal of Bioscience and Bioengineering 2015; 3(5): 76-79.

Prior to my coming to Poland, I taught Chemistry at Government Secondary School Agudu, Nigeria. In 2019, I completed my MSc. in Chemistry with a specialization in medicinal chemistry at the Wroclaw University of Science and Technology (WUST) under the Ignacy Lukasiewicz scholarship. During my M.Sc. studies, I conducted my thesis at the Department of Bioorganic Chemistry, delving into the synthesis of aminophosphonic acids. This research involved utilizing cyclobutanone and its derivatives as substrates, and I had the privilege of being mentored by Prof. Paweł Kafarski.

Research goals

The main aim of this work was to explore the application of chiral auxiliaries, with a particular focus on the use of TADDOL-derived *H*-phosphonates for the asymmetric synthesis of α-substituted phosphonates and phosphonic acids via the addition of the TADDOL-derived *H*-phosphonate to the carbon-heteroatom bond.

The rationale behind the choice of the TADDOL-derived *H*-phosphonate is its convenient derivatization from readily available, low-cost esters of tartaric acid. These esters are commercially available in both optically pure (*R*,*R*) and (*S*,*S*) forms, allowing the synthesis of either (*R*,*R*)- or (*S*,*S*)-TADDOL-derived *H*-phosphonate (Figure 1). The experiment was to assess the effect of these chiral centers on the stereochemical outcomes of the reactions under investigation. In addition, both (*R*,*R*)- and (*S*,*S*)-TADDOL-derived *H*-phosphonates have shown remarkable versatility, offering stability as solids and serving as highly accessible chiral auxiliaries, facilitating the stereoselective incorporation of phosphorus into a wide range of substrates.

The primary synthetic strategy revolved around leveraging the easily accessible substrates containing carbon-heteroatom double bonds. These substrates encompassed a range of compounds, including C=N derivatives like imines (aldimines and ketimines), and hydrazones, along with α-amido sulphones serving as imine surrogates. Moreover, C=O compounds, specifically aldehydes and ketones, were employed as substrates in the proposed approach (Scheme A). The core objective of this research initiative was to introduce a new stereogenic center at the α-carbon atom attached to the phosphorus atom with a high degree of stereoselectivity. A key ambition was to potentially manipulate the chirality at the newly formed carbon center by utilizing (*R*,*R*)- or (*S*,*S*)-TADDOL-derived *H*-phosphonates, thus controlling the stereochemical outcome of the reactions.

I hypothesized that by meticulously optimizing the reaction conditions specific to each studied reaction, it would be feasible to attain precise control over the stereochemistry of the reaction, ultimately leading to the formation of the desired products with high stereoselectivity. Furthermore, utilizing a chiral auxiliary offered the possibility of enriching the reaction product, especially when dealing with a mixture of diastereoisomers. This purification process involved isolating one of the diastereoisomers using techniques such as crystallization or column chromatography. Finally, the cleavage of the chiral auxiliary from the pure, single

diastereoisomer product should yield enantiomerically pure substituted phosphonic acid derivatives, which serve as analogues of amino acids.

The developed protocols could potentially serve as valuable tools for medicinal chemists, particularly in their pursuit of incorporating the phosphorus atom into molecules with high stereoselectivity, aiding in the discovery of novel and enhanced pharmaceutical compounds.

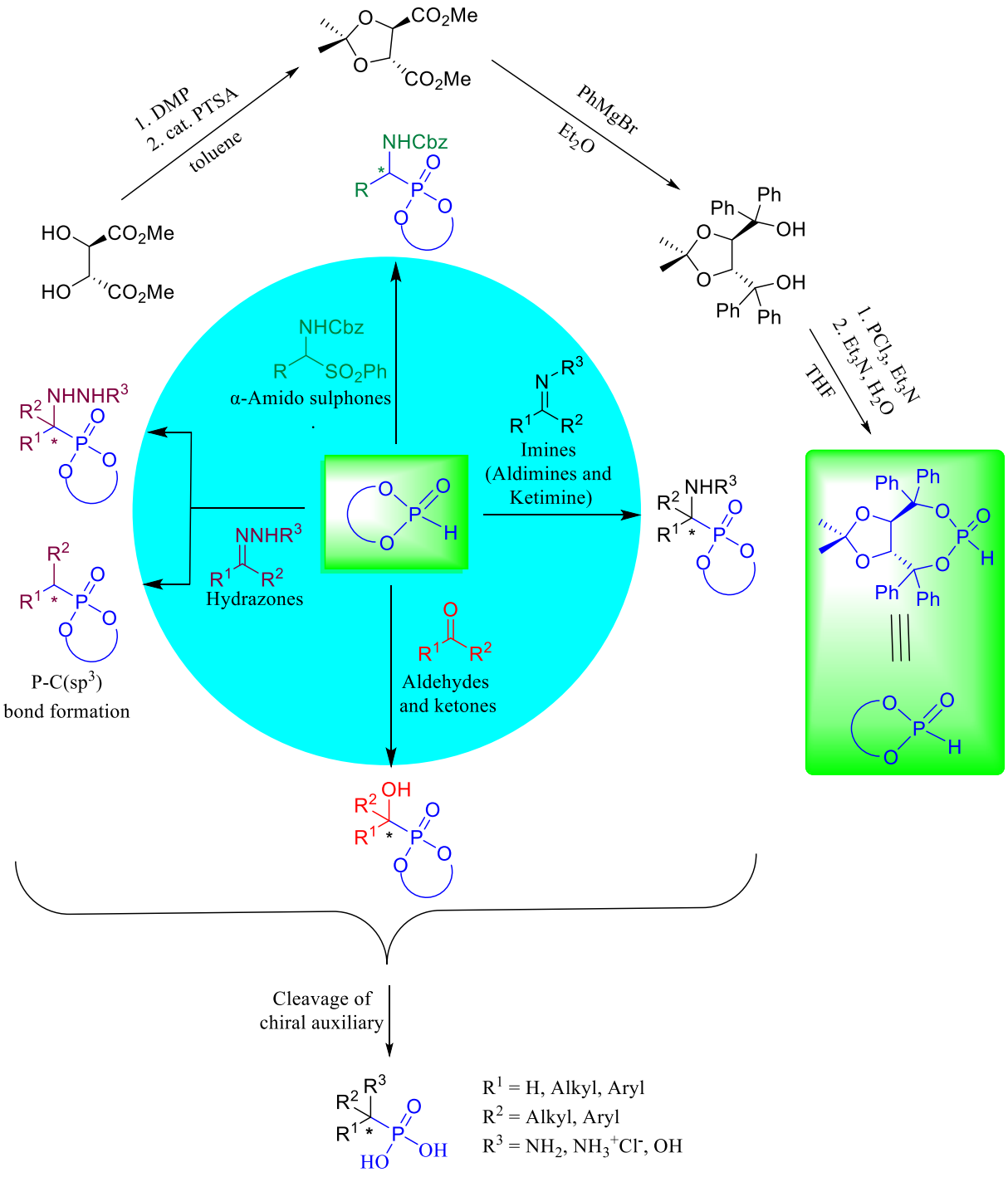

Figure 1. *The general concept of the research and the synthesis of phosphorus-containing chiral auxiliary.*

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Asymmetric hydrophosphonylation of hydrazones

Introduction

1.0. Introduction

The isolation of aminoethylphosphonic acid (AEP) **1**, a molecule bearing the C-P bond, was achieved by Horiguchi and Kandatsu in 1959 from the rumen of sheep protozoa (Figure 2)[1] However, before this groundbreaking isolation, Chavane was the first scientist to predict its existence in nature as a component of living matter in the early 1940s[2]. Since then, the chemistry of organophosphorus compounds has garnered significant attention from scientists worldwide, owing to their diverse range of applications in the chemical[3–6], agrochemical (insecticides, fungicides, herbicides)[7–9], and pharmaceutical industries[10–14] Additionally, these compounds have demonstrated utility as ligands for catalysis [15–19].

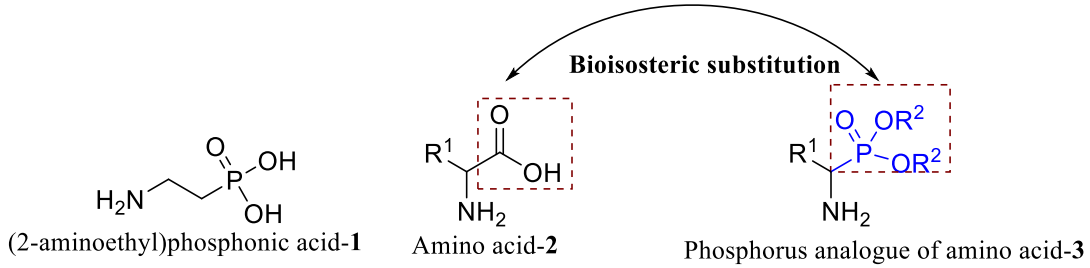


Figure 2*. First natural occurring aminophosphonic acid **1**, structure of amino acid **2** and its phosphorus-containing analogues **3**.*

Especially, the biological and pharmacological importance of α-aminoalkylphosphonic acids, α-hydroxyphosphonic acids, and their corresponding esters (phosphonates) have drawn significant interest within the range of recognized organophosphorus compounds[20,21]. The term amino (phosphonic/phosphinic/phosphine oxide) acid **3** refers to an analogue of natural amino acid **2** wherein the planar and less bulky carboxylic acid functionality (-COOH) is replaced by the phosphonic acid $P(O)(OH)_2$, phosphinic P(O)(OH)R (where R could be H, alkyl, or aryl), phosphine oxide $P(O)R_2$ (where R could be alkyl or aryl), or any other related phosphorus moiety (Figure 2). This substitution gives rise to the N-C-P molecular scaffold, which offers various possibilities for structural modifications that hold significant biological importance (Figure 3)[22]. In contrast, hydroxyphosphonic acid is formed by substituting the amine functional group of aminophosphonic acid with a hydroxyl group (-OH).

Most organophosphorus compounds are structurally analogous to their corresponding amino acids and exhibit a transition state that mimics peptide hydrolysis. However, they differ significantly in terms of geometry, with phosphonic acid adopting a tetrahedral shape in contrast to the planar shape of the carboxylic acid moiety. Additionally, these compounds vary in steric

bulk, as the carbon atom has a smaller radius compared to the phosphorus atom. Furthermore, their acidity differs, with the phosphonic group being more acidic than the carbonylic group. These distinctions provide a deeper understanding of the structural characteristics of this class of compounds when compared to their amino acid counterparts. Despite sharing similar properties, organophosphorus compounds, particularly (amino)phosphonic acids, are often recognized by enzymes and receptors as false substrates or inhibitors[22]

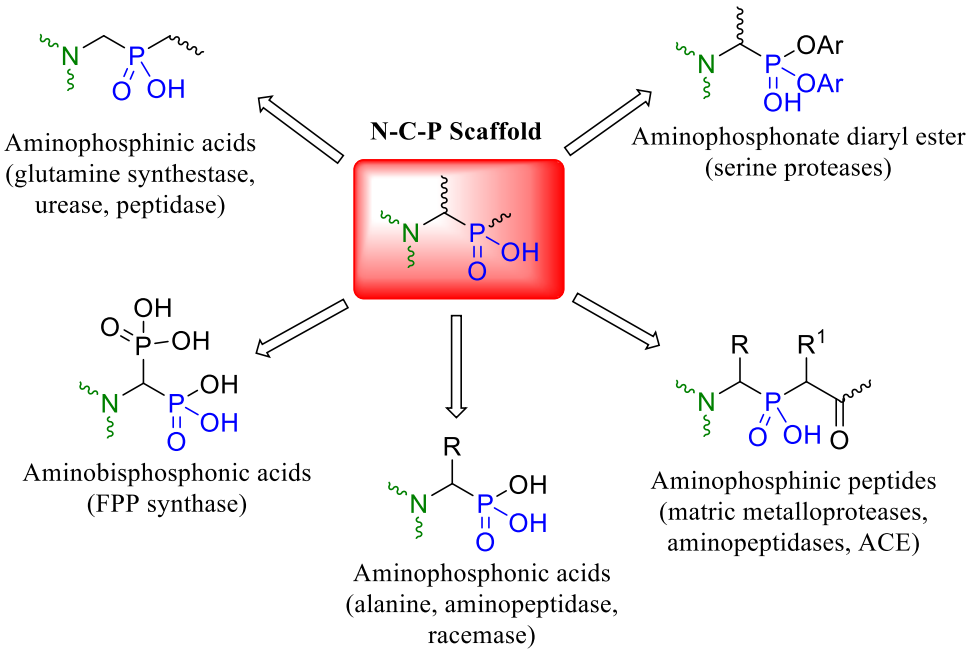


***Figure 3**. Compounds with N-C-P scaffold and their medicinally relevant molecular targets.*

Because of the interesting and broad applications of α-substituted phosphonic acids and their esters, their synthesis, especially through asymmetric methods, continues to present a formidable challenge. As precise stereoselective control is crucial for regulating biological and chemical processes, it becomes essential to obtain molecules with accurate control over chirality, especially at the chiral carbon center connected to the phosphorus atom. Given the importance of chiral organophosphorus compounds, it is not unexpected that several approaches have emerged to facilitate their asymmetric synthesis[23–26].

Despite considerable advances, there is still a tremendous need for the development of simple and scalable strategies for the asymmetric synthesis of phosphorus-containing compounds due to their biological and pharmaceutical importance and this will be the focus of this research.

2.0. Applications of chiral substituted phosphonates and phosphonic acids

2.1. The biological activity of chiral substituted phosphonates and phosphonic acids

Enzymes act as biological catalysts, accelerating metabolism and chemical reactions in the body. They are vital for facilitating nearly all metabolic processes within cells, ensuring their occurrence at a rate that supports life[27]. However, excessive rapidity in these reactions can adversely affect cellular function. Therefore, inhibitors are necessary to prevent or regulate these enzymatic reactions. In 1959, Mastalerz was the first to describe phosphonic acid analogue of glutamic acid **4** as an enzyme inhibitor of avian brain glutamine synthetase[28]. Ever since several aminophosphonic and hydroxyphosphonic acids have been discovered and proven to be effective inhibitors of enzymes. Among these, is the tripeptidic α-hydroxyphosphonate **6**, a class of transition state analogues with good inhibitory activity against aspartyl protease renin, an enzyme that plays a crucial role in the regulation of blood pressure and fluid balance in the body. Replacing the ester group in **5** with its bioisostere, a phosphonate group, led to the formation of **6** with improved binding interactions (Figure 4)[29].

Aminopeptidase is an enzyme that plays a crucial role in removing amino acids from the N-terminus of proteins and peptides. Although they are vital for the proper functioning of both prokaryotic and eukaryotic cells but often emerge as a key factor in the development of devastating human diseases such as cancer, malaria, and diabetes[30]. In the quest to understand and control aminopeptidase activity, numerous inhibiting agents have been synthesized, including (*R*)-phospholeucine **7** (Figure 4). This compound, serving as an isostere of natural hydrophobic aliphatic amino acids, effectively inhibits leucine aminopeptidase (LAP) with a K_i value of 0.23 μM[31]. The inhibition of aminopeptidase by (*R*)-phospholeucine underscores its potential as a valuable tool for studying the role of aminopeptidases and investigating their significance in diverse biological processes.

The discovery of penicillin by Alexander Fleming in 1928 was a turning point in medicine[32]. Since then, several antibiotics have been discovered that led to a revolution in the treatment of bacterial diseases. Substituted phosphonates and their corresponding phosphonic acids represent a fascinating class of antibiotics that are now accessible.

In the early 1940s, phosphanilic acid **8** was the first organophosphorus compound with antibacterial properties to be synthesized[33]. However, little attention was given to research on the antibacterial properties of organophosphorus compounds until the 1970s, when numerous natural antibiotic phosphonopeptides were discovered. Alafosfalin **9**, an analogue of alanine

and potent inhibitor of alanine racemase, arose because of the great interest in the discovery of peptides containing C-terminal phosphonic acid.

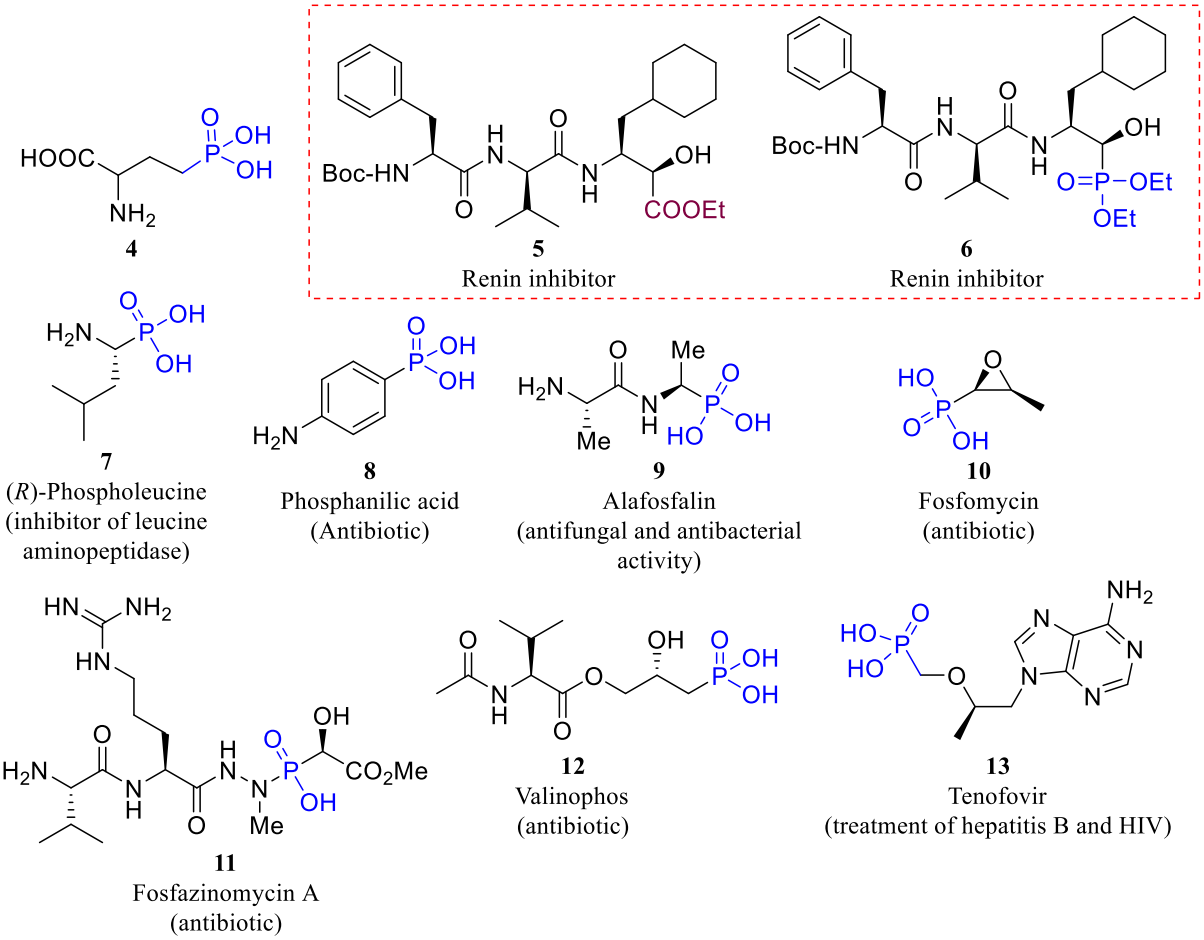


***Figure 4**. Some examples of biologically active chiral organophosphorus compounds with C-stereogenic centers near the phosphorus atom.*

This phosphonopeptide is groundbreaking in understanding the mechanism of action of phosphorus-containing peptides as antibiotics. The target component of this molecule is the peptide fragments. This allows the peptides to be efficiently transported across the bacterial or fungal membranes, releasing aminophosphonic acids upon hydrolysis. These acids exert their toxic effect by inhibiting important enzymes[34]. This mechanism of action is exhibited by most phosphonopeptides derived from bacteria, including bialaphos (produced by *Streptomyces viridochromogene*)[35], plumbemycins (produced by *Streptomyces plumbeus*), rhizotocin (produced by *Bacillus subtilis*)[36], and fosmidomycin (produced by *Streptomyces lavenulae*)[37].

There are two major challenges in treating bacterial infections: Firstly, the rise of multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens, and secondly, the lack of significant progress in developing new effective antibiotics specifically designed to combat

MDR and XDR bacteria. Recently, fosfomycin **10** has received increasing attention due to its proven efficacy against both Gramme-positive and Gramme-negative MDR and XDR bacteria. This compound acts as a self-moderating inhibitor of UDP-N-acetylglucosamine enolpyruvyltransferase, which impairs peptidoglycan biosynthesis and leads to bacterial cell death[38]. Fosfazinomycin A **11** is another phosphorus-containing antibiotic obtained from *Streptomyces lavendofoliae* 630 and is a natural product with phosphonate properties[39]. The presence of Val–Arg dipeptide's C-terminal carboxylate, which is linked to methyl 2-hydroxy-2-phosphono-acetate (Me-HPnA) via a distinct hydrazide bond gives it a unique structural feature that enables it to exhibit it antibacterial property[40]. The phosphonopeptide, valinophos **12** is recently isolated from *Streptomyces durhamensis*[41]. This compound possesses an uncommon 2,3-dihydroxypropylphosphonate (DHPPA) fragment, with N-acetyl-L-valine attached to the primary alcohol moiety, and its presence effectively suppressed the growth of *Mycobacterium smegmatis*.

Tenofovir **13** falls into the category of nucleotide analogue reverse transcriptase inhibitors (NtRTIs) and is frequently prescribed to address infections caused by human immunodeficiency virus (HIV-1) and hepatitis B virus (HBV). Its mechanism of action targets reverses transcriptase and HBV polymerase enzymes, which play a critical role in the replication of HIV-1 and HBV viruses in infected individuals. By interrupting the replication process, tenofovir effectively reduces viral load in the body[42,43]. This reduction in viral loading not only slows the progression of the disease but also strengthens the immune system's ability to fight these viruses.

The biological importance of chiral phosphonates and phosphonic acids is evident in their role as enzyme inhibitors, potential antibiotics, and antiviral agents. These compounds offer valuable tools for regulating enzymatic reactions, studying aminopeptidase activity, and combating bacterial infections and viral diseases. The discovery of these compounds and their wide range of mechanisms of action have played a role in advancing the field of medicine and enhanced our understanding of biological processes. They offer great promise in addressing the challenges posed by drug-resistant pathogens and the need for new therapeutic options. Overall, chiral phosphonate and phosphonic acids represent a significant class of compounds with immense potential in various areas of biology and medicine[44].

2.2. Applications of substituted phosphonates and phosphonic acids in agriculture

In 1972, the multinational agrochemical company Monsanto (now owned by Bayer AG) made a groundbreaking advancement in the field of phosphorus-containing herbicides. They discovered and developed a derivative of aminophosphonic acid called glyphosate (N-phosphonomethylglycine) **14** (Figure 5). This significant breakthrough can be attributed to the efforts of John E. Franz, a chemist employed by Monsanto[45]. While exploring novel chemical compounds with potential herbicidal properties, Franz stumbled upon glyphosate and its remarkable ability to effectively eliminate a wide range of weeds, while exhibiting minimal toxicity towards animals. Subsequently, glyphosate, marketed as Roundup, has since emerged as the predominant and highly efficient weed control tool in agriculture, forestry, and horticulture.

The phytotoxicity of glyphosate-containing herbicides can be explained from a mechanistic standpoint by their ability to inhibit a crucial enzyme called 5-enolpyruvyl shikimate-3-phosphate synthase (EPSPS) **15**. EPSPS plays a fundamental role in the shikimate acid pathway, which is vital for the biosynthesis of three aromatic amino acids (tyrosine, tryptophan, and phenylalanine), as well as many other aromatic compounds in algae, higher plants, bacteria, and fungi. This enzyme is found in the chloroplasts, where it catalyzes the transfer of phosphoenolpyruvate (PEP) and shikimate-3-phosphate (S3P) to produce 5-enolpyruvyl-shikimate-3-phosphate and inorganic phosphate (Figure 5). Notably, this pathway is not present in animals. The herbicide glyphosate can effectively bind to the substrate binding site of the enzyme EPSPS due to its structural resemblance to PEP. As a result, it obstructs and hinders the enzyme's transportation into the chloroplast. By doing so, the herbicide inhibits the normal functioning of the shikimic acid pathway, leading to a deficiency of aromatic amino acids. Ultimately, this deprivation of essential nutrients causes the plant to die from starvation.[46].

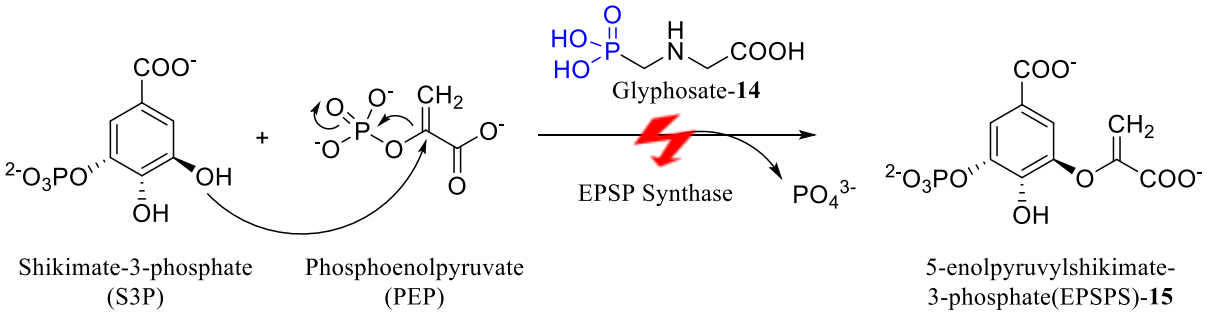
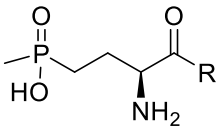


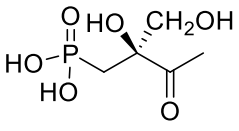
***Figure 5**. Mechanism of glyphosate in inhibiting 5-enolpyruvyl-shikimate-3-phosphate synthase.*

In recent years, the utilization of glyphosate has become a topic of contention and discussion because there are concerns regarding its potential repercussions on both health and the environment. Several studies have indicated possible connections between exposure to glyphosate and several health problems, including cancer and other detrimental effects on human well-being. The classification of glyphosate as a probable human carcinogen by the International Agency for Research on Cancer (IARC), a division of the World Health Organization, has intensified the ongoing debate[47]. Glyphosate's safety is continually being assessed by regulatory bodies across the globe, leading to the implementation of regulations and restrictions on its usage in various countries. Ongoing scientific research and studies are being conducted to enhance a better understanding of the potential impacts of glyphosate on human health and the environment, to provide more comprehensive insights.

The presence of carbon-phosphorus bonds (C−P) in natural products (NPs) has been pivotal in advancing herbicide research. This is due to the wide range of chemical characteristics and highly promising biological effects demonstrated by natural C−P phytotoxins, which offer exciting prospects for developing natural herbicides with novel targets. At present, a variety of natural herbicides containing C−P bonds have been discovered (Figure 6). Among the numerous compounds in this category, glufosinate **16** has emerged as a widely recognized natural herbicide that has gained global popularity and is commercially available under various trade names, including Basta, Buster, Finale, Harvest, Ignite, Liberty, and Rely. This herbicide was first introduced to the market in the 1980s, establishing its presence as a prominent solution for weed control among farmers, gardeners, and agricultural professionals worldwide.



Glufosinate (R = OH), **16**
Bialaphos (PPT) (R = L-Ala-L-Ala), **17**
Trialaphos: R = L-Ala-L-Ala-L-Ala), **18**
Phosalacine (R = L-Ala-L-Leu), **19**



Phosphonothrixin, **20**

Figure 6*. Naturally occurring C-P bond containing molecules with herbicidal properties.*

Glufosinate (Phosphinothricin) **16**, acts as an herbicide by inhibiting the enzyme glutamine synthetase (GS) in plants. GS is crucial for nitrogen metabolism in higher plants as it converts ammonia and glutamate into glutamine. This enzyme plays a significant role in assimilating ammonia derived from nitrogen fixation, immediate nitrate, and soil uptake, as well as reassimilating ammonia from various cellular processes[48]. By inhibiting GS, glufosinate

disrupts the normal nitrogen assimilation process such as photorespiration and protein degradation, leading to the accumulation of toxic ammonia, inhibition of photorespiration, and the rapid production of reactive oxygen species (Figure 7)[49,50]. The herbicidal effect of glufosinate **16** can be reversed by glutamine, indicating the importance of GS inhibition in its mode of action[51].

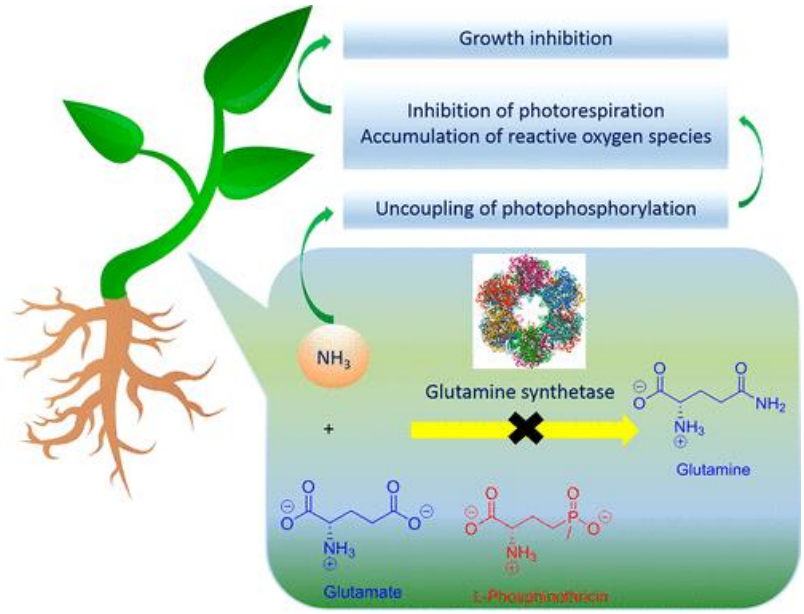


***Figure 7**. Mechanism of action of Glufosinate as a potent inhibitor of glutamine synthetase (GS) in higher plants*[50].

Bialaphos **17** is also a phosphorus-containing herbicide that inhibits the activity of glutamine synthetase and has a similar mode of action to glufosinate **16**. In addition to glyphosate, glufosinate, and bialaphos, scientists have identified and extensively studied more than 40 small molecules that possess naturally occurring carbon-phosphorus bonds. Notable examples among these compounds are trialaphos **18**, phosalacine **19**, and phosphonothrixin **20** (Figure 5)[50]. These discoveries present promising opportunities for the future development of herbicides that address the increasing demand for environmentally safe alternatives, featuring distinct modes of action and the ability to combat the rising herbicide resistance observed in commercially available products.

3.0. General methods for the synthesis of chiral α-substituted phosphonates

The synthesis of chiral α-substituted phosphonates and their derivatives has advanced significantly, utilizing diverse substrates and methods. Approximately 50% of research papers dedicated to this class of compounds commonly use aldehydes and ketones as starting materials[52]. These versatile and abundant substrates offer functional groups that can be

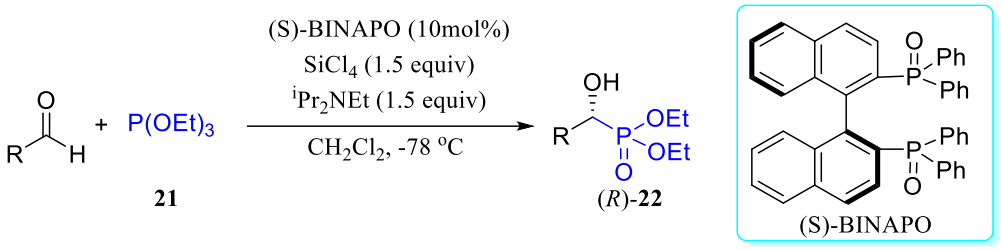
selectively manipulated to introduce desired chirality and substitution patterns, playing a crucial role as building blocks for synthesizing structurally diverse chiral α-substituted phosphonates with applications in biological and pharmaceutical sectors.

The synthesis of α-substituted phosphonates is generally based on classical methods such as Abramov, Pudovik, and Kabachnik-Fields reactions (these methods involve the addition of phosphorus-containing nucleophiles to carbon-heteroatom bonds such as C=O and C=N). In this part, I do not specifically address the phospha-Michael reaction, which is a method of synthesizing organophosphorus compounds through the addition of phosphorus-containing nucleophiles to C=C. Nevertheless, this approach has been subject to modifications that have resulted in the development of several protocols[26,44,53].

While many research papers focus on the synthesis of α-substituted phosphonates and their derivatives, the objective of this section is to provide a concise overview of the current state-of-the-art in their synthesis. The aim is not to delve into intricate protocol details but to establish a foundation for the subsequent discussion on hydrophosphonylation using phosphorus-containing chiral auxiliary, which is the primary subject of this section.

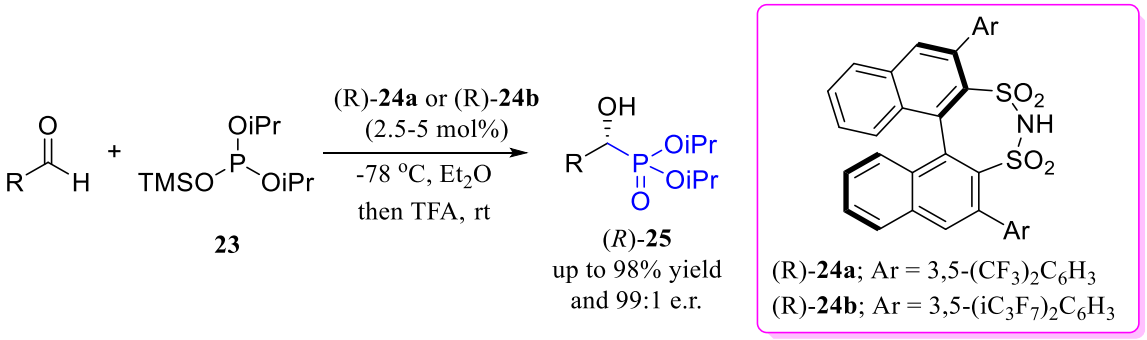
3.1. The C-P bond formation via Abramov reaction

The Abramov reaction, named after Russian chemist Vasilii Semenovich Abramov, is a reaction in which a C-P bond is formed by adding trialkyl phosphite to carbonyl compounds, resulting in the formation of α-hydroxyphosphonates[54,55]. In this reaction, the overall mechanism entails the phosphorus acting as a nucleophile and attacking the carbon atom of the carbonyl group. The first asymmetric Abramov phosphonylation of aldehydes with trialkyl phosphites, catalyzed by chiral Lewis bases, was reported in 2008 by the Nakanishi research group. Before this, the stereoselective synthesis of α-hydroxyphosphonates following Abramov's protocol was unknown. In their study (Scheme 1)[56], the Nakanishi research group utilized BINAP dioxide (BINAPO) as the chiral Lewis base in combination with $SiCl_4$ complex to activate the prochiral aldehyde. This activation facilitated the enantioselective attack of the trialkyl phosphite **21**, resulting in the formation of α-hydroxyphosphonates **22**. The reaction provided good yields but exhibited poor enantioselectivity (52% ee in the best case).



Scheme 1. *First asymmetric synthesis of α-hydroxyphosphonate via Abramovic protocol*

Benjamin List et al. successfully demonstrated the effective application of chiral disulfonimide catalysis in the enantioselective Abramov reaction, leading to the formation of α-hydroxyphosphonates with remarkably high enantiomeric ratios (Scheme 2)[57].



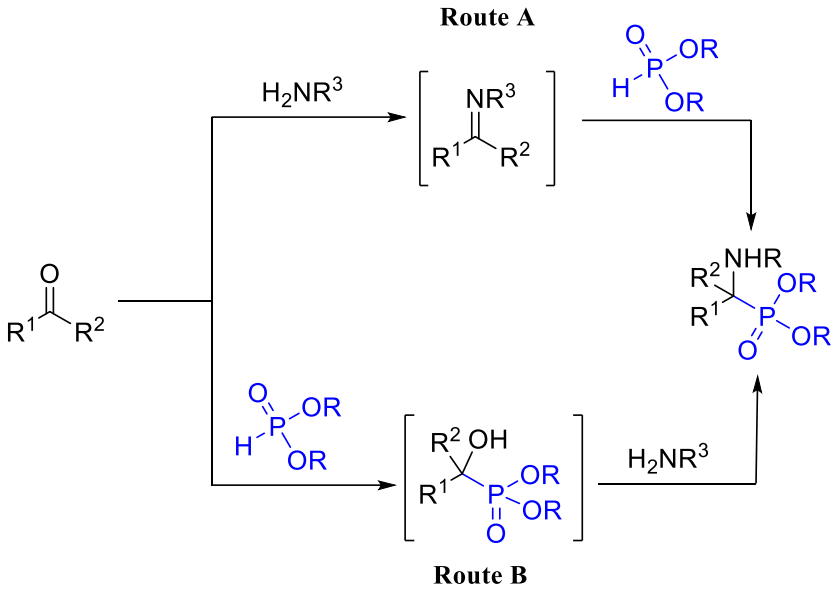
Scheme 2. *Enantioselective synthesis of α-hydroxyphosphonates catalyzed by disulfonimide* ***24***.

Their protocol involved the addition of silylphosphite **23** to aromatic, heteroaromatic, and bulky aldehydes, catalyzed by disulfonimide **24**. This approach yielded adducts **25** with nearly quantitative yields (98%) and achieved high enantioselectivity (up to 98% ee). The significant achievement in the enantioselective synthesis of the products in this approach was made possible through the incorporation of chiral disulfonimide silyl-Lewis acid, which effectively overcame the challenges commonly encountered with metal-based catalyst systems which include low selectivity and issues with reactivity that usually resulted in low yields[57–59]

3.2. The C-P bond formation via Kabachnik-Fields reaction

Kabachnik-Fields reaction is a classical and most widely used method in the synthesis of α-aminophosphonates, α-aminophosphinates or tertiary phosphine which was first reported independently by Russian chemist Martin Kabachnik and English chemist Ellis K. Fields in the early 1950s[60–62]. This reaction involves a one-pot three-component coupling of an aldehyde (or ketone), a primary or secondary amine, and a phosphite ester under various reaction conditions (Scheme 3). The precise mechanism of the Kabachnik-Fields reaction is still not completely understood. The most likely pathway involves the formation of an imine *in situ* through the

condensation of a carbonyl compound with an amine. This initial step is followed by the hydrophosphonylation of the generated imine using a phosphite ester (Scheme 3, route A)[63].



***Scheme 3**. C-P bond formation via Kabachnik-Fields reaction*

In an alternative pathway, the reaction proceeds by the addition of dialkyl *H*-phosphonate to the carbonyl group of the oxo component to give the α-hydroxyphosphonate. Subsequently, the hydroxyphosphonate undergoes substitution by the amine, resulting in the formation of the desired α-aminophosphonate product (Scheme 3, route B)[64]. A key challenge in the Kabachnik-Fields reaction arises from the coexistence of two nucleophiles: a "hard" nucleophile (amine) and a "soft" nucleophile (*H*-phosphonate). These nucleophiles compete for the electrophilic center of the carbonyl compound, leading to the formation of aminophosphophosphonates as desired products accompanied by the undesired generation of hydroxyphosphonate or derivative of its phospha-Brook rearrangement [65–68].

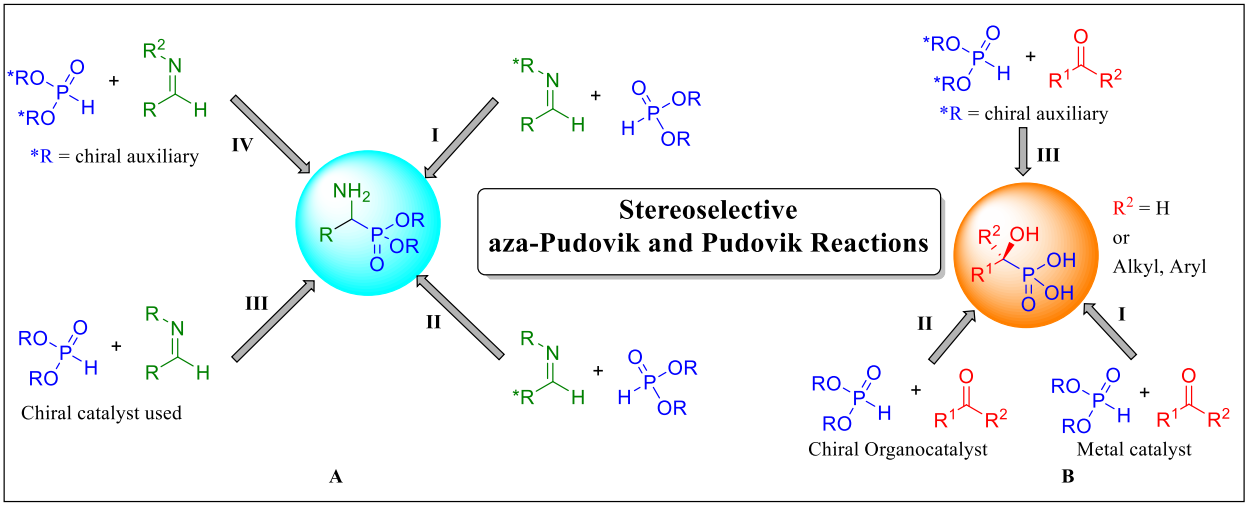
For a more comprehensive understanding of the various enantioselective methodologies employed in the synthesis of optically active α-aminophosphonates through the Kabachnik-Fields reaction, please refer to Chapter 2, section 1.1 (page 89-98).

3.3. The C-P bond formation via Pudovik reaction

The Pudovik reaction is a powerful transformation in organic chemistry that involves the direct condensation of *H*-phosphonate with carbonyl compounds, imines, or oxoiminium derivatives [52,69]. This reaction leads to the formation of α-aminophosphonates precisely known as the aza-Pudovik reaction, or α-hydroxyphosphonates, known as the Pudovik reaction. These compounds serve as important intermediates in synthesizing α-aminophosphonic or α-

hydroxyphosphonic acids. The (aza)-Pudovik reaction is widely regarded as one of the most versatile and practical methods for preparing substituted α-aminophosphonates and α-hydroxyphosphonates with diverse applications in the pharmaceutical and agrochemical industries.

In recent years, significant progress has been made in the development of stereoselective protocols of the (aza)-Pudovik reaction, enabling the synthesis of optically active α-phosphonates. Within this context, in general four distinct routes have been identified:



***Scheme 4**. The stereoselective synthesis of α-aminophosphonates and α-hydroxyphosphonates via aza-Pudovik reaction (A) and Pudovik reaction (B).*

I. The addition of *H*-phosphonates to *chiral* imines, which are conveniently formed through the condensation of aldehydes with chiral amines (Scheme 4, AI)
II. Condensation of chiral aldehydes with non-chiral imines to generate chiral imines that undergo hydrophosphonylation with *H*-phosphonates to form enantioenriched α-aminophosphonates (Scheme 4, AII).
III. The third approach is the addition of *H*-phosphonates to non-chiral imines (Scheme 4, AIII) or carbonyl compounds (Scheme 4, BI, BII), facilitated by the presence of a chiral catalyst which can be a transition metal complex or an organocatalyst.
Chapters 2 and 3 of this dissertation will explore Points I, II, and III in more detail.
IV. The fourth approach in the (aza)-Pudovik reaction involves the addition of chiral *H*-phosphonates, often utilizing phosphorus-containing chiral auxiliaries, to non-chiral imines (Scheme 4, AIV) or carbonyl compounds (Scheme 4, BIII).

In this dissertation I will primarily focus on strategy IV, undertaking more extensive research and engaging in in-depth discussions.

4.0. Synthesis of substituted phosphonates via H-P species bearing chiral auxiliary attached to the phosphorus atom

4.1. General concept of chiral auxiliary and H-P species bearing chiral auxiliary

The preparation of diverse biological molecules with high asymmetric induction and precise stereocontrol has been the focus of several developed methods. One of the approaches used to control the stereochemical outcome of the products in organic reactions has been the use of chiral auxiliaries[70]. A chiral auxiliary is a stereochemically active group or unit that is temporarily introduced into an organic compound to regulate/control the stereochemical outcome of the reaction[71]. In this asymmetric approach, the substrate is covalently bonded to a chiral auxiliary, resulting in a diastereoselective reaction where the asymmetric induction is controlled or regulated by the chirality of the chiral auxiliary. Upon the formation of the new stereogenic center, the chiral auxiliary can be cleaved and potentially reused (Figure 8).

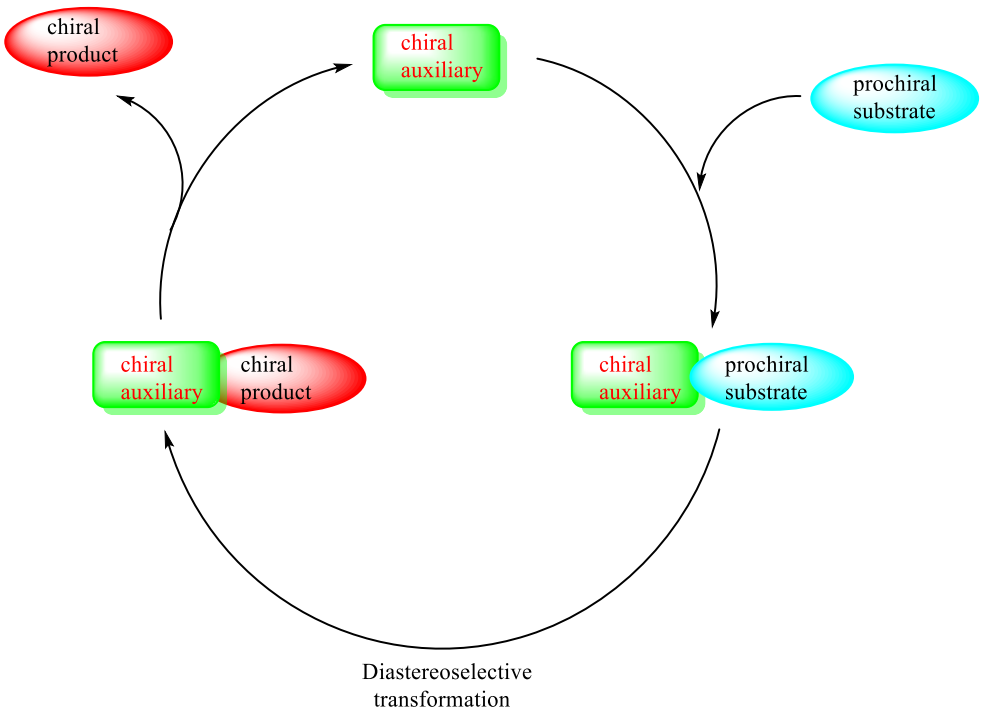


***Figure 8**. General concept of chiral auxiliary in asymmetric synthesis*

Chiral auxiliaries utilized in asymmetric synthesis predominantly originate from natural sources, including carbohydrates, amino acids, terpenes etc. However, their use in reaction setups is limited by several factors, including challenges in obtaining them with enantiomeric purity on a large scale and limitations in accurately identifying their structural properties[72,73]. To overcome these challenges, synthetic auxiliaries have been developed as alternatives to naturally occurring ones (Figure 9)[70].

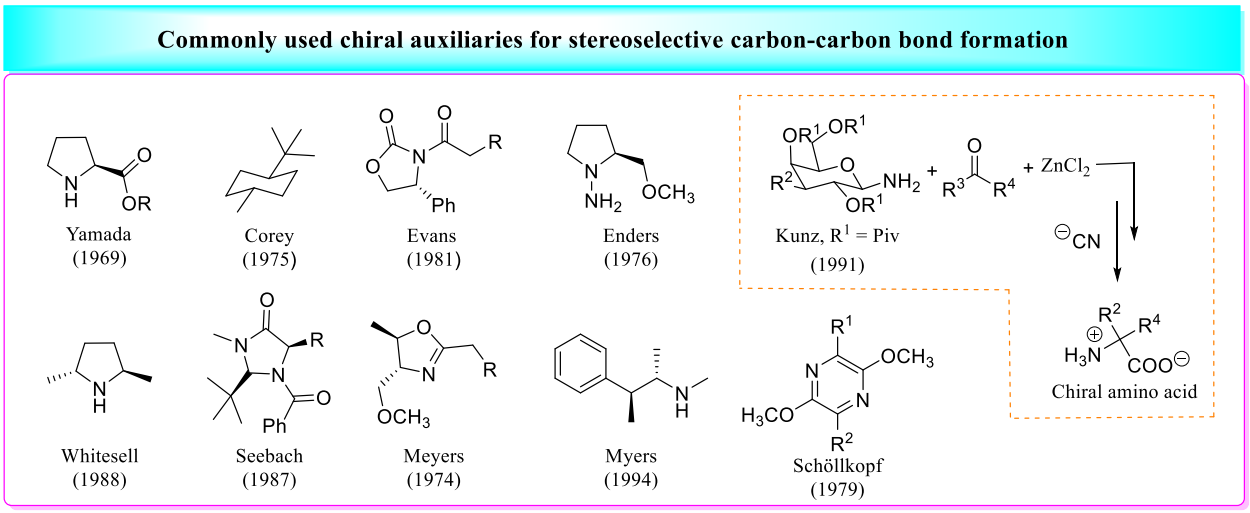


***Figure 9**. Representative examples of chiral auxiliary used in asymmetric synthesis of compounds through C-C bond formation.*

When selecting a chiral auxiliary for a reaction or developing new ones, there are several factors to consider, which include ease of preparation, ability to easily be incorporated into an achiral substrate, ability to provide a high level of asymmetric induction, ease of removal from the resulting product under mild conditions, and potential for recovery and reuse due to their often high cost and the requirement for stoichiometric quantities in a reaction[70,72,73]. Figure 9 showcases several examples of chiral auxiliaries that are commonly employed in the synthesis of highly stereoselective compounds through C-C bond formation and diverse molecular structures with significant biological activity. For example, in 1991, Kunz's research team successfully carried out a stereoselective Strecker reaction by employing carbohydrates, specifically pivaloylated galactosylamine (R^2 = H) and pivaloylated arabinosylamine (R^2 = Me) as chiral auxiliaries. In the presence of a Lewis acid catalyst, this reaction resulted in the formation of enantiopure amino acids after hydrolysis (Figure 9)[74,75]. Therefore, the use of the chiral auxiliary strategy has not only played a crucial role in advancing asymmetric synthesis, but it continues to offer highly practical and dependable procedures for the efficient synthesis of chiral compounds with exceptional stereoselectivity[70,76].

The H-P species bearing a chiral auxiliary bonded to a phosphorus atom (such as the readily accessible and cost-effective chiral alcohols e.g. TADDOL, BINOL, and menthol) represents an interesting approach in the synthesis of chiral organophosphorus compounds[70,77]. The reaction of these chiral H-P species with different partners, including carbonyl, imines, alkenes, and alkynes compounds, provides a convenient route in obtaining a wide range of chiral organophosphorus compounds with up to five asymmetric centers (Figure 10). Furthermore,

employing these H-P species with chiral auxiliary attached to the phosphorus atom serves as a valuable and straightforward tool for monitoring the stereochemical outcome of the reaction using ^{31}P and/or ^{1}H NMR spectroscopy since the addition of such chiral H-P species leads to the formation of diastereomeric pairs in the product, which can be distinguishable using NMR spectroscopy.

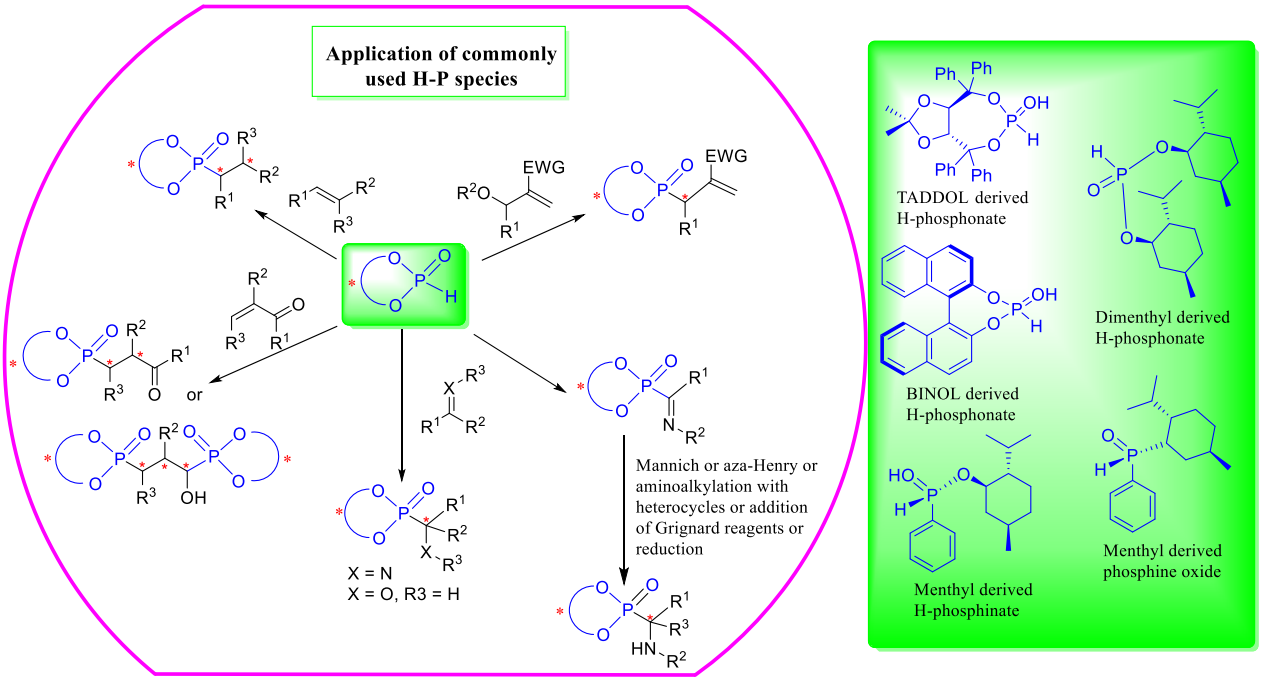
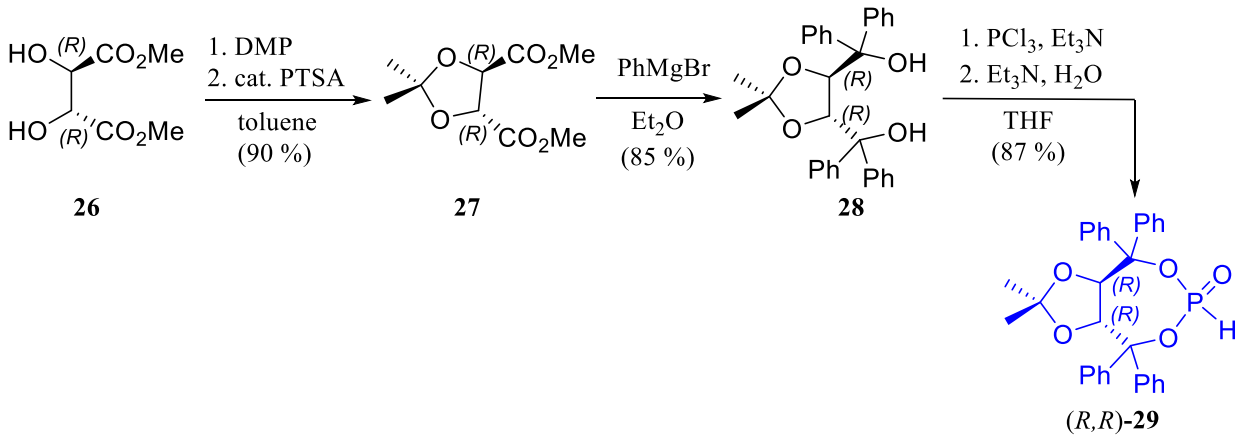


Figure 10. *Application of commonly used phosphorus-containing chiral alcohols in the asymmetric preparation of organophosphorus compounds*

In the following sections, I will present a comprehensive overview of recent advancements in asymmetric synthesis of organophosphorus compounds containing C- and, in certain instances, P-stereogenic centers. These advancements involve the use of chiral H-P species derived from TADDOL, BINOL, or menthol, which function as chiral auxiliaries attached to the phosphorus atom. Significant emphasis will be placed on essential aspects such as the methodologies used to assess the reaction stereoselectivity, determination of the absolute configuration of the newly formed stereogenic carbon atom (in some cases phosphorus atom), and isolation of optically pure products. To enhance a comprehensive understanding of this subject matter, the sections are organized based on the type of phosphorus-containing chiral auxiliary used in the reaction.

4.2. Application of TADDOL derived *H*-phosphonate in the synthesis of phosphorus-containing compounds

The TADDOL and its derivatives have gained recognition as privileged chiral ligands and catalysts[78], establishing them as crucial sources of chirality in the field of asymmetric synthesis[79–81]. The synthesis of (*S*,*S*)- or (*R*,*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxalane (TADDOL) **28** has been well-established for decades[82–84] and involves a two-step transformation process. The starting material for this synthesis is the readily available and cost-effective tartaric acid dimethyl ester **26**, which is commercially available and can be purchased in both enantiomeric forms. The subsequent reaction of (*R*,*R*)-**28** with PCl_3 followed by hydrolysis of the resulting chloride, leads to TADDOL-derived *H*-phosphonate **29**, which is a white solid with excellent stability in the presence of air and moisture, allowing it to be stored for extended periods without any special precautions (Scheme 5)[84,85]. Importantly, this synthetic route can be successfully applied, even on a multigram scale, enabling the production of significant quantities of the desired compound **29**.



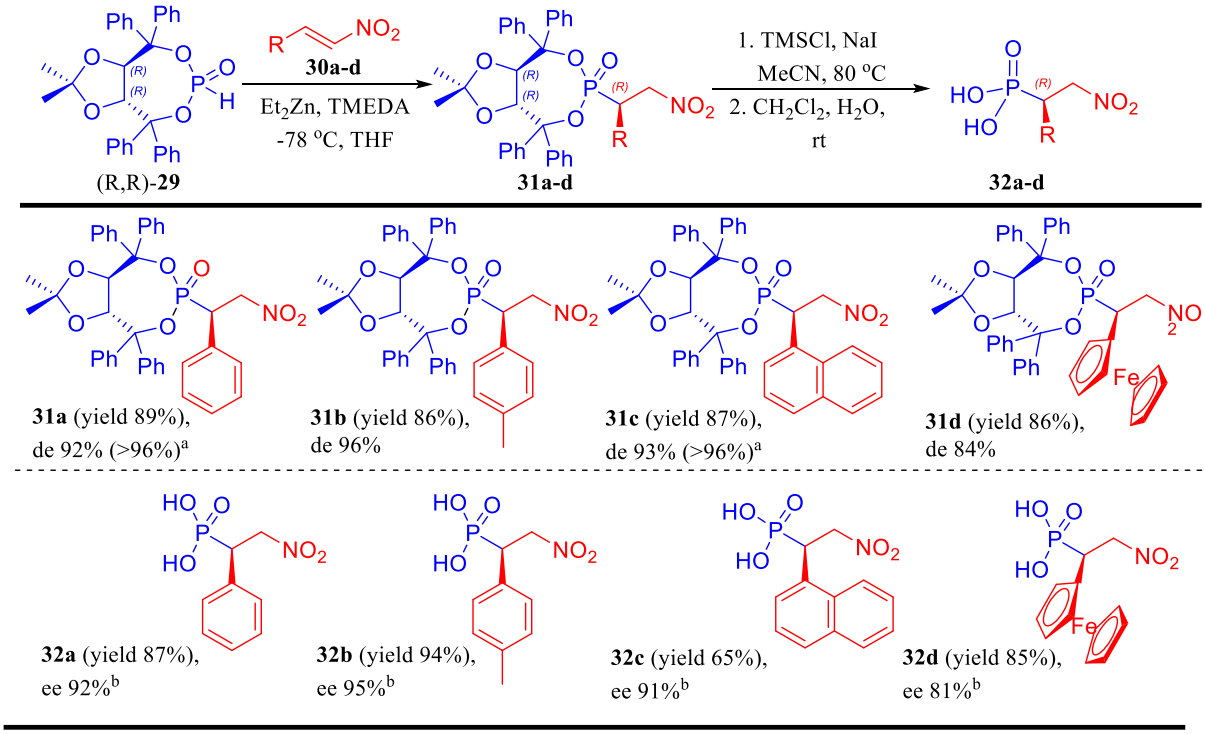
26 **27** **28** (*R*,*R*)-**29**

Scheme 5. *Preparation of TADDOL derived H-phosphonate* ***29****. DMP = 2,2-dimethoxypropane; PTSA = p-toluenesulfonic acid.*

4.2.1. Diastereoselective phospha-Michael addition of (*R*,*R*)-TADDOL *H*- phosphonate to C=C double bond

Enders and his team published several articles on the use of enantiomerically pure (*R*, *R*)-**29** in the asymmetric synthesis of phosphorus-containing compounds. In their groundbreaking research, they employed (*R*,*R*)-TADDOL derived *H*-phosphonate **29** to achieve the asymmetric synthesis of β-nitrophosphonates **31** through phospha-Michael addition to aromatic nitroalkenes **30** (Scheme 6)[85]. The developed procedure relied on the utilization of diethylzinc (Et_2Zn), which, upon reaction with (*R*,*R*)-**29**, formed a highly reactive organozinc-

phosphorus adduct[86,87] that underwent smooth addition to nitroalkenes. Initial experiments aimed at achieving high diastereoselectivity of the reaction necessitated low temperatures (-78 °C), which caused the organozinc-phosphorus adduct to exhibit poor solubility[85]. To address this issue, the addition of N,N,N',N'-tetramethylenediamine (TMEDA) was found to improve solubility, allowing the phospha-Michael addition to proceed at such low temperatures. As a result, the desired β-nitrophosphonates **31** were obtained with favorable yields (86-89%) and high diastereoselectivities (de 84-96%) (Scheme 6).

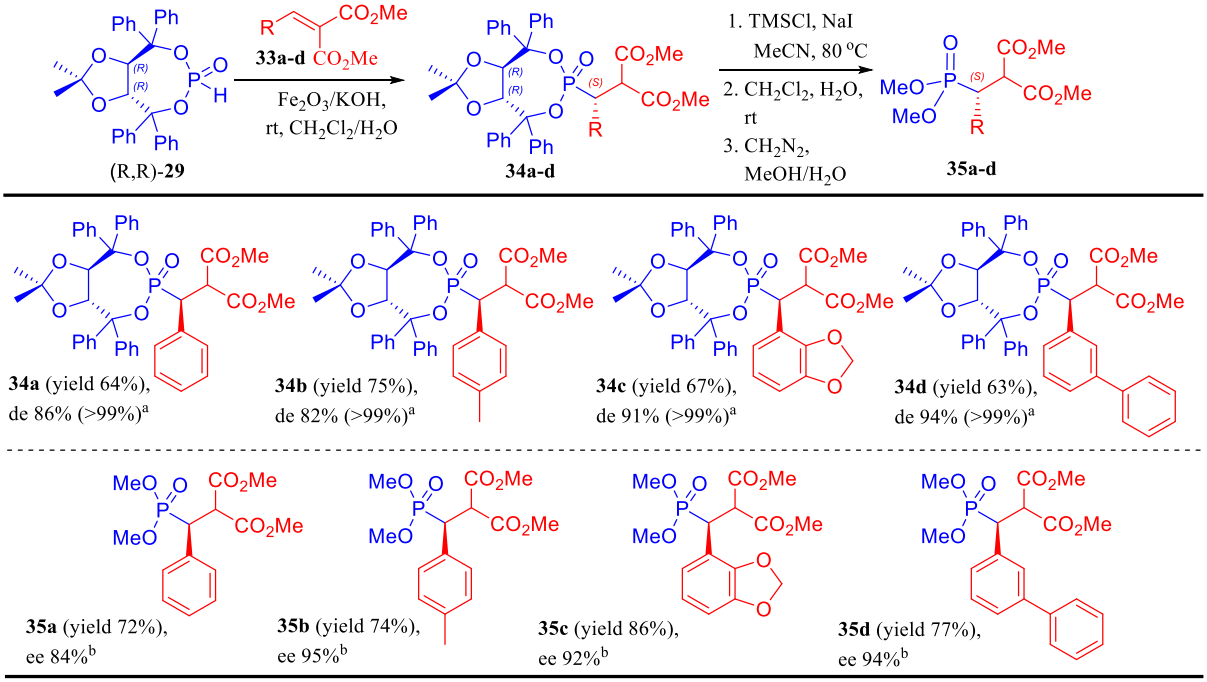


Scheme 6. *Selected examples of phospha-Michael addition of (R,R)-**29** to aromatic nitroalkenes.* [a] *de after the separation of the epimer by chromatography.* [b] *ee was determined by HPLC on a chiral stationary phase of the methyl ester derivatives.*

Alternatively, a variety of bases were assessed for their efficacy in performing conjugate additions, including *n*-butyllithium, sodium or potassium hydride, and *n*-butyllithium in the presence of copper salts or dibutylmagnesium. However, these attempts yielded significantly lower diastereoselectivity compared to the previous method[88]. The authors proposed that the main epimer has an (*R)* configuration at the newly formed C-stereogenic centre, based on the analysis of β-nitrophosphonates **31** by single crystal X-ray analysis. It is important to note that the reaction did not display significant asymmetric induction when aliphatic nitroalkenes were employed. Subsequently, the chiral auxiliary attached to the phosphorus atom was removed in racemization-free and mild conditions using TMSCl and NaI to give optically pure β-

nitrophosphonic acids **32** with yields ranging between 65% and 94% and high enantioselectivity (*ee* 81–95%) (Scheme 6)[85].

Continuing their research, Enders' group reported the diastereoselective phospha-Michael addition of enantiopure (*R,R*)-**29** to α,β-unsaturated malonates **33** using Fe_2O_3/KOH as a solid base under heterogeneous conditions. The desired β-substituted β-phosphono malonates **34** were successfully synthesized through this protocol with good yields (64-75%) and excellent diastereoselectivity (*de* >99%), and the newly formed chiral carbon center was assigned (*S*) configuration. (Scheme 7)[89]. When aliphatic malonates were used, the desired addition products were obtained with high yields but exhibited low diastereoselectivity (*de* 15–30%).



Scheme 7*. Selected examples of phospha-Michael addition of (R,R)-**29** to selected malonates.* [a]*de values determined after-epimer separation by chromatography.* [b]*ee determined by HPLC using a chiral stationary phase.*

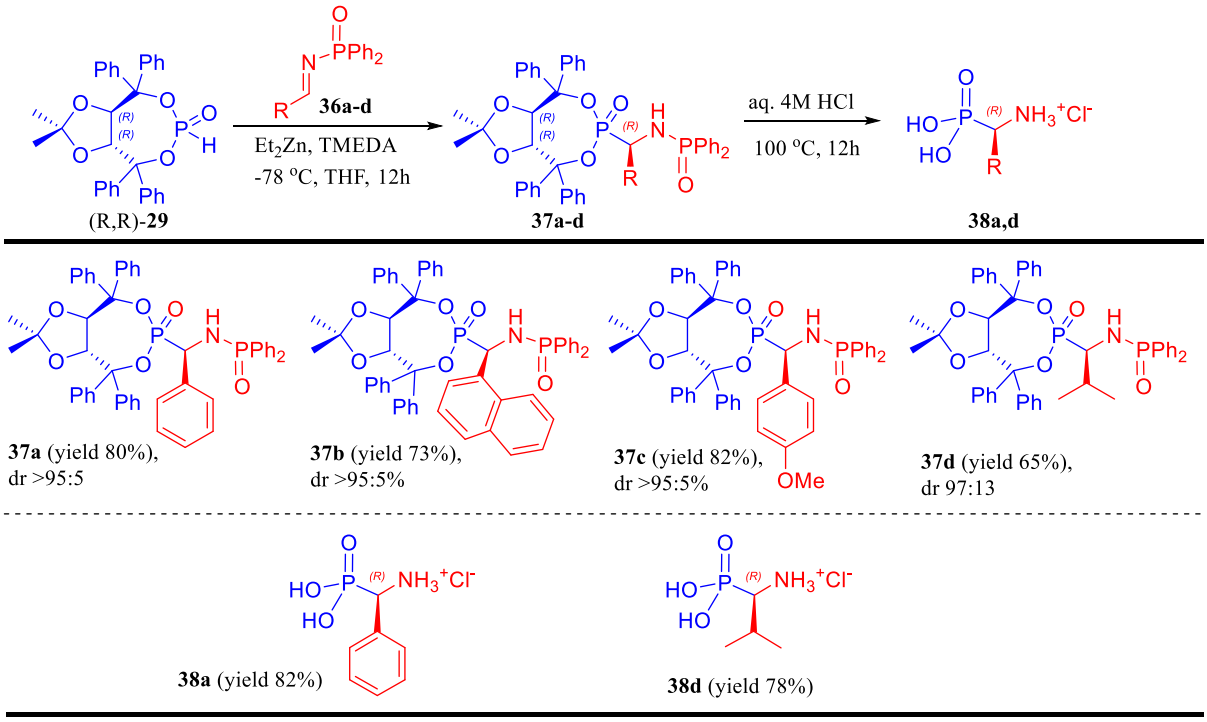
After the subsequent removal of the chiral auxiliary attached to the phosphorus atom, highly polar acids were obtained, which were not isolated but directly esterified with CH_2N_2 to form the corresponding methyl esters **35** (Scheme 7)[89]. The diastereoselectivities and yields of the conjugate addition reaction were influenced by various factors. According to the authors, the presence of solid support (metal oxide) played a crucial role in the success of the reaction outcome. The Fe_2O_3 facilitated the activation of the P–H bond in (*R,R*)-TADDOL *H*-phosphonate **29** for deprotonation with a base, such as KOH. The utilization of only KOH did not yield any product. The diastereoselectivity of the reaction system depended significantly on the molar ratio of the base and the *H*-phosphonate used, with the optimal combination found to

be a 1:2.5 molar ratio of (*R,R*)-**29** to KOH. In addition, the pre-treatment method of the solid base strongly influenced the reaction outcome, which involved drying under a high vacuum at 140 °C for 72 hours. Similarly, the selection of the solvent played a crucial role, with the highest diastereoselectivity achieved when CH_2Cl_2 was employed. Conversely, the use of oxygen-containing solvents like MeOH, THF, acetone, or Et_2O resulted in a significant reduction in diastereoselectivity. Interestingly, when the reaction took place in CH_2Cl_2 with trace amounts of water, the diastereoselectivity obtained in the product was observed to be time-dependent, improving with longer reaction times. The authors proposed that this behavior could be attributed to the retro-Michael addition of the reaction product, establishing an equilibrium that ultimately led to the complete conversion of the starting materials into the major diastereoisomers[88].

4.2.2. The utility of enantiopure (*R,R*)-TADDOL derived *H*-phosphonate 29 in the diastereoselective hydrophosphonylation of imines and aldehydes

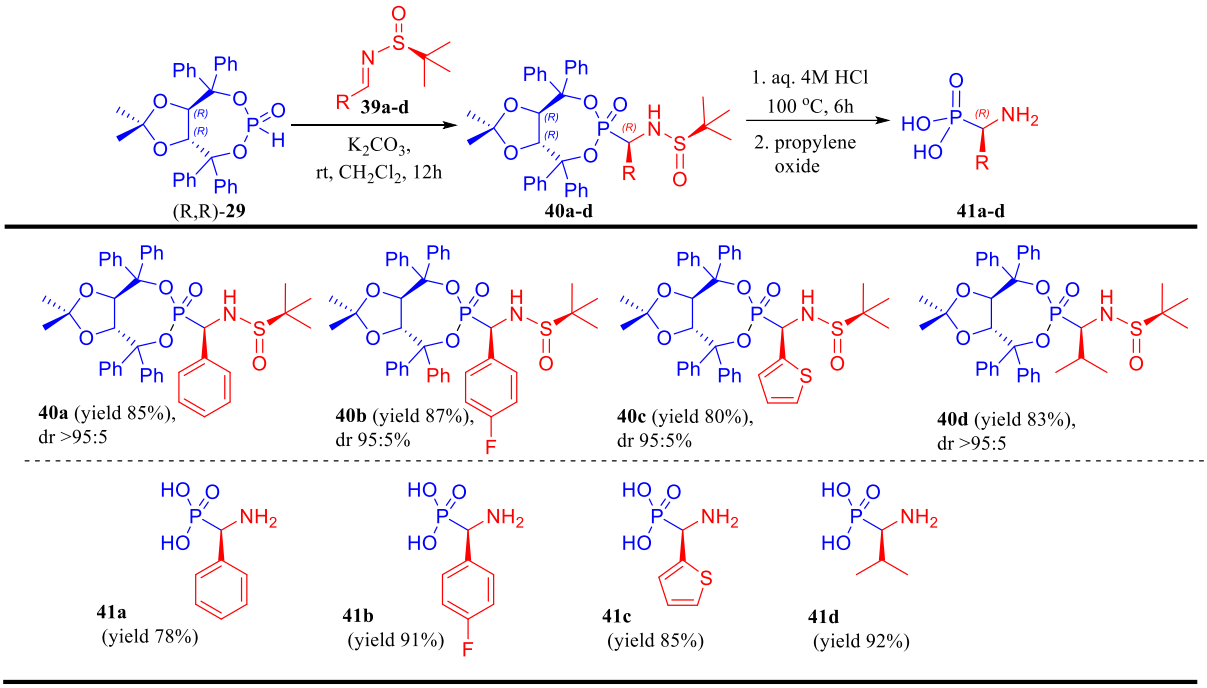
The hydrophosphonylation of aldimines, known as the aza-Pudovik reaction, and carbonyl compounds, known as the Pudovik reaction, is recognized as the most direct method for synthesizing α-amino and α-hydroxyphosphonates[24–26,44]. Our research group has presented a reaction that employed the use of (*R,R*)-TADDOL *H*-phosphonate **29** for the hydrophosphonylation of imines[90]. This involves the addition of (*R,R*)-**29** to aromatic and aliphatic *N*-diphenyl- phosphinyl aldimines **36** in the presence of Et_2Zn and TMEDA in THF at -78 °C, the desired α-aminophosphonates **37a-d** were obtained in good yields (65-82%) and exhibited high diastereoselectivities (*dr* up to >95: 5) (Scheme 8). Crucially, in each instance, the pure major diastereomer was successfully isolated through simple column chromatography. When alternative protecting groups on the iminic nitrogen, such as benzyl and *para*-toluenesulfonyl, were employed, or different bases like LDA or only Et_2Zn were used for metalation of the *H*-phosphonate, the desired products were obtained; however, the diastereoselectivities were significantly lower (dr of 75:25 in the best case). The effectiveness of the developed methodology was attributed to the presence of a bulky *H*-phosphonate with an (*R,R*)-TADDOL chiral auxiliary attached to the phosphorus atom, a large diphenylphosphinyl group on the iminic nitrogen, which influenced the stereoselective nucleophilic addition and electronic activation of the imine. Additionally, a combination of the above-stated factors with the use of Et_2Zn played a crucial role in achieving the desired outcomes. Using Et_2Zn resulted in the formation of an extremely reactive organozinc-phosphorus adduct, which requires the presence of TMEDA to improve its solubility and ensure high reaction yields[85–88]. By cleaving

the chiral auxiliary bound to the phosphorus atom and the diphenylphosphinyl group of **37a,d** under acidic conditions (Scheme 8), enantiomerically pure (*R*)-α-aminophosphonic acids **38a,d** were obtained with satisfactory yields of 82% and 78%, respectively (Scheme 8)[90].



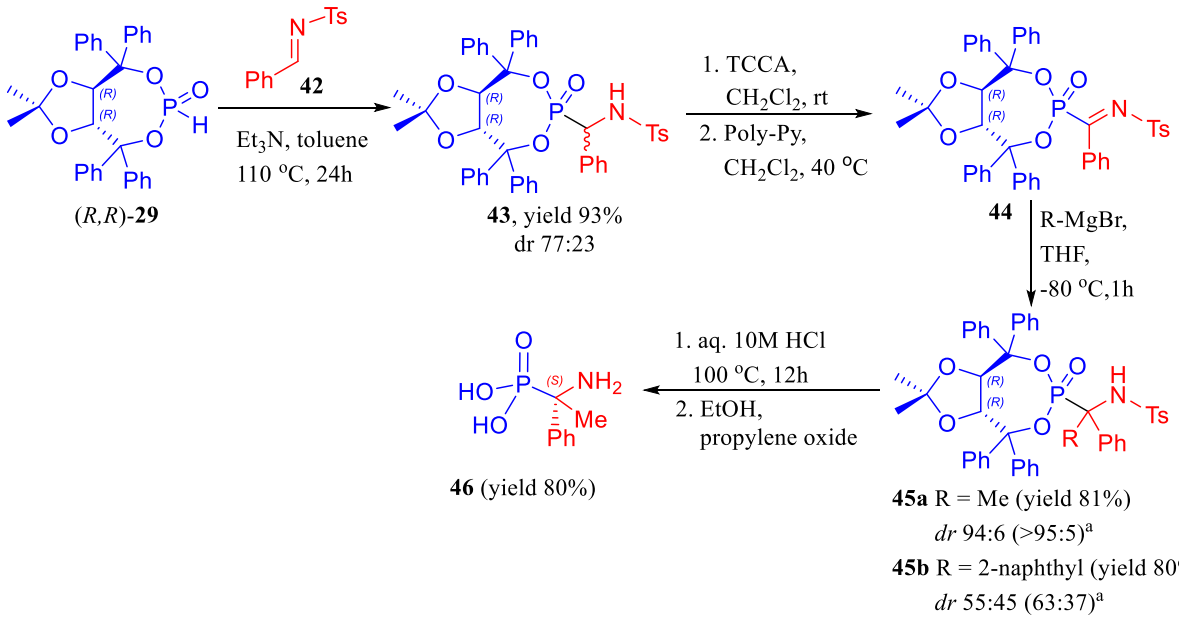
Scheme 8. *Aza-Pudovik addition of (R,R)-TADDOL H-phosphonate* **29** *to selected N-diphenylphosphinyl aldimines* ***36a-d*** *–. dr values are established based on* ^{31}P *NMR of the crude reaction mixture.*

Building upon the previous work carried out in our group on the asymmetric synthesis of α-aminophosphonates, an enhanced procedure for the highly diastereoselective hydrophosphonylation of chiral imines was developed. This new protocol involves the utilization of enantiomerically pure (*S*)-*N*-*tert*-butylsulfinyl imines **39a–d** at room temperature, with K_2CO_3 acting as the base (Scheme 9)[91]. The desired α-aminophosphonates **40a–d** were obtained with good yields (80-87%) and excellent diastereoselectivities (*dr* >95:5 in the majority of cases). As a result, the pure major diastereomers could be easily isolated through a straightforward crystallization method. After subsequent removal of the chiral auxiliary attached to the phosphorus atom and the *tert*-butylsulfinyl protecting group, enantiomerically pure (*R*)-α-aminophosphonic acids **41a–d** were obtained with satisfactory yields ranging from 72% to 92%. Notably, employing the opposite enantiomer of the imine, specifically (*R*)-*N*-*tert*-butylsulfinyl imine, resulted in a significant reduction in the diastereoselectivity of the reaction (*dr* of 22:78). This protocol offers several notable advantages, including a wide substrate scope, mild and straightforward reaction conditions, high yields, excellent diastereoselectivity, and easy isolation of the major diastereoisomer (Scheme 9).



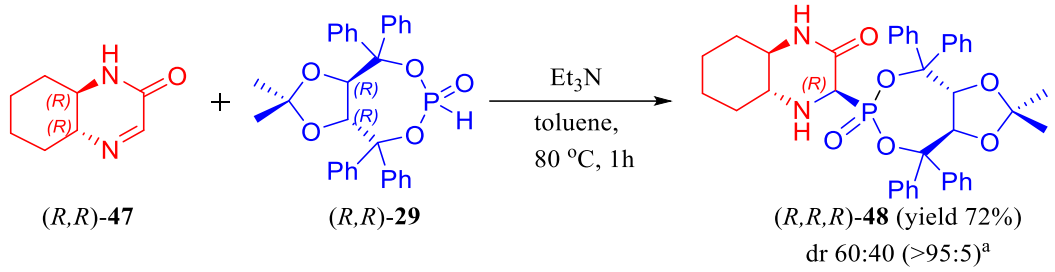
Scheme 9. *Aza-Pudovik addition of (R,R)-TADDOL H-phosphonate* **29** *to selected (S)-N-tert-butylsulfinylimines* **39a-d**. *dr values are established based on* ^{31}P *NMR of the crude reaction mixture*.

Vicario et al. employed (*R,R*)-TADDOL *H*-phosphonate **29** to perform hydrophosphonylation on imine **42**, resulting in the synthesis of α-aminophosphonate **43**. Despite the high yield of 93%, the diastereoselectivity was found to be poor (*dr* of 77:23). Subsequently, chlorination of **43** was carried out using an excess of trichloroisocyanuric acid (TCCA) followed by treatment with an excess of poly-(4-vinylpyridine) (Poly-Py) to afford the α-ketiminophosphonate **44** (Scheme 10)[92]. The nucleophilic addition of Grignard reagents to **44** was carried out at −80 °C in THF. The desired tetrasubstituted α-aminophosphonate **45b** was obtained in a good yield of 80% but poor *dr* of 55:45 when bulky 2-naphthylmagnesium bromide was added. However, excellent diastereoselectivity was achieved when using smaller methylmagnesium bromide. The resulting tetrasubstituted α-aminophosphonate **45a** was obtained with a yield of 81% and *dr* 94:6, enabling the isolation of the major diastereoisomer via simple crystallization from Et_2O (Scheme 10). The major diastereoisomer underwent simultaneous removal of the chiral auxiliary attached to the phosphorus atom and deprotection of the nitrogen atom under acidic conditions, resulting in an 80% yield of the enantiomerically tetrasubstituted α-aminophosphonic acid **46** with (*S*) configuration (Scheme 10).



***Scheme 10**. Synthesis of tetrasubstituted α-aminophosphonates from trisubstituted α-aminophosphonates with the use of enantiopure (R,R)-**29**. [a] dr values after chromatographic purification. Ts – toluenesulfonyl.*

Recently our group reported the hydrophosphonylation of (*R*,*R*)-hexahydroquinoxalinone **47** using (*R*,*R*)-**29** in the presence of Et_3N in toluene at 80 °C (Scheme 11)[93]. The resulting bicyclic α-aminophosphonate **48** was obtained in a pure form with a yield of 72%, although with poor diastereoselectivity (*dr* 60:40). DFT calculations performed for the reaction of imine **47** with dimethyl *H*-phosphonate indicated that the energy levels of the two resulting epimers of the α-aminophosphonate were similar, which corresponded with the observed experimental diastereomeric ratio (*dr* ca. 1:1). The interconversion of the two epimers under the reaction conditions likely hindered their formation with significant diastereoselectivity, even when utilizing chiral (*R*,*R*)-**29**. Nonetheless, the (*R*,*R*)-TADDOL chiral auxiliary attached to the phosphorus atom present in the structure of α-aminophosphonate **48** allowed for a straightforward separation of a pure major diastereomer through column chromatography. The configuration at the newly formed asymmetric carbon in the major diastereoisomer of **48** from X-ray analysis was (*R*). Unfortunately, the pure diastereoisomer **48** underwent rapid epimerization during its storage in solution. This behavior can be attributed to the structure of the bicyclic α-aminophosphonate, where the presence of both carbonyl and phosphonate groups makes the proton attached to the stereogenic α-carbon susceptible to dissociation, resulting in epimerization.

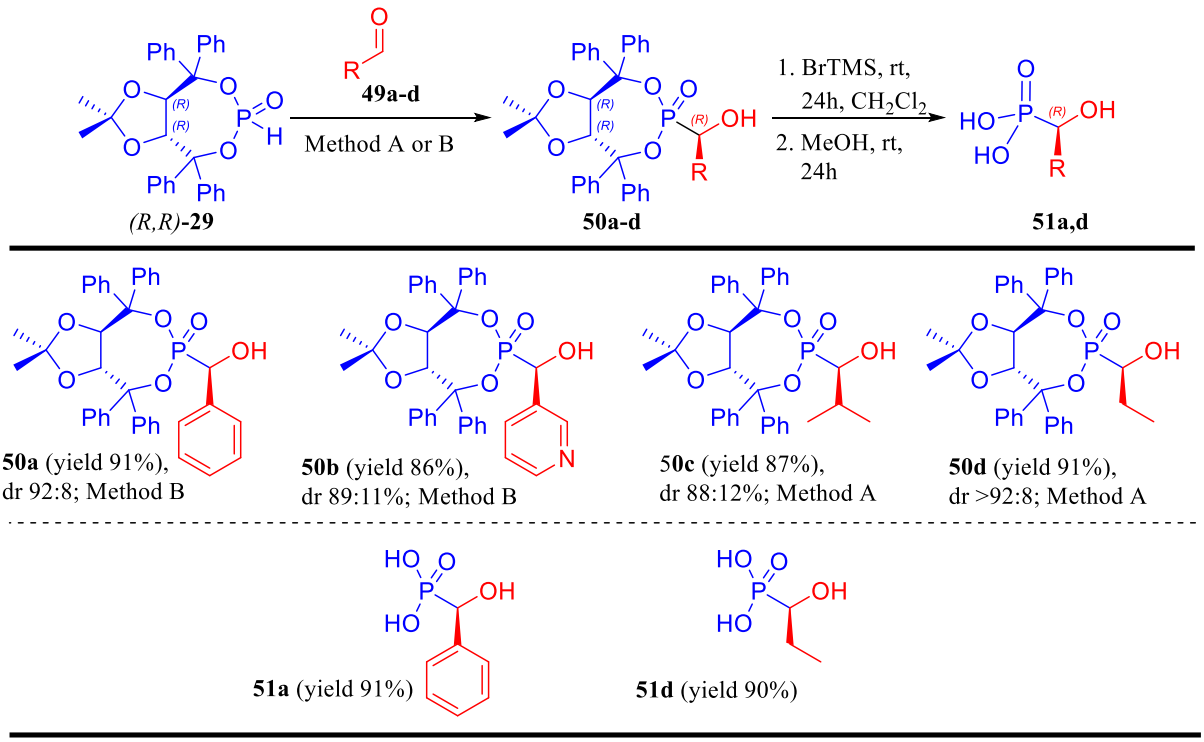


(*R,R*)-**47** (*R,R*)-**29** (*R,R,R*)-**48** (yield 72%) dr 60:40 (>95:5)[a]

Scheme 11. *Asymmetric synthesis of hexahydroquinoxalin-2(1H)-one-derived α-aminophosphonate* **48**. [a] *major epimer isolated by column chromatography.*

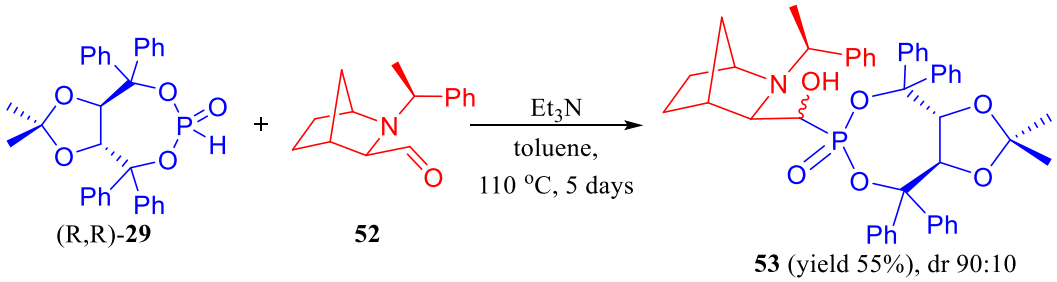
Having investigated the effectiveness of (*R,R*)-**29** in the hydrophosphonylation of imines leading to the asymmetric synthesis of α-aminophosphonates, (*R,R*)-**29** was also applied for the preparation of α-hydroxyphosphonates using aldehydes as substrates in the hydrophosphonylation reaction[94]. Notably, carbonyl compounds present a greater challenge as substrates for asymmetric hydrophosphonylation. Unlike imines, in which various stereodirecting groups can be introduced on the iminic nitrogen atom, simple aldehydes lack such possibilities. Consequently, the successful preparation of α-hydroxyphosphonates in an asymmetric manner relied on employing an H-P nucleophile with a chiral auxiliary attached to the phosphorus atom and meticulous optimization of the reaction conditions.

In this regard, a highly effective and widely applicable approach has been devised for the diastereoselective hydrophosphonylation of aldehydes **49**, employing (*R,R*)-TADDOL-derived *H*-phosphonate **29** (Scheme 12)[94]. The diastereoselectivity of the reaction is notably affected by the selection of a suitable base. Additionally, performing the reaction at a low temperature of -78 °C played a significant role in achieving the desired diastereoselective outcome. For aromatic and heteroaromatic aldehydes, the utilization of Et_2Zn and TMEDA resulted in the most favorable outcomes, while the application of lithium diisopropylamide **(**LDA) proved advantageous for aliphatic aldehydes. In both cases, the corresponding α-hydroxyphosphonates **50** were obtained with high asymmetric induction (up to >92:8 *dr*) and satisfactory yields (up to 91%) as shown in Scheme 12. Furthermore, the major diastereoisomer could be readily isolated through simple crystallization from Et_2O. Under mild reaction conditions, the chiral auxiliary was easily cleaved, leading to the formation of enantiomerically pure (*R*)-α-hydroxyphosphonic acids **51a, d** with good yields (91% and 90% respectively).



Scheme 12. *Seclected example of Pudovik reaction between enantiopure (R, R)-***29** *and aldehydes* **49a–d.** ***Method A:*** *Et_2Zn, TMEDA, −78 °C, THF, 12 h;* ***Method B:*** *LDA, −78 °C, THF, 12 h. BrTMS – bromotrimethylsilane.*

Furthermore, the utility of (*R*, *R*)-**29** in the hydrophosphonylation of the more challenging 2-azanorbornane-derived aldehyde **52** was investigated (Scheme 13)[95]. However, it was quickly realized that configurationally stable and rigid bicyclic aldehyde **52** exhibited low reactivity toward the hydrophosphonylation reaction. Upon subjecting aldehyde **52** to heating with (*R*, *R*)-**29** in the presence of Et_3N in toluene at 110 °C for 5 days, resulting in the formation of the desired α-hydroxyphosphonate **53** with good diastereoselectivity (dr 90:10). However, low conversion (50%) was observed, which was attributed to the thermal instability of (*R*, *R*)-**29**, leading to its decomposition into (*R*, *R*)-TADDOL **28**.

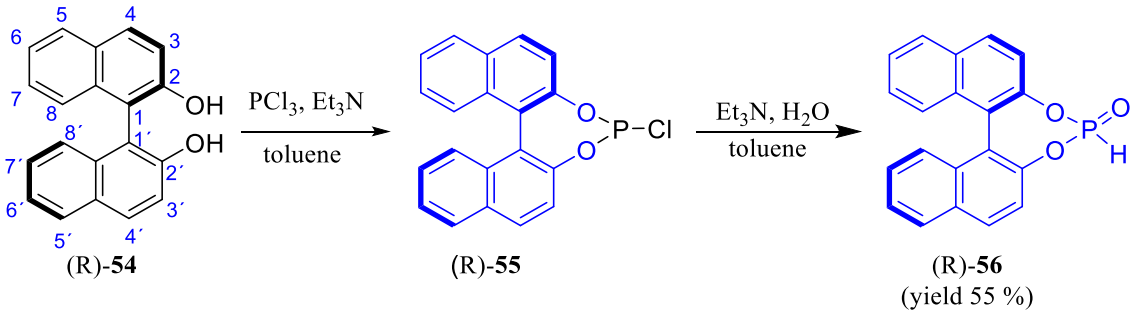


Scheme 13. *Diastereoselective synthesis of 2-azanorbornane-derived α-hydroxyphosphonate* **53**.

4.3. Application of BINOL *H*-phosphonate and its derivative, as chiral auxiliary use in the synthesis of substituted phosphonates

1,1′-Binaphthyl-2,2′-diol abbreviated as BINOL, holds a significant position in the field of organic chemistry as one of the most exemplary axially chiral C2 symmetric molecules[96–98]. Its chiral nature stems from the steric hindrances between 2,2′-hydroxyls and 8,8′-hydrogens, which impede the free rotation of the two 2-naphthol units around the 1,1′-bond. This restriction in rotation defines the chirality of BINOL (Scheme 14). The fixed structure and C2 symmetry of the chiral binaphthyl molecules are crucial for inducing chirality and like TADDOL, BINOL is recognized as one of the few highly esteemed chiral ligands[78].

The synthesis of BINOL *H*-phosphonate **56** has been well-established, which involves a classical procedure where PCl_3 is added to the diol **54** in the presence of Et_3N, followed by the hydrolysis of the resulting chloride **55** using H_2O and Et_3N (Scheme 14)[99–101]. Alternative approaches using tert-butanol or formic acid instead of H_2O/Et_3N for the hydrolysis step have also been documented in the literature to achieve higher yields of **56** as stable white solid[102]. Nevertheless, literature references indicate instances where **56** decomposes back to the initial BINOL compound **54** when subjected to column chromatography. Therefore, crystallization is the recommended method of purification[99,100]. Furthermore, a rapid transesterification process involving BINOL *H*-phosphonate **56** and its corresponding aminophosphonates when the reaction is conducted in alcoholic solvents during the hydrophosphonylation of imines was observed[90]. This behavior can be attributed to the relatively easy cleavage of endocyclic P-O bonds in BINOL *H*-phosphonate, which arises from the twisted structure of the BINOL auxiliary and the inherent instability of the seven-membered ring, including four sp^2 carbons.

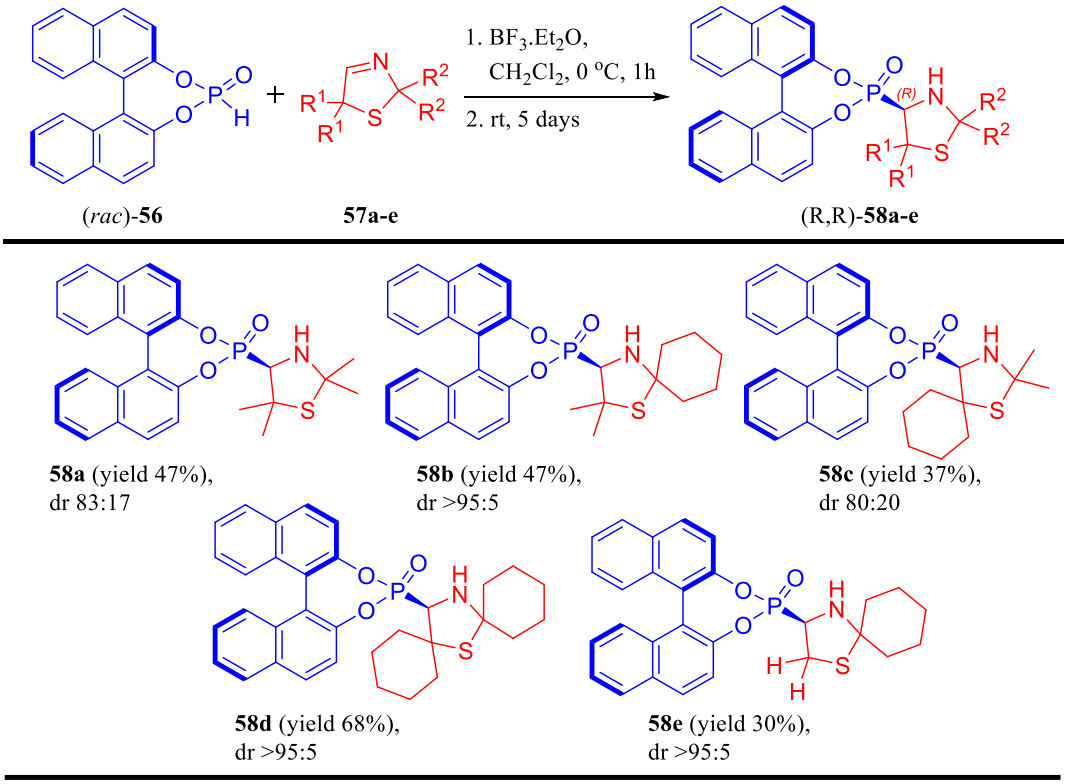


Scheme 14. *Synthesis of (R)-BINOL H-phosphonate* ***56.***

4.3.1. Addition of BINOL derived *H*-phosphonate to C=N and C=C double bonds

The research group of Martens was the first to report a highly diastereoselective hydrophosphonylation of imines derived from 3-thiazoline **57a–e**. Their method involved the

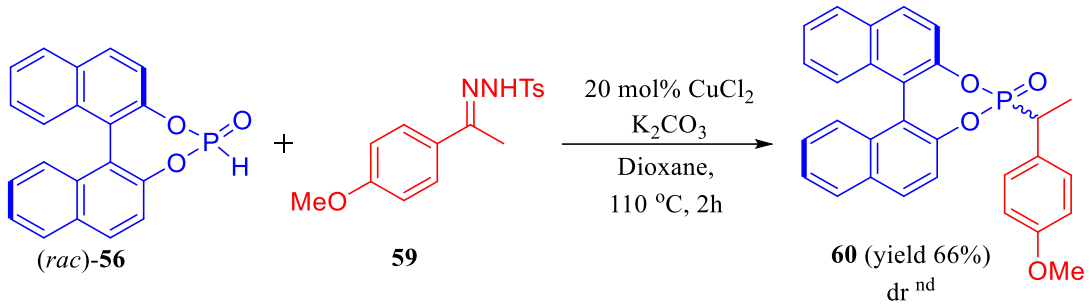
utilization of racemic BINOL-derived *H*-phosphonate **56** in the presence of $BF_3 \cdot Et_2O$, resulting in the synthesis of the corresponding 4-thiazolidynylphosphonates **58a–e** (Scheme 15)[103,104]. This synthetic approach holds significant importance due to the notable biological activity observed in derivatives of thiazole, thiazoline, and thiazolidine compounds and this makes the asymmetric synthesis of such compounds highly valuable[105–108]. High diastereoselectivity (up to *dr* > 95:5) was obtained in the synthesized aminophosphonates **58a–e**, although the yields were moderate (30-68%). The diastereoselectivity of the hydrophosphonylation reaction was greatly influenced by the steric hindrance of the R^2 substituents in imines **57**. Notably, the diastereoselectivity improved as the size of the substituent increased (Scheme 15). Pure major diastereoisomers were isolated by column chromatography from products **58a** and **c** and the crystals obtained from these compounds were subjected to X-ray analysis and revealed an (*R*) configuration on both the BINOL *H*-phosphonate moiety and the newly formed stereogenic carbon center. However, the article did not provide any information regarding attempts to remove the chiral auxiliary attached to the phosphorus atom or any subsequent transformations with the obtained products.



Scheme 15. *Diastereoselective hydrophosphonylation of 3-thiazolines* ***57*** *with (rac)-BINOL H-phosphonate* ***56.***

An interesting use of (*rac*)-BINOL *H*-phosphonate **56** in the Cu-catalyzed reductive coupling of N-tosylhydrazones with *H*-phosphine oxides were investigated by Wu et al[109]. In the presence of $CuCl_2$ (20 mol%), K_2CO_3, and dioxane at 110 °C, the utilization of (*rac*)-**56** and N-

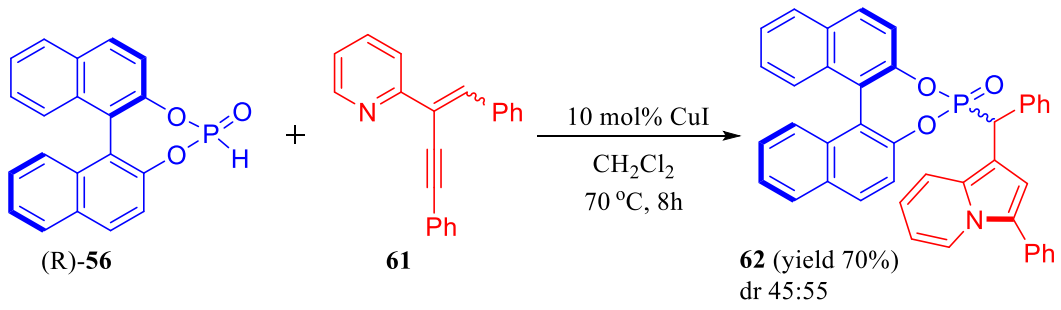
tosylhydrazone **59** resulted in the successful formation of product **60**. This product exhibited a novel C(sp^3)–P bond with a yield of 66% (Scheme 16). Unfortunately, the authors did not investigate either the reaction diastereoselectivity or make any efforts to remove the chiral auxiliary from the resulting product in Scheme 16[109].



(*rac*)-**56** **59** **60** (yield 66%) dr [nd]

Scheme 16*. The formation of C(sp^3)–P bonds through Cu-catalyzed reductive coupling of N-tosylhydrazone **59** with H-phosphonate **56** derived from BINOL.* [nd]*not determined.*

Mahesh and Anand recently presented an application of (*R*)-BINOL *H*-phosphonate **56** in the copper-catalyzed synthesis of organophosphorus compounds[110]. An elegant procedure for synthesizing indolizine-based phosphonates involving a Cu-catalyzed 5-endo-dig-cyclization of 2-(2-enynyl)pyridines, followed by remote hydrophosphonylation, was developed. The reaction between pyridine derivative **61** and (*R*)-**56**, performed in the presence of CuI (10 mol%) in CH_2Cl_2 at 70 °C for 8 hours, led to the desired indolizine-derived phosphonate **62** with a satisfactory yield of 70%. However, the diastereoselectivity of the reaction was low, with a diastereomeric ratio of 45:55 (Scheme 17)[110]. The authors did not engage in optimizing the reaction conditions to enhance the diastereoselectivity, nor did they make any efforts to isolate the diastereomers or remove the chiral auxiliary attached to the phosphorus atom.



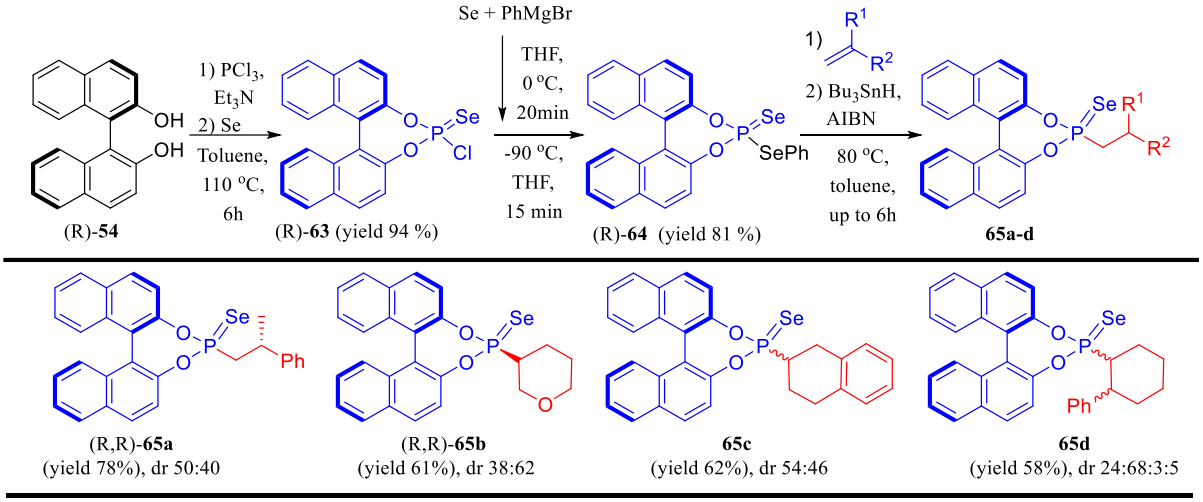
(R)-**56** **61** **62** (yield 70%) dr 45:55

Scheme 17 *Cu-catalysed hydrophosphonylation of 2-(2-enyl)pyridine* **61** *with (R)-*56*.*

4.3.2. Diastereoselective reactions of BINOL derived phosphonoselenoyl chloride and it's derivative with alkenes, Grignard reagents and halides

Murai and coworkers have published several articles focusing on the application of (*R*)-BINOL-derived phosphonoselenoyl chloride **63** and its derivatives as novel chiral

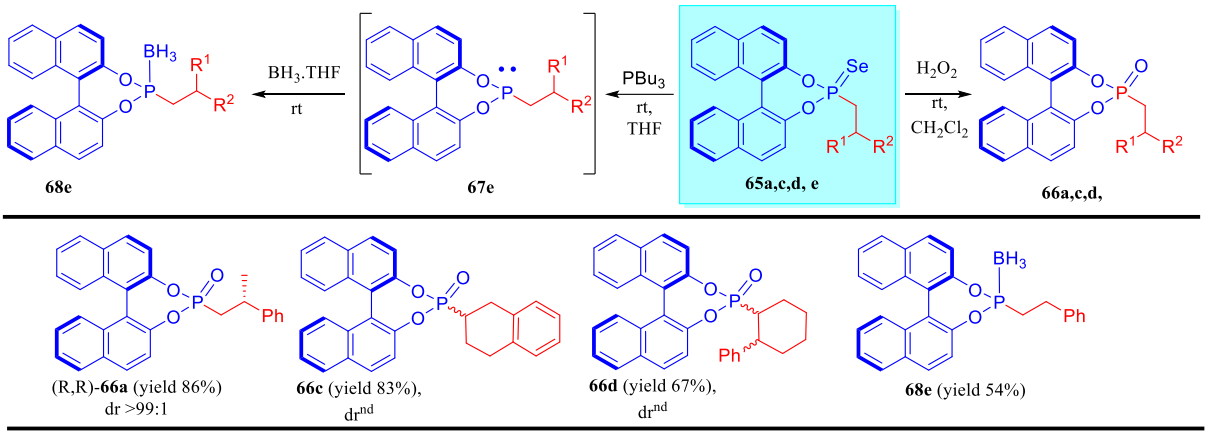
molecular tools for the efficient and diastereoselective synthesis of diverse C-stereogenic organophosphorus compounds. The (*R*)-BINOL-derived phosphonoselenoyl chloride **63** was conveniently prepared by reacting (*R*)-BINOL with PCl_3 in the presence of Et_3N, followed by the addition of selenium (Scheme 18)[111] which was then transformed to (*R*)-**64** for utilization in the hydrophosphonylation of alkenes (Scheme 18)[112]. Under radical conditions, the reaction proceeded in an anti-Markovnikov manner. Various alkenes were subjected to reaction with (*R*)-**64**, employing Bu_3SnH and AIBN, resulting in the formation of the desired phosphorylated products **65** with good yields (up to 78%) and diastereomeric ratio of 38:62 in the best case (Scheme 18)[112].



Scheme 18. *Selected examples of hydrophosphonylation of alkenes with (R)-***64***. dr was determined based on* ^{31}P *NMR of the crude reaction mixture. For* **65a** *and* **65b**, *the absolute configuration was given for the major diastereomer based on X-ray analysis.* Bu_3SnH *– tributyltin hydride; AIBN – azobisisobutyronitrile.*

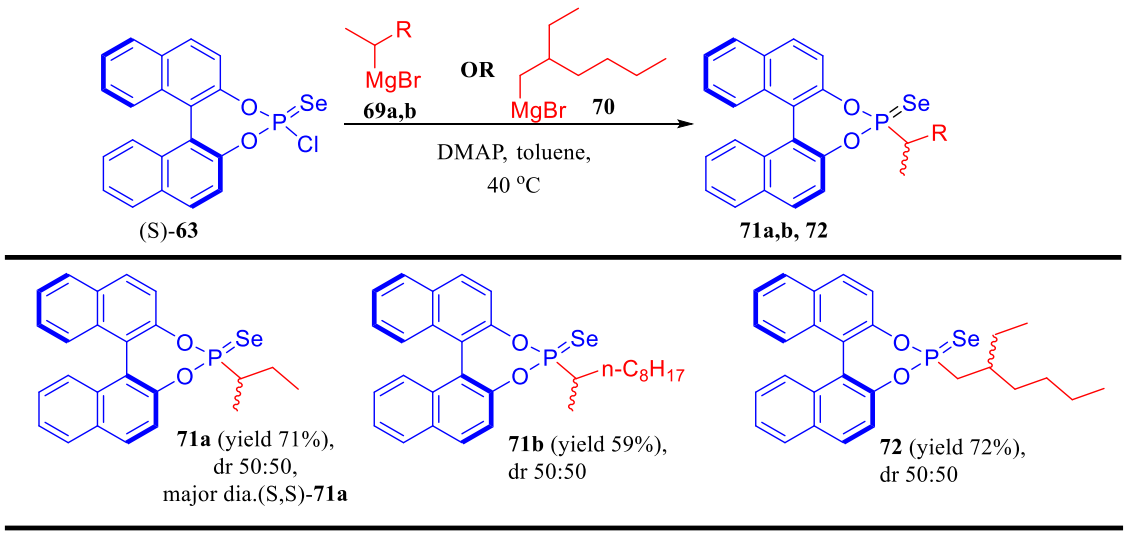
Significantly, the selectivity of the diastereoisomers could be enhanced by incorporating large substituents at the 3,3'-positions of the binaphthyl group. For instance, a similar compound to **65c** was synthesized by replacing the 3,3'-positions of the BINOL segment with triisopropylsilyl groups. This analog gave a high diastereoselectivity (92:8 dr) and a good yield of 67%[112]. This improvement in selectivity highlights the importance of bulky substituents in achieving favorable outcomes in this reaction system. The diastereoisomers obtained were easily separated by column chromatography in most cases. When pure crystals of diastereoisomers of **65a** and **65b** were analyzed by X-ray, their absolute configuration at the newly formed stereogenic carbon center was established to be (*R*).

To showcase their practical value as versatile components, phosphonoselenoic acid esters **65** were converted into the corresponding phosphonic acid esters **66** and phosphonite boranes **68** using the classical methods (Scheme 19). Notably, no racemization was observed when pure diastereoisomer **65a** (*dr*>99:1) was transformed into its oxygen counterpart **66a.**



Scheme 19*. Selected examples of further transformations of phosphonoselenoic acid esters* **65.** *[nd]-not determined.*

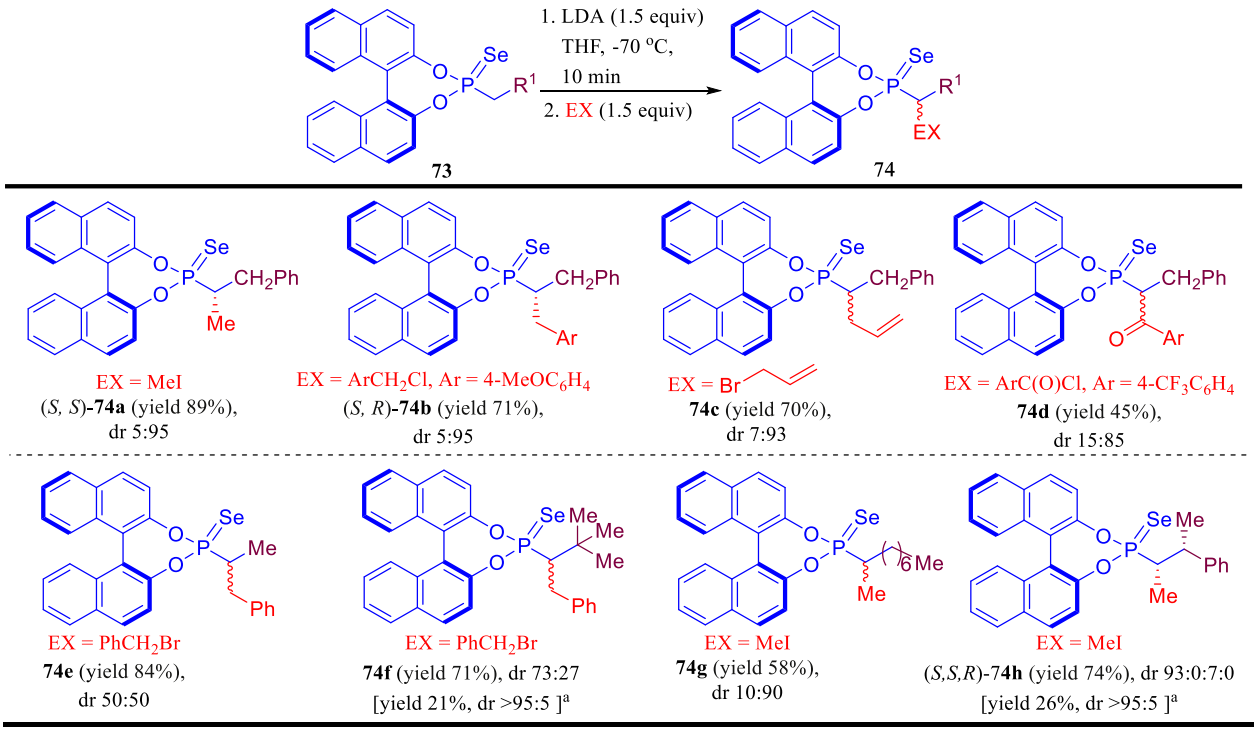
In continuation of their investigation into the utility of BINOL phosphonoselenoyl chloride **63**, Murai et al. reported their findings on the reaction of (*S*)-**63** with Grignard reagents[113]. In their study, they employed chiral Grignard reagents, specifically *sec*-butylmagnesium bromide **69a**, *sec*-decylmagnesium bromide **69b**, and 2-ethylhexylmagnesium bromide **70**, all in their racemic forms. The reaction yielded the desired products **71a**, **71b**, and **72** as mixtures of diastereoisomers, although no diastereoselectivity was observed (Scheme 20)



Scheme 20*. Addition of chiral Grignard reagents to (S)-***63***. dr was determined based on [31]P NMR of the crude reaction mixture. The configuration on the major diastereomer was given based on X-ray analysis. DMAP – 4-dimethylaminopyridine.*

Straightforward chromatography or crystallization techniques can be used to separate the diastereomers, which are clearly distinguishable by ^{31}P NMR. In the case of compound **71a**, X-ray analysis showed that the molecule's absolute configuration at the stereogenic carbon is (*S*)[113].

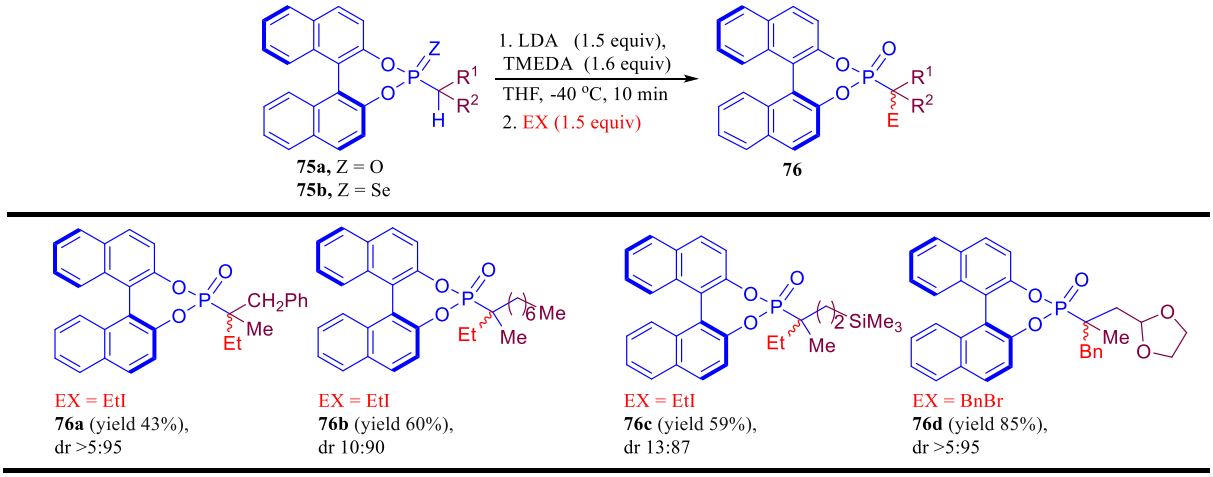
In a recent publication, Murai et al. presented their findings on the application of (*S*)-BINOL-derived phosphonoselenoates **73** and phosphonates **75a** in a diastereoselective sequential deprotonation-alkylation reaction. This methodology resulted in the synthesis of novel organophosphorus compounds possessing tri- and tetrasubstituted carbon centers adjacent to the phosphorus atom, denoted as **74** and **76** respectively (Scheme 21 and 22)[114]. For phosphonoselenoates **73**, the deprotonation process proceeded smoothly using LDA at a temperature of -70 °C in THF. Subsequently, the appropriate halides were added to the carbanion generated *in-situ*, leading to the formation of desired trisubstituted alkylated products **74**. This reaction gave favorable yields (up to 89%), and displayed high diastereoselectivity, with a diastereomeric ratio of up to 5:95 (Scheme 21). Notably, for products **74f** and **74h**, simple recrystallization of the initial crude product resulted in an enhancement of the diastereoselectivity and the presence of the BINOL moiety enable the diastereomers to be distinguishable using ^{31}P NMR[114].



Scheme 21. *Selected examples of deprotonation–alkylation of different BINOL-derived phosphonoselenoates* ***73*** *with different halides. dr was determined based on* ^{31}*P NMR of the crude reaction mixture. The configuration on major diastereomer was given based on X-ray analysis.* [a] *Yield and dr of* ***74g*** *and* ***74h*** *after recrystallization.*

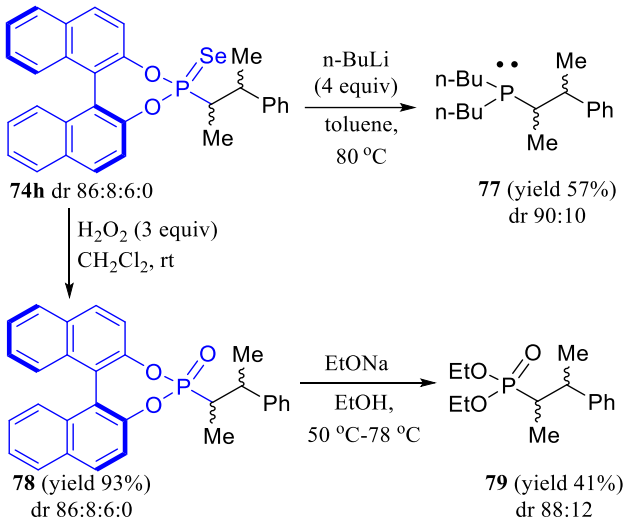
Through X-ray analysis of the crystals, it was found that compounds **74a**, **74b** and **74h** have absolute configurations of (*S, S*), (*S, R*), and (*S, S, R*) respectively, for their newly formed chiral carbon centers (Scheme 21). The authors put forward a hypothesis suggesting that the presence of the BINOL component significantly influences the stereochemical outcome of the carbon

atom connected to the phosphorus. They propose that, in the deprotonation-alkylation reaction, the electrophile approaches the racemic carbon center, which is formed during the deprotonation process, from the site with minimal steric hindrance. It is plausible that an unfavorable nonbonding interaction could occur between the incoming electrophile and a binaphthyl group of the lithiated phosphonoselenoate[114]. Conversely, the formation of tetrasubstituted carbon centers adjacent to the phosphorus atom was only achievable by employing trisubstituted phosphonates **75a** (Scheme 22). For obtaining the highest possible yields (up to 85%) and diastereoselectivity (*dr* up to >5:95), the deprotonation step was performed using LDA in the presence of TMEDA at a temperature of -40 °C in THF. In contrast, analogous phosphonoselenoates **75b** did not undergo the deprotonation-alkylation reaction (Scheme 22)[114].



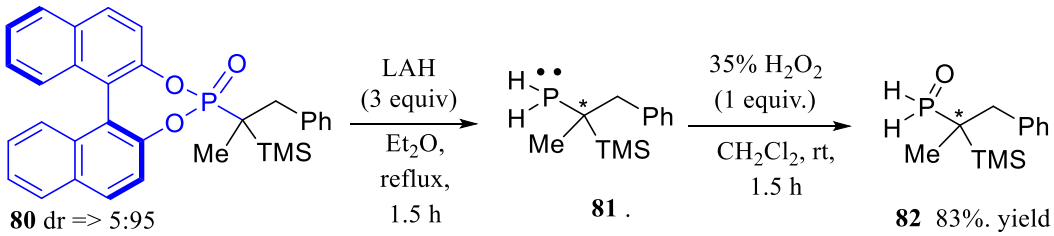
Scheme 22. *Diastereoselective formation of carbon with quaternary chiral centre bound to the P-atom from the reaction of various BINOL-derived phosphonates* **75** *with halides. dr was determined based on* ^{31}P *NMR of the crude reaction mixture.*

To showcase the practicality of the synthesized (*S*)-BINOL-derived alkylated phosphonoselenoates, the authors carried out derivatization and the subsequent removal of the chiral auxiliary attached to the phosphorus atom, using phosphonoselenoate **74h** (*dr* 86:8:6:0) as a representative substrate (Scheme 23). Subjecting **74h** to dialkylation-deselenation using n-BuLi, resulted in the formation of the desired chiral phosphine **77** with dr of 90:10. This phosphine demonstrates suitability for various applications, particularly as a ligand in catalysis. Additionally, the transformation of phosphonoselenoate **74h** into the corresponding phosphonate **78** was achieved through a reaction with H_2O_2, followed by alcoholysis with EtONa. This process yielded the desired diethyl phosphonate **79**, albeit with a moderate yield of 41% and a diastereomeric ratio of 88:12[115,116].



Scheme 23. *Derivatization of BINOL-derived phosphonate* **74h** *with the recovery of the chiral auxiliary in each case. dr was determined based on* ^{31}P *NMR of the crude reaction mixture.*

In a recent publication, Murai's group explored the utility of tetrasubstituted phosphonate **80** in the synthesis of primary phosphine and its oxide with a quaternary stereogenic carbon center adjacent to the phosphorus atom. Upon treatment with LAH in diethyl ether, tetrasubstituted phosphonate **80** underwent reduction to afford the corresponding primary phosphine **81**. The subsequent oxidation of **81** using H_2O_2 in CH_2Cl_2 led to the formation of primary phosphine oxide **82**, with a yield of 83% (Scheme 24)[117]. Unfortunately, the absolute configuration of adduct **82** was not determined. It is worth noting that the authors emphasize the recoverability of the BINOL chiral auxiliary, which serves as an added benefit of this valuable tool consistently employed with success by the Murai group[115,116].



Scheme 24*. Utility of BINOL derived phosphonate in the synthesis of primary phosphine and phosphine oxide with quaternary carbon center.*

4.4. Stereoselective preparation of organophosphorus compounds using menthyl-derived H-P species

(-)-Menthol, also known as (*1R,2S,5R*)-2-isopropyl-5-methylcyclohexanol, is a widely accessible, naturally occurring, and cost-effective chiral building block that is commonly

employed in the preparation of chiral *H*-phosphonates, phosphinates, and phosphine oxides. These compounds serve as H-P species with a chiral auxiliary attached to the phosphorus atom, enabling their application in the asymmetric synthesis of organophosphorus compounds with both carbon- and in some cases phosphorus-chiral centers[118,119].

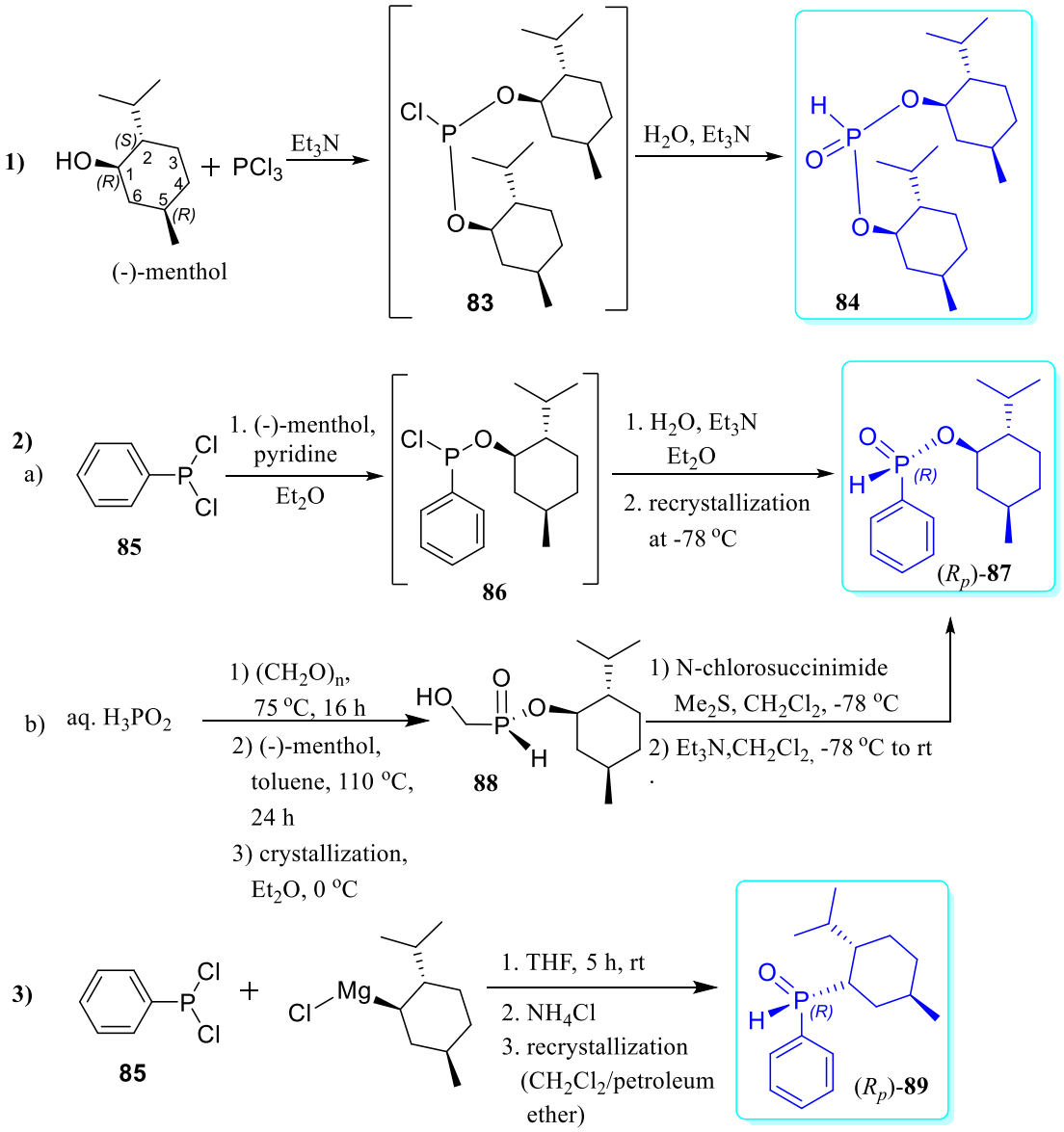
The (−)-O,O-di-(*1R,2S,5R*)-menthyl *H*-phosphonate **84** can be synthesized conveniently by reacting (−)-menthol with phosphorus trichloride in the presence of Et_3N, followed by the hydrolysis of the formed dimenthyl chlorophosphite **83** (Scheme 25, reaction 1)[120]. On the other hand, the preparation of (−)-(*1R,2S,5R*)-menthyl phenyl-*H*-phosphinate (R_P)-**87** is more challenging but well-documented in the literature. Today, there are reliable synthetic protocols available to obtain diastereomerically pure (R_P)-**87** even on a multi-gram scale (Scheme 25, reactions 2a and 2b). The leading approach employed in the synthesis involves the reaction of dichloro(phenyl)phosphine **85**, pyridine, and (-)-menthol, followed by multiple recrystallization steps of the diastereoisomer mixture at low temperatures. This method was initially pioneered by Emmick and Letsinger[121], further developed by Mislow et al.[122], and more recently refined by Han et al. (Scheme 25, reaction 2a)[118].

An alternative approach for the synthesis of (R_P)-**87** was recently reported by Montchamp (Scheme 25, reaction 2b)[123,124]. This protocol involves the use of (hydroxymethyl)-*H*-phosphinate (S_P)-**88**, which can be easily obtained by reacting aqueous hypophosphorous acid with paraformaldehyde, followed by azeotropic distillation with menthol in toluene and subsequent crystallization at 0 °C to give **88** with 10% yield but with diastereomeric excess of >99%. Stereoselective cleavage of the hydroxymethyl group using the Corey-Kim oxidation unveils the P(O)H moiety, yielding (R_P)-**87** in 91% yield and de >99% (Scheme 25, reaction 2b). Moreover, (−)-menthol can be employed for the synthesis of chiral phosphine oxide (R_P)-**89**. The procedure described in the literature involves the reaction between (−)-menthyl-magnesium chloride and $PhPCl_2$ **85**, followed by recrystallization of the resulting crude product. This process affords diastereomerically pure (R_P)-**89** with a yield of 34% (Scheme 25, reaction 3)[125].

4.4.1. Reactions of menthyl-derived *H*-phosphinate and phosphine oxide with alkenes

Zhao's research team conducted a study where they utilized chiral phosphine oxide (R_P)-**89** as a nucleophilic chiral auxiliary attached to the phosphorus atom. They effectively utilized this compound to selectively synthesize organophosphorus derivatives with multiple stereogenic centers by adding (R_P)-**89** to alkenes and alkynes[126–128]. The first article described a one-pot reaction carried out in the presence of KOH in DMSO at room temperature, where

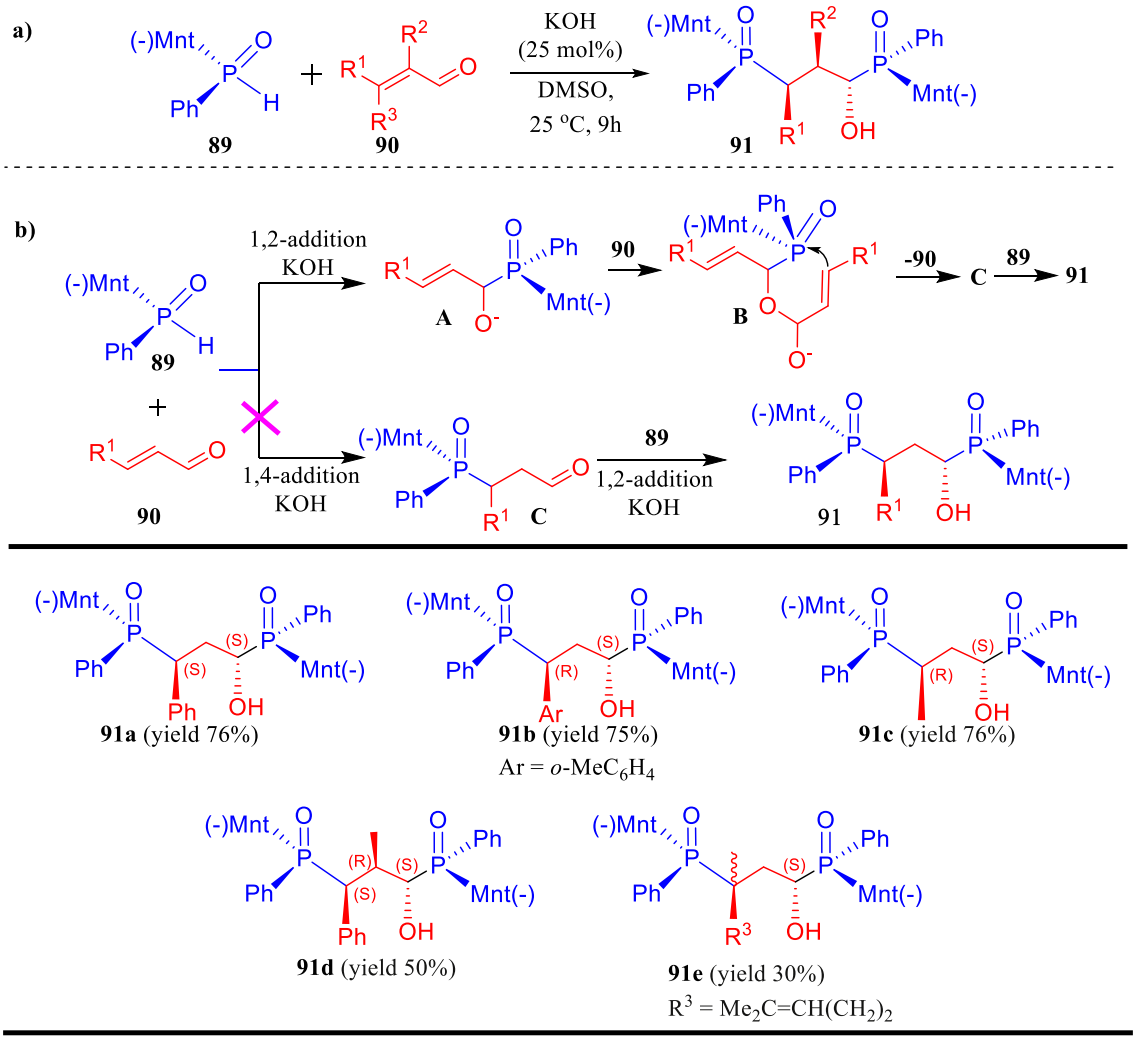
(R_P)-**89** reacted with α,β-unsaturated aldehydes **90**. This reaction resulted in the highly stereoselective synthesis of a series of 1,3-bisphosphinylpropanes **91** in good to moderate yields



Scheme 25*. Syntheses of (−)-O,O-di-(1R,2S,5R)-menthyl-H-phosphonate* **84***, (−)-O-(1R,2S,5R)-menthyl phenyl H-phosphinate* (R_P)-**87** *and (−)-(1R,2S,5R)-menthyl phenylphosphine oxide* (R_P)-**89**.

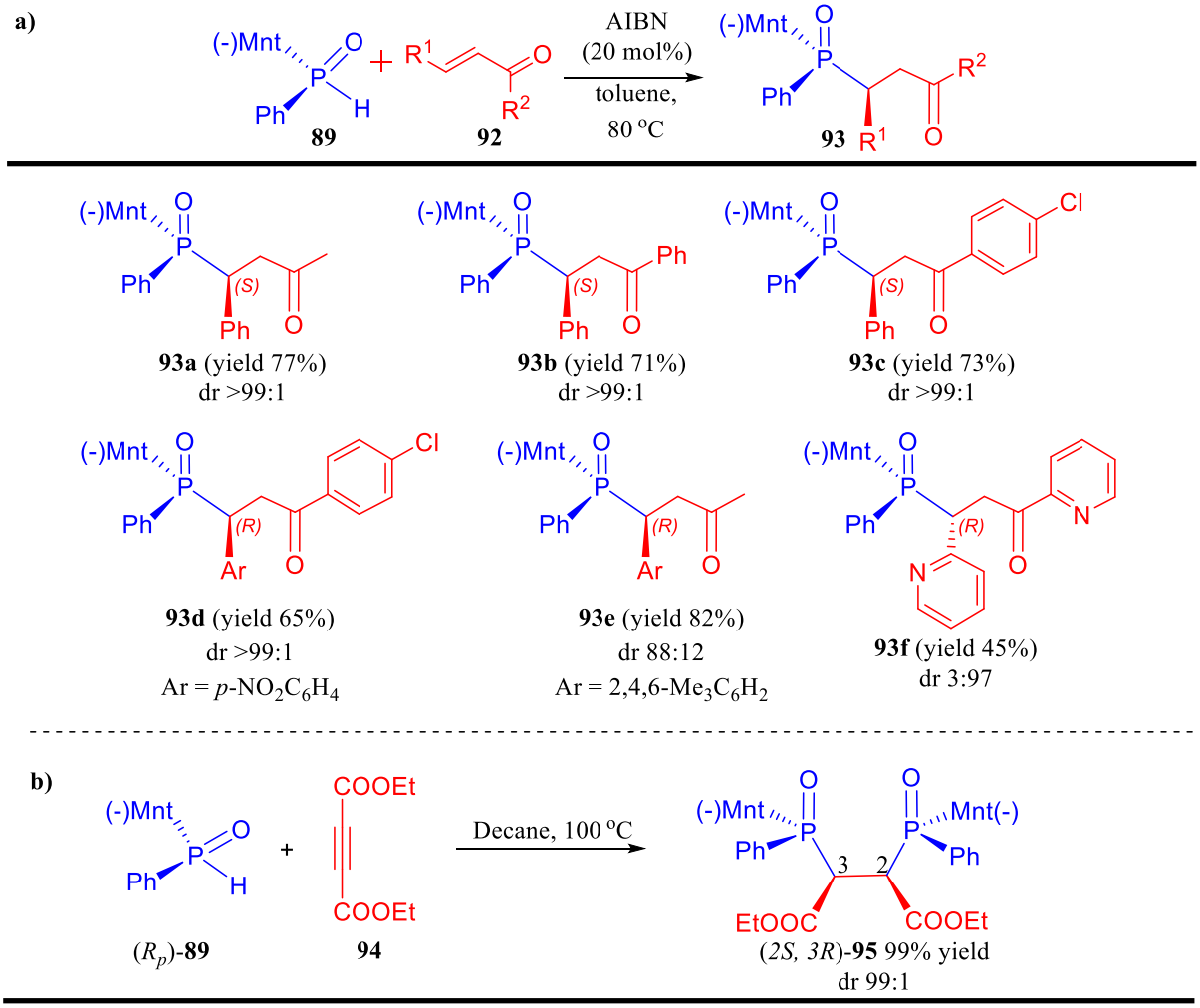
and with up to five chiral centers (Scheme 26)[126]. When the reaction protocol was applied to cinnamaldehyde (product **91a**) and its phenyl-substituted derivatives (product **91b**), crotonaldehyde (product **91c**), 2-methyl cinnamaldehyde (product **91d**), and citral (product **91e**), the pure stereoisomers of **91** were obtained with satisfactory yields (Scheme 26). The authors attributed the high stereoselectivity observed in the reaction to a unique mechanism that differs from the well-known Michael 1,4-addition of (R_P)-**89** to the aldehyde's double bond, followed by a 1,2-addition of the second molecule of (R_P)-**89** to the carbonyl group in

intermediate **C**. Instead, the mechanism involves the initial 1,2-addition, forming intermediate **A**, followed by the addition of the second molecule of the aldehyde and a stereoselective intramolecular phosphinyl migration to form intermediate **B**. This is followed by the elimination of the aldehyde and subsequent addition of (*R*P)-**89**, resulting in the stereoselective formation of product **91** (Scheme 26b).



Scheme 26 *a) Selected examples of reaction of vinyl aldehydes* **90** *with (−)-(1R,2S,5R)-menthyl phenylphosphine oxide (*R*P)-**89** leading to P,C-stereogenic 1,3-bisphosphinylpropanes* **91**. *b) Postulated reaction mechanism. (−)Mnt = 1R,2S,5R-menthyl.*

Subsequently, the authors directed their attention to the addition of (*R*P)-**89** to unsaturated ketones **92** and devised a procedure that selectively produced β-phosphino ketones **93** (Scheme 27a)[127]. The protocol relied on heating the reagents in toluene at 80 °C while employing a catalytic amount of AIBN (20 mol%). This catalyst was observed to accelerate the reaction rate and marginally enhance the dr. It is worth noting that the reaction exhibited exceptional stereoselectivity (*dr* >99:1 in most instances), making it easier to isolate the major diastereomers by simply recrystallizing the crude products from hexane.

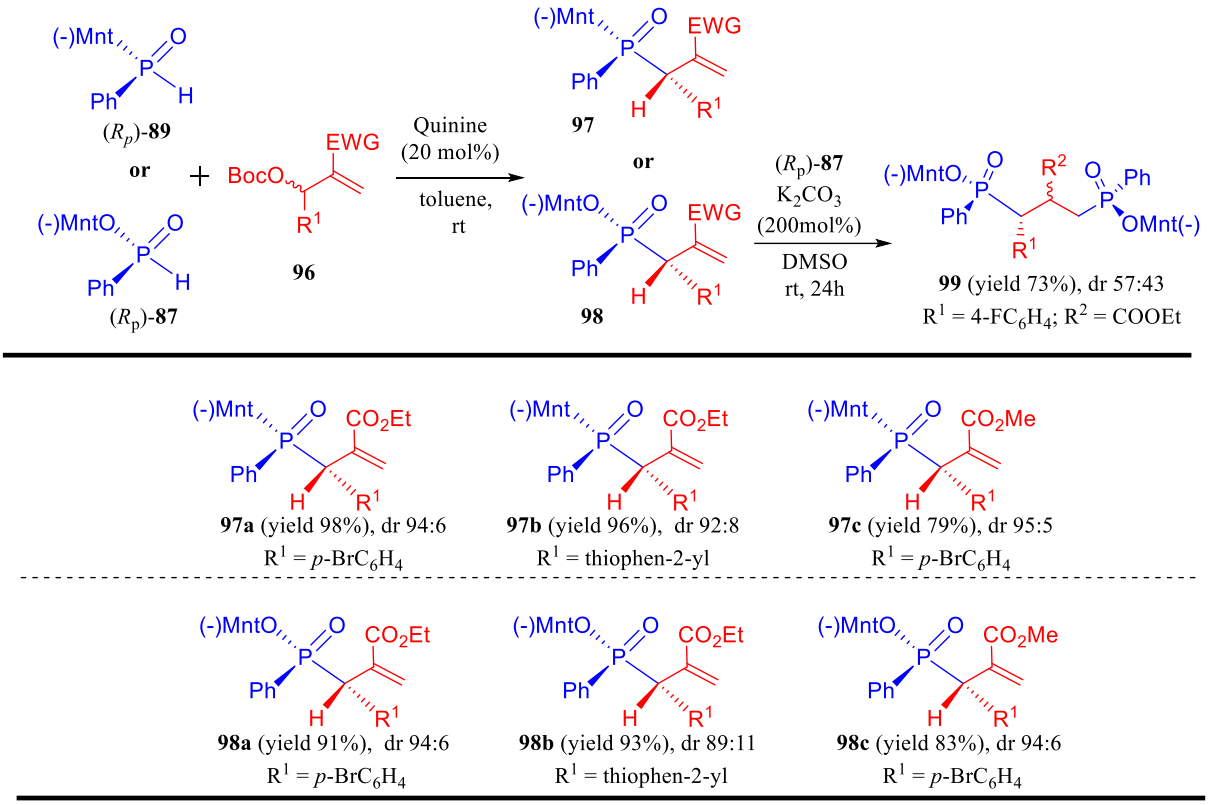


Scheme 27. *a) Selected examples of preparation of β-phosphino ketones via the addition of chiral (R_P)-**89** to vinyl ketones **92**. Yields and dr are given for isolated products. AIBN = azobisisobutyronitrile. (−)Mnt = 1R,2S,5R-menthyl. b) Synthesis of P,C-chirogenic bis-phosphine via stereoselective thermal addition of (R_P)-**89** to active alkyne. The yield and dr was estimated by $^{31}P\{^1H\}$NMR spectroscopy.*

In their continued effort in investigating the utility of (R_P)-**89** as a chiral auxiliary attached to the phosphorus atom, Zhao et al. recently published their findings on the addition of (R_P)-**89** to the triple bond of diethyl but-2-ynedioate **94**. This reaction took place at 100 °C in a non-polar solvent, specifically decane, resulting in the synthesis of a bis-phosphine derivative **95** with an impressive yield of 99% and excellent diastereoselectivity (*dr* 99:1). Furthermore, the structure of (*2S,3R*)-**95** was conclusively confirmed through X-ray diffraction analysis (Scheme 27b)[128]

Teck-Peng Loh et al. reported another utility of (R_P)-**89** and (−)-O-(1*R*,2*S*,5*R*)-menthyl phenyl-*H*-phosphinate (R_P)-**87** in a reaction with alkenes. This study focused on the use of allylic carbonates **96** as substrates in the presence of a catalytic amount of quinine (20 mol%) in toluene at room temperature (Scheme 28)[129]. The reactions gave the products **97** and **98** with high diastereoselectivity, and the major diastereomers were readily separated using flash chromatography**.** The products' absolute configuration was determined through X-ray crystal

analysis. To exemplify the practicality of the obtained P, C-stereogenic allylic compound **98**, it was subjected to a subsequent reaction with (R_P)-**87** in the presence of K_2CO_3 in DMSO at room temperature. This reaction resulted in the formation of 1,3-bisphosphinylpropane **99** as a mixture of diastereomers (73% yield, *dr* 57:43), which was separated by flash chromatography to isolate the major diastereomer (Scheme 28).



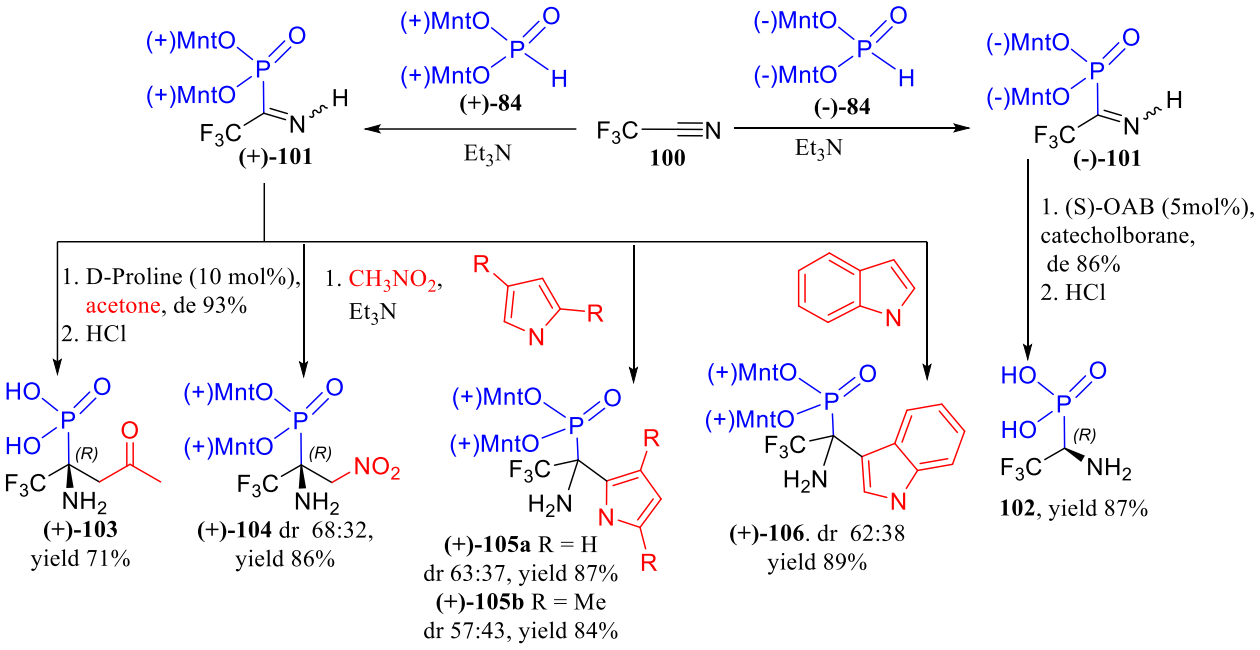
Scheme 28. *Selected examples of diastereoselective P–C bond formation between allylic carbonates* **96** *and chiral* (R_P)-**87** *and* (R_P)-**89** *in the presence of quinine. Yields are reported for isolated products. dr was established based on* ^{31}P *NMR of the crude reaction mixture. (−)Mnt = 1R,2S,5R-menthyl.*

In a separate investigation, the authors aimed to employ (R_P)-**87** in a barium-catalyzed C-OH/P-H dehydrative cross-coupling. However, their attempts proved unsuccessful, as (R_P)-**87** did not react under the optimized conditions, unlike the tested diaryl phosphine oxides[130].

4.4.2. Reactions of menthyl-derived H–P reagents bearing chiral auxiliary bound to the phosphorus atom with imines

Onys'ko et al. investigated the application of optically pure (−) and (+)-O,O-di-(*1R,2S,5R*)-menthyl *H*-phosphonate **84** in the synthesis of N–H iminophosphonates[131,132]. This was achieved through a reaction with trifluoroacetonitrile **100** in the presence of Et_3N, resulting in the formation of N–H iminophosphonates **101**. These iminophosphonates were then utilized as key intermediates for the asymmetric synthesis of C-stereogenic organophosphorus

compounds (Scheme 29)[131,132]. For example, utilizing (-)-**101** in the diastereoselective hydrogenation using catecholborane and (*S*)-OAB as a catalyst (5 mol%) resulted in a diastereomeric mixture of α-aminophosphonate (*de* 86%), which was subsequently isolated through chromatography to afford the major diastereomer. α-Aminophosphonic acid **102**, with an (*R)* configuration at the stereogenic carbon atom, was obtained in an enantiomerically pure form with an 87% yield through the cleavage of the menthyl groups from the major diastereomer of α-aminophosphonate [131].

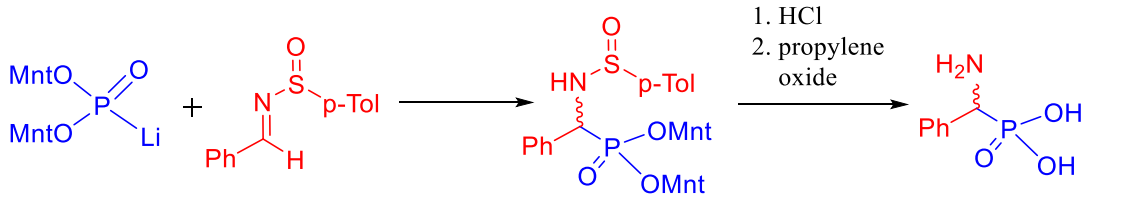


Scheme 29. *Reactions of optically active O,O-dimenthyl α-iminotrifluoroethylphosphonates (+)-***101** *and (−)-***101**. *Yields are reported for isolated products. (S)-OAB = (S)-1-methyl-3,3-diphenyl-tetrahydro pyrrolo[1,2c][1,3,2] oxazaborole. (−)Mnt = 1R, 2S, 5R-menthyl; (+)Mnt = 1S, 2R, 5S-menthyl.*

Significantly, the authors made a noteworthy observation regarding the stereodirecting properties of the dimenthoxyphosphonyl group. They found that even in the absence of a chiral catalyst and using non-chiral reducing agents, asymmetric induction was observed, with a diastereomeric excess of up to 34% when $NaBH_4$ was employed. Additionally, when N–H iminophosphonate (+)-**101** underwent a Mannich reaction with acetone in the presence of D-proline as a catalyst (10 mol%), the desired α-amino-α-trifluoromently-γ-oxobutylphosphonate was obtained with high stereoselectivity (*de* 93%). The major diastereomer was easily separated through chromatography, and its subsequent hydrolysis to the corresponding phosphonic acid (+)-**103** confirmed an (*R*) configuration at the stereogenic carbon (Scheme 29)[131]. To further demonstrate the utility of the dimenthoxyphosphonyl group as an effective stereodirecting chiral auxiliary attached to the phosphorus atom, the aza-Henry reaction and aminoalkylation of electron-rich heterocycles such as pyrrole and indole, using N–H iminophosphonate (+)-**101**

were performed. High yields were obtained in all cases, yielding diastereomerically enriched products (+)-**104** (dr 68:32), (+)-**105a** (dr 63:37), (+)-**105b** (dr 57:43), and (+)-**106** (dr 62:38) respectively (Scheme 29)[131].

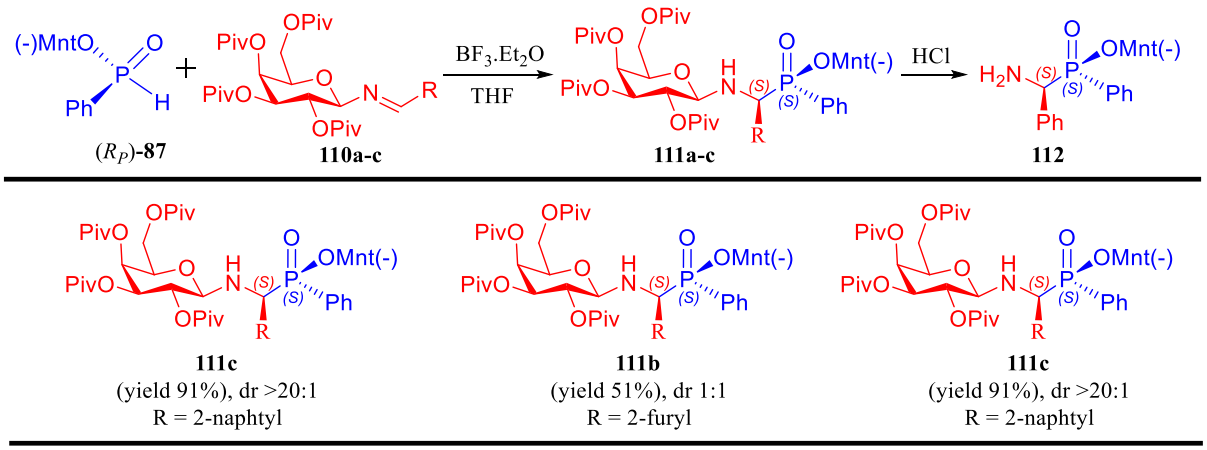
Łyżwa reported the application of optically pure (−)- and (+)-lithium salts of O,O-di-(*1R,2S,5R*)-menthyl *H*-phosphonate **107** in the hydrophosphonylation of enantiopure *N*-(p-tolylsulfinyl)-benzaldimines (+)-**108a** and (-)-**108b** at −78 °C. This double asymmetric addition resulted in the formation of α-aminophosphonates **109** with high diastereoselectivity up to 100:0 dr (Scheme 30)[133]. The enantiomers of (−)-**107a** and (+)-(*S*)-**108a**, as well as (+)-**107b** and (−)-(*R*)-**108b**, were identified as matched pairs of isomers, while the enantiomers (−)-**107a** and (−)-(*R*)-**108b**, or (+)-**107b** and (+)-(*S*)-**108a**, were identified as mismatched pairs. In each case, the major diastereoisomer was selectively isolated using chromatography. The absolute configuration of the newly formed stereogenic carbon center was determined by hydrolyzing the pure diastereomers of α-aminophosphonates **109** to the corresponding α-aminophosphonic acids **41a**, which revealed either (*R*)- or (*S*)-configuration (Scheme 30).



Scheme 30. *Asymmetric addition of lithium salts of chiral H-dimenthyl phosphonates (+)-***107** *and (−)-***107** *to chiral sulfinylimines (+)-***108a** *and (−)-***108b**. [a] *Yield of major diastereomer 88%,* [b] *yield of major diastereomer 77%,* [c] *yield of major diastereomer 75%,* [d] *yield of major diastereomer 86%. (−)Mnt = 1R,2S,5R-menthyl; (+)Mnt = 1S,2R,5S-menthyl.*

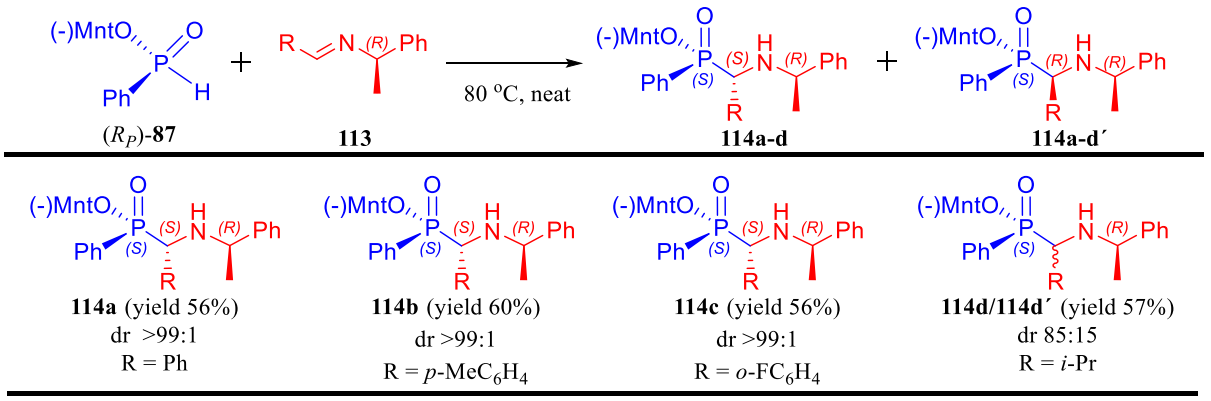
Miao's research group successfully utilized the optically pure enantiomer of *P*-chiral (−)-O-(*1R,2S,5R*)-menthyl phenylphosphinate (R_P)-**87** in a diastereoselective Lewis acid catalyzed phospha-Mannich addition with O-pivaloylated N-galactosylimines **110** (Scheme 31)[134]. Aromatic and substituted aromatic imines **110** showed favorable results, with good to excellent yields (up to 91%) and diastereoselectivity (dr up to >20:1) in the adducts **111** under the optimized reaction conditions. However, for imines with heterocyclic and aliphatic substituents, the yields and diastereoselectivities were comparatively lower, and in some cases showed no reactivity. Through X-ray analysis, the absolute configuration of (S_C, S_P) was assigned for the

product β-N-glycoside-α-aminophosphinates **111**, providing conclusive evidence that the phospha-Mannich reaction effectively retained the initial configuration at the phosphorus atom. Finally, under acidic conditions, the elimination of the O-pivaloylated N-galactosyl substituent from compound **111a** led to the formation of enantiomerically pure α-aminophosphinate **112** with a yield of 86%, and notably, no racemization occurred (Scheme 31).



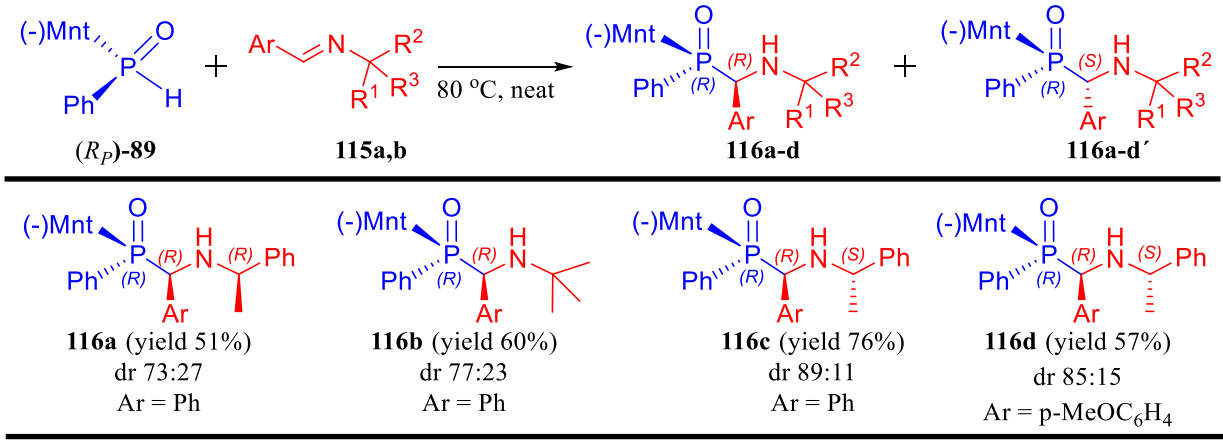
Scheme 31. *Selected examples of diastereoselective synthesis of α-aminophosphinates* **111a–c** *via the phospha-Mannich reaction of (RP)-***87** *with aldimines* **110a–c**. *Yields are reported for isolated products. dr was established based on ^{31}P NMR of the crude reaction mixture. (−)Mnt = 1R,2S,5R-menthyl.*

In their study, Zhao et al. utilized (*RP*)-**87** in the phospha-Mannich reaction, employing pure enantiomers of (*R*)-1-phenylethanimines **113**, obtained from various substituted aromatic and aliphatic aldehydes. The reaction led to the formation of the corresponding α-aminophosphinates **114** with excellent diastereoselectivity of dr >99:1 (Scheme 32)[135]. In the X-ray analysis, the absolute configuration of the major diastereomers was determined to be (*S*) at the newly formed stereogenic carbon and (*S*) at the phosphorus stereogenic center, confirming that the reaction took place while preserving the configurations at the starting materials (Scheme 32). Notably, when (*S*)-1-phenylethanimine or non-chiral imines were used, the diastereoselectivity of the reaction with (*RP*)-**87** was significantly low, resulting in a racemic mixture (dr 50:50). According to the authors, the chirality observed at the stereogenic carbon atom was primarily influenced by chiral aldimine rather than chiral phosphorus. Notably, (*RP*)-**87** demonstrated a matched effect when reacting with (*R*)-1-phenylethanimines but showed a mismatched effect when used with (*S*)-1-phenylethanimines[135].



Scheme 32. *Selected examples of reaction of (R_P)-**87** with enantiomerically pure (R)-1-phenylethanimines **113**. Yields and dr are reported for isolated products after recrystallization. (−)Mnt = 1R, 2S, 5R-menthyl.*

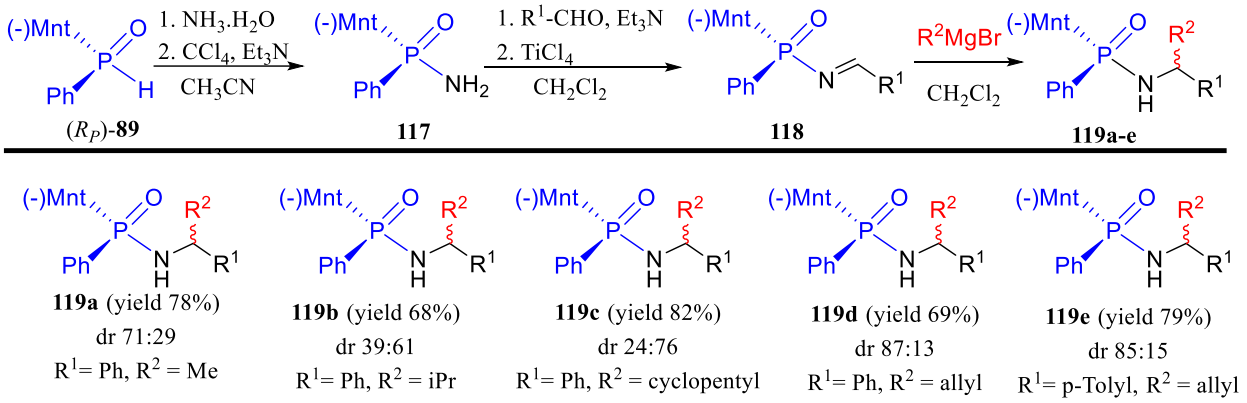
In continuation of their study, the same research team employed (−)-(*1R, 2S ,5R*)-menthyl phenylphosphine oxide (*R_P*)-**89** as a chiral auxiliary bound to a phosphorus atom in the phospha-Mannich reaction involving both chiral and non-chiral imines **115** (Scheme 33)[136]. The reactions utilizing (*R_P*)-**89** with (*R*)-1-phenylethanimines **115a** or non-chiral imines **115b** yielded the desired α-aminophosphinates **116**, albeit with moderate yields and diastereoselectivity of up to 77:23 dr (Scheme 33).



Scheme 33. *Selected examples of reaction of (R_P)-**89** with imine **115**. dr was established based on ^{31}P NMR of the crude reaction mixture. Yields are given for isolated products. (−)Mnt = 1R, 2S, 5R-menthyl.*

Importantly, in each case, the diastereomers could be easily separated using preparative TLC. Notably, enhanced yields and diastereoselectivities were achieved when (*R_P*)-**89** reacted with (*S*)-1-phenylethanimines (product **116c, d**) (Scheme 33). The improved diastereoselectivity was attributed to the matched interaction between (*S*)-1-phenylethanimines and (*R_P*)-**89**. Furthermore, the authors emphasized that the main source of chirality was primarily derived from the stereogenic phosphorus atom. The absolute configuration of the major stereoisomers of the products was assigned as (*R_P*, *R_C*) (Scheme 33).

In a recent publication regarding the utility of (R_p)-**89**, Zhao et al. reported its use in the Atherton-Todd coupling reaction with ammonia solution, resulting in the synthesis of (S_P)-(−)-menthyl phenylphosphinamide **117** with a yield of 94% and a diastereomeric ratio exceeding 99:1. Subsequently, **117** was subjected to condensation with aromatic aldehydes in the presence of $TiCl_4$/Et_3N, leading to the formation of *N*-phosphonyl imines **118**. Finally, the imines were subjected to a 1,2-addition reaction with Grignard reagents, yielding *P*-chiral phosphinamides **119** (Scheme 34)[137]. The desired products were obtained with good yields, although the diastereoselectivity was moderate.

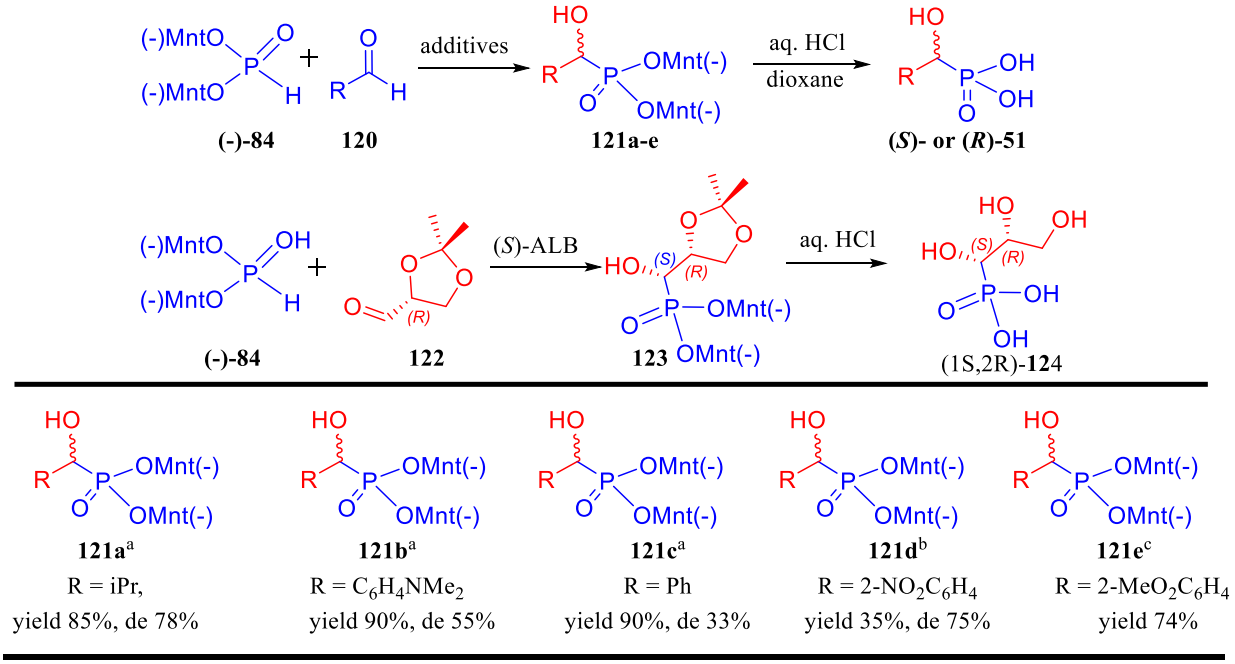


Scheme 34. *Selected examples of utility of (R_P)-**89** in the synthesis of imines **118** and their reaction with Grignard reagents. dr was determined by ^{31}P NMR. The yield provided corresponds to an isolated mixture of diastereomers, with (−)Mnt representing 1R, 2S, 5R-menthyl.*

4.4.3. Addition of menthyl-derived H–P reagents to carbonyl compounds

The group of Kolodiazhnyi reported that the base-catalyzed addition of (−)-O,O-di-(*1R,2S,5R*)-menthyl-*H* phosphonate **84** to non-chiral aldehydes exhibits substrate dependency and displays high stereoselectivity when reacting with isopropyl aldehyde to afford α-hydroxyphosphonate **121a** with a *de* of 78% (Scheme 35)[138]. In contrast, the reactions with 4-(dimethylamino) benzaldehyde resulted in much lower stereoselectivity (de 55%), leading to the formation of α-hydroxyphosphonate **121b**. Similarly, when benzaldehyde was employed, the stereoselectivity was significantly reduced (de 33%), yielding α-hydroxyphosphonate **121c**. The presence of the chiral auxiliary attached to the phosphorus atom facilitated the isolation of pure major diastereomers for α-hydroxyphosphonates **121a–c**. In each case, after undergoing acidic hydrolysis, the corresponding (*R*)-α-hydroxyphosphonic acids **51** were conveniently obtained (Scheme 35). In subsequent studies, Kolodiazhnyi et al. showcased that the diastereoselectivity in the reaction between aromatic aldehydes and (−)-**84** could be enhanced by the addition of a catalytic amount of cinchonine alkaloids, with the specific structure of the

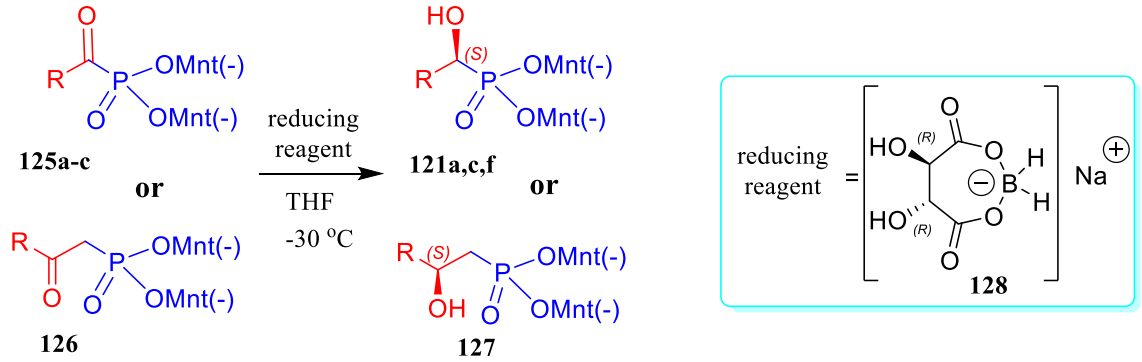
alkaloids playing a crucial role in determining the stereochemical outcome of the reaction[139]. For instance, when 2-nitrobenzaldehyde was employed alongside cinchonidine, the desired (*R*)-α-hydroxyphosphonate **121d** was obtained with a diastereomeric excess of 75%.



Scheme 35. *Hydrophosphonylation of aldehydes with (−)-***84***. In the case of products* **121a–c***, dr was determined by analyzing the* ^{31}P *NMR spectra of the crude product. The major diastereomer was isolated through crystallization.* [a]*As base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed.* [b]*Catalytic quantity of cinchonidine was utilized.* [c]*Catalytic quantity of quinine was used. (S)-ALB stands for (S)-aluminium lithium bis(binaphthoxide). (−)Mnt = 1R,2S,5R-menthyl.*

Conversely, the utilization of quinine resulted in the formation of the corresponding (*S*)-α-hydroxyphosphonate **121d**. Significantly, the application of cinchonine alkaloids in a comparable reaction using a non-chiral dimethyl *H*-phosphonate yielded the product with poor enantioselectivity (*ee* ≤33%), thus clearly emphasizing the stereodirecting properties and applicability of the menthyl-derived *H*-phosphonate (−)-**84**. Furthermore, Kolodiazhnyi and co-workers also investigated the reaction of 2,3-d-isopropylidene-(*R*)-glyceraldehyde **122** as a chiral aldehyde with (−)-**84**. After performing extensive experiments, it was determined that the optimal diastereoselectivity (*de* 85%) could be achieved by employing (*S*)-aluminium lithium bis(binaphthoxide) as a catalyst in THF at ambient temperature. It is worth noting that the diastereomers could be readily separated through crystallization, obtaining them in a pure form, and subsequently subjected to hydrolysis, yielding enantiomerically pure hydroxyphosphonic acid (*1S,2R*)-**124** (Scheme 35)[140].

In their continued work in exploring the utility of (−)-**84**, Kolodiazhnyi's group demonstrated that racemic α-hydroxyphosphonates containing a dimenthyl auxiliary, obtained from the reaction of aldehydes with (−)-**84** catalyzed by DBU, could be employed to synthesize the corresponding α-ketophosphonates **125a–c**. The α-ketophosphonates were obtained through oxidation using pyridinium dichromate/trimethylchlorosilane, followed by a diastereoselective reduction to yield optically pure α-hydroxyphosphonates **121a, c, f** (Scheme 36)[141,142]. Using a similar approach, β-ketophosphonate **126** was synthesized through a three-step, one-pot process starting with dimethyl methylphosphonate. Firstly, the dimethyl methylphosphonate reacted with butyl lithium to form the carbanion, which then underwent a reaction with cuprous bromide to form the cuprous derivative. Finally, the cuprous derivative reacted with acyl chlorides to afford the desired β-ketophosphonates. Through experimentation using readily available chiral molecules, the authors identified the adduct (*R*)-**128** as the most effective reducing agent, derived by reacting (*R*,*R*)-tartaric acid with sodium borohydride. The reduction of α- and β-ketophosphonates using (*R*)-**128** resulted in the formation of α- and β-hydroxyphosphonates with an (*S*) configuration (**121** and **127** respectively). Conversely, the reduction of α- and β-ketophosphonates using (*S*)-**128** produced (*R*)-α- and β-hydroxyphosphonates. These results demonstrate that the stereochemical outcome of the reduction process for both α- and β-ketophosphonates depends on the configuration of the tartaric acid. Consequently, the asymmetric induction of (*1R,2S,5R*)-menthyl groups and (*R, R*)-tartaric acid showed a matching effect, enhancing the diastereofacial selectivity. Conversely, asymmetric inductions of (*1R, 2S, 5R*)-menthyl groups and (*S, S*)-tartaric acid had a mismatched effect, leading to decreased stereoselectivity.



121a R = iPr, yield 97.6%, dr 16:84

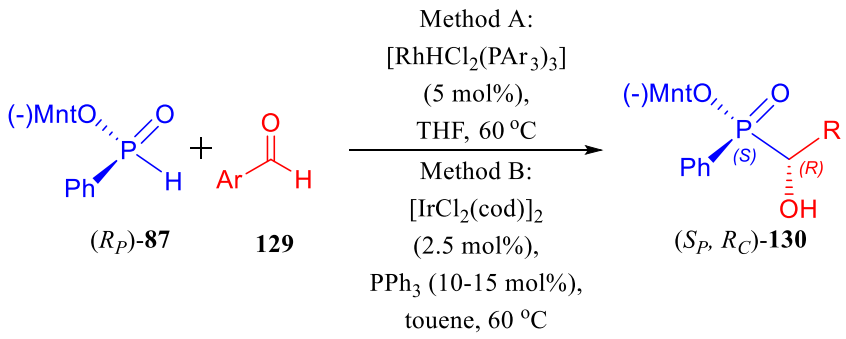
121c R = Ph, yield 95%, dr 3.8:96.2

121f R = 2-FC_6H_4, yield 97%, dr 9.8:90.2

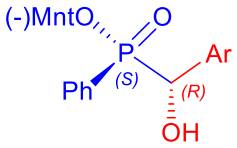
127 R = CH_2Cl, yield 94%, dr 2:98

Scheme 36. *Selected examples of diastereoselective reduction of α- and β-ketophosphonates leading to α- and β-hydroxyphosphonates (−)Mnt = 1R,2S,5R-menthyl.*

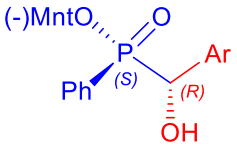
Han and co-workers investigated the application of (−)-O-(1R,2S,5R)-menthyl phenyl-*H*-phosphinate (R_P)-**87** in the diastereoselective hydrophosphonylation of aldehydes **129** using either rhodium or iridium catalysts (Scheme 37)[143].



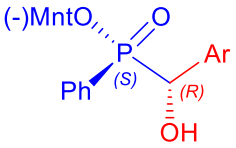
(R_P)-**87** **129** (S_P, R_C)-**130**



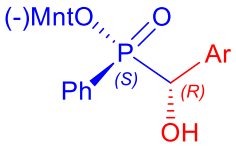
130a Method A: Ar = Ph, yield 94%, dr 95:5 Method B: yield 95%, dr 97:3



130b Method A: Ar = 4-$CF_3C_6H_4$, yield 99%, dr 88:12 Method B: yield 92%, dr 88:12



130c Method A: Ar = 2-furane, yield 75%, dr 95:5 Method B: yield 88%, dr 95:5



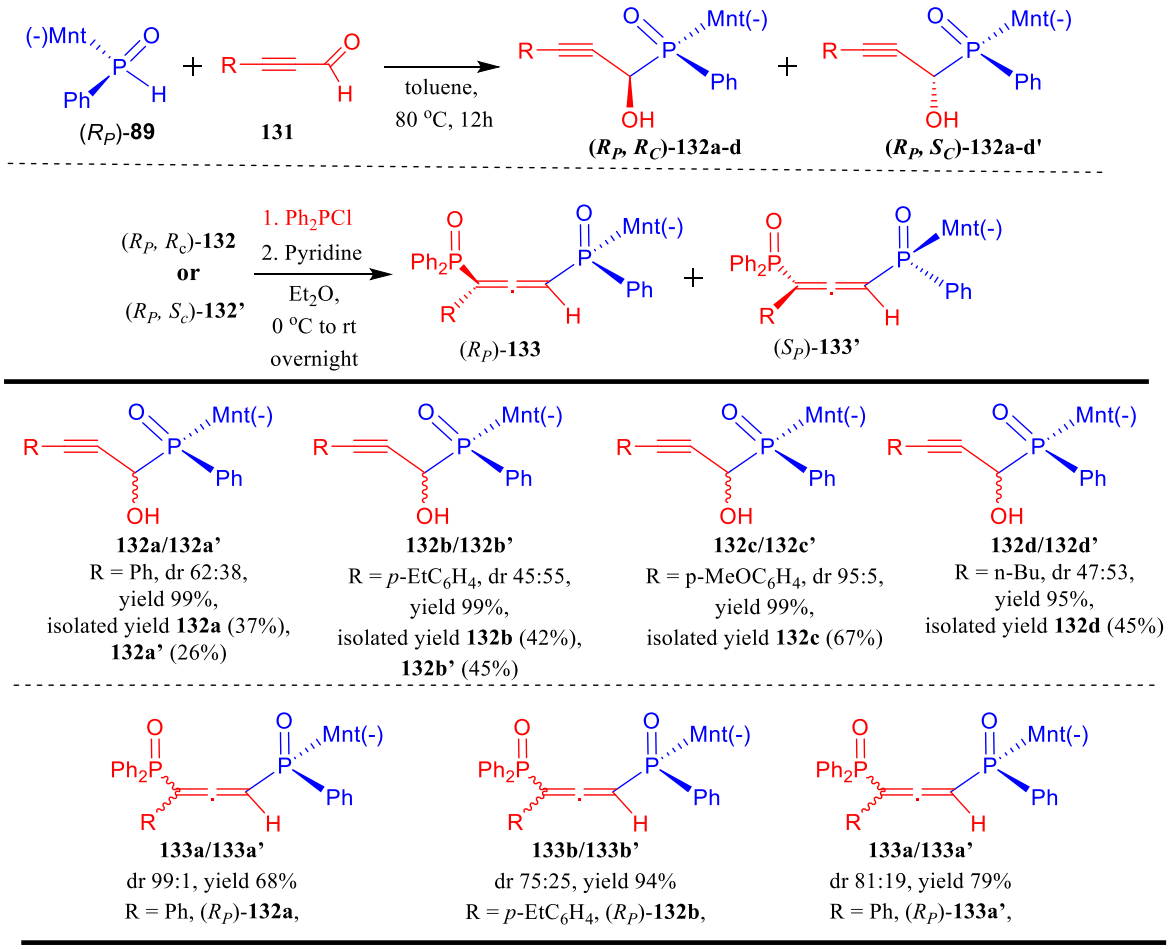
130d Method A, Ar = 1-naphtyl, yield 76%, dr 93:7 Method B: yield 83%, dr 95:5

Scheme 37*. Selected examples of rhodium or iridium catalysed hydrophosphonylation of aldehydes with* (R_P)-**87** *leading to P- and C-stereogenic α-hydroxyphosphinates* **130.** *dr was estasblished based on* ^{31}P *NMR of the crude product. cod – 1,5-cyclooctadiene. (−)Mnt = 1R, 2S, 5R-menthyl.*

During the process of optimizing the catalyst's structure, it was discovered that the addition of diluted HCl to Wilkinson's catalysts [$RhCl(PPh_3)_3$] resulted in the formation of a rhodium-containing catalyst [$RhHCl_2(PPh_3)_3$], which in the hydrophosphonylation reaction gave the best diastereoselectivity (*dr* up to 95:5) in the desired product **130**. As a substitute approach, a variety of iridium catalysts were examined, and it was observed that [$IrCl(cod)_2$] in combination with PPh_3 produced similar outcomes, with a diastereomeric ratio of up to 97:3. By employing a straightforward crystallization process, it was possible to isolate the pure major diastereomer. The X-ray analysis of the crystals showed an (*R*) configuration on the hydroxy carbon and (*S*) on the phosphorus. Based on these findings, the authors proposed that the reaction likely follows a transition-metal-catalyzed mechanism, directed by an optically pure menthyl-derived *H*-phosphinate

In a recent study by Chang-Qui Zhao and Qiang Li et al., an intriguing application of (−)-(*1R,2S,5R*)-menthyl phenylphosphine oxide (R_P)-**89** was introduced. This compound was

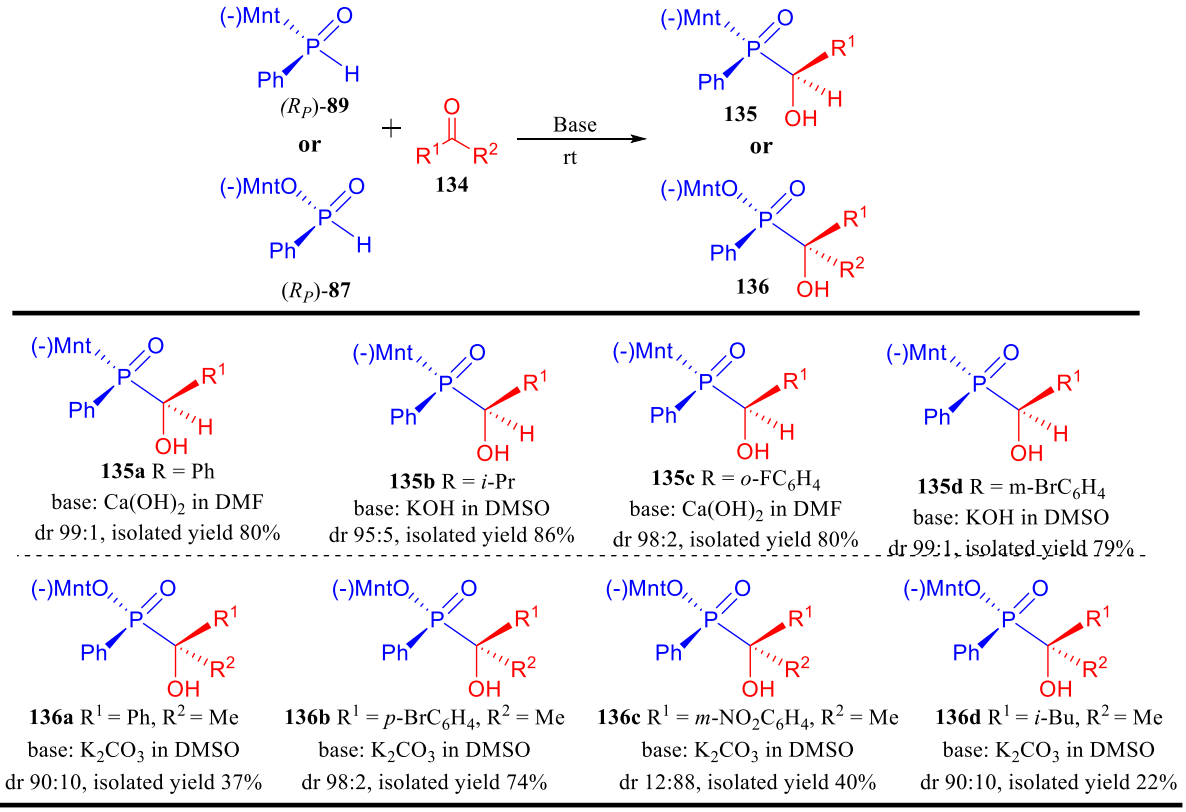
utilized in the reaction with alkenylaldehydes **131** to generate α-phosphinyl propargyl alcohols **132** (Scheme 38).



Scheme 38. *Selected examples of stereoselective preparation of P-axial-stereogenic allenyl bisphosphine oxides from optically pure α-hydroxyphosphinates* **132** *via chirality transfer. dr was determined based on* ^{31}P *NMR spectra of the crude product. Diastereoisomers could be easily separated and obtained in pure form by means of crystallization or chromatography. (−)Mnt = 1R,2S,5R-menthyl.*

These alcohols were transformed into *P*,axial-stereogenic allenyl phosphine oxides **133** in the presence of pyridine and Ph_2PCl (Scheme 38)[144]. Although the addition of (R_P)-**89** to aldehydes **131** did not consistently give high diastereoselectivity, the presence of a chiral auxiliary attached to the phosphorus atom facilitated the convenient separation of pure diastereomers from the reaction mixture. When the pure diastereoisomers of **132** were subjected to a subsequent reaction with Ph_2PCl in the presence of pyridine, it was observed that (R_P)-**133** was predominantly formed (for example, dr of 99:1 for **133a)** in the case of (R_P,R_C)-**132**. On the other hand, employing (R_P,S_C)-**132'** also yielded (R_P)-**133** as the major product, albeit with lower stereoselectivity (for example, *dr* of 81:19 for **133a**). The authors attributed these results to the primary influence of stereogenic phosphorus on controlling axial chirality.

Han et al. continue their investigation on the potential of (−)-(*1R,2S,5R*)-menthyl phenylphosphine oxide (R_P)-**89** and (−)-O-(*1R,2S,5R*)-menthyl phenylphosphinate (R_P)-**87** in reactions with aldehydes or ketones under simple base-catalyzed conditions (Scheme 39)[145,146].



Scheme 39. *Selected examples of nucleophilic addition of (R_P)-**89** and (R_P)-**87** to aldehydes and ketones. dr was established based on ^{31}P NMR of the crude product. The diastereoisomers could be easily separated and obtained in pure form by means of crystallization or chromatography. (−)Mnt = 1R, 2S, 5R-menthyl.*

The most favorable outcomes for ketones were achieved by utilizing K_2CO_3 as a base in DMSO at room temperature. High yields and diastereoselectivity (*dr* ≥90:10) were achieved when utilizing aromatic and *p*-substituted aromatic ketones, leading to the formation of corresponding quaternary α-hydroxyphosphinates **136**. The major diastereomer predominantly exhibited an (*R*) configuration at the asymmetric carbon atom, while retaining the configuration at the phosphorus atom. However, ortho or meta-substituted aromatic ketones yielded less satisfactory results, with even reversed selectivity observed in ketones with a meta-substituted group. (Scheme 39, compound **136c**).

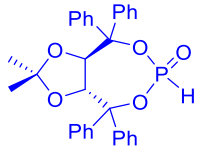
When aliphatic ketones were employed, the yields were relatively low. Conversely, for aldehydes, the use of $Ca(OH)_2$ in DMF or KOH in DMSO yielded the most favorable outcomes. The desired α-hydroxyphosphine oxides **135** were obtained with good yields and high diastereoselectivity, irrespective of the aldehyde's structure (*dr* ≥95:5) with the major diastereomer having an (*S*) configuration at the stereogenic carbon atom and an (*R*)

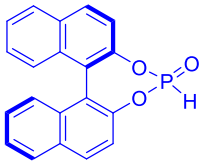
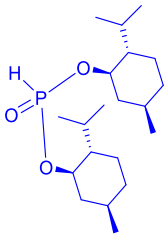
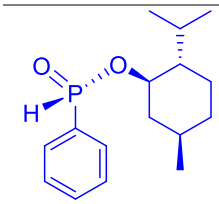
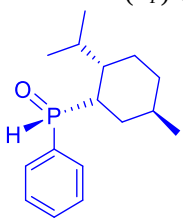
configuration at the phosphorus atom. By monitoring the reactions over time, an enhancement in diastereoselectivity was observed and the authors hypothesized that the additions of (R_P)-**89** to aldehydes and (R_P)-**87** to ketones were reversible, with different thermodynamic stabilities for the formed diastereomers.

In this introduction, I have tried to give a brief overview of the biological activity and synthesis of substituted phosphonates and phosphonic acids, especially in an asymmetric fashion, with emphasis on the use of optically pure *H*-phosphonates, phosphinates, and phosphine oxides derived from chiral alcohols as chiral auxiliaries and highly diastereoselective tools for the preparation of structurally diverse chiral organophosphorus compounds (Table 1).

In conclusion, in medicinal chemistry, the use of organophosphorus compounds as biologically active agents necessitates in many cases their preparation asymmetrically, considering the significance of stereochemistry in relation with biological activity. This consideration is essential during the process of retrosynthetic planning. The biological activity of these compounds is heavily influenced by the absolute configuration of the carbon atom adjacent to the phosphorus, as it interacts with chiral biological molecules like enzymes.[10,13,147]. Prominent examples include (*R*)-phospholeucine, which serves as a more potent inhibitor of leucine aminopeptidase compared to its opposite enantiomer, and (*S*, *R*)-alafosfalin, which demonstrates the most potent antibacterial activity among the four available stereoisomers (Figure 4, compounds **7** and **9**, respectively). Consequently, the development of a protocol enabling the asymmetric formation of *P*-substituted carbon stereocenters with high enantioselectivity or diastereoselectivity is desirable. However, this task remains formidable, potentially stemming from the following inherent challenges:

Table 1. *Summarized comparison of H-P species with a chiral auxiliary attached to the phosphorus atom used in the asymmetric synthesis of organophosphorus compounds with C- and P-stereogenic centers.*

Chiral auxiliary bound to Phosphorus atom	Advantages (+) and Disadvantages (-)	Possible application	Ref.
 TADDOL *H*-phosphonate (R,R)-**29**	+ Easily synthesized from tartaric acid esters in four steps. + Easy cleavage of the chiral moiety using aq. HCl or BrTMS. - Decomposes in solution into TADDOL upon heating above 80 °C.	1. Stereoselective synthesis of C-stereogenic organophosphorus compounds. 2. Highly diastereoselective addition to C=C bond (de ≥90%) 3. Highly diastereoselective addition to C=N (chiral and non-chiral imines) and C=O bond (aldehydes and ketones) (de ≥90%)	85, 88, and 89 90-95

 BINOL *H*-phosphonate (*R*)-**56**	+ Easily prepared from BINOL and PCl_3 in two steps. + Easy removal of chiral part with nBuLi or EtONa to recover theBINOL. - Purification by column chromaography leads to decomposition into BINOL.	1. Stereoselective synthesis of C-stereogenic organophosphorus compounds. 2. Addition to cyclic imines with good dr (95:5) but moderate yields (≤50%) 3. Catalytic addition to hydrazones and C=C bonds with low dr (1:1.2) 4. Diastereoselective reactions of Se derivative of (*R*)-56 with Grignard reagents and halides 5. Good stereodirecting properties	 103 and 104 109 and 110 112-114
 Dimenthyl *H*-phosphonate **84**	+ Easily synthesized from menthol and PCl_3 in two steps. + Easily cleavage of chiral part with aq. HCl.	1. Stereoselective synthesis of C-stereogenic organophosphorus compounds. 2. Highly diastereoselective addition to chiral imines (dr ≥92:8). 3. Moderate diastereoselectivity in addition to C=O bond (chiral and non-chiral alde- hydes) (de ≤85%). 4. Moderate stereodirecting properties.	 133 138-142 131, 141-142
 Menthyl *H*-phosphinate (R_P)-**87**  Menthyl phosphine oxide (R_P)-**89**	+ Several available protocols for their preparation are described in literature. - Synthesis becomes more challenging due to the chirality on the P-atom, in contrast to other H-P species with a chiral auxiliary attached to phosphorus, such as (*R*, *R*)-**29**, (*R*)-**56**, and **84**.	1. Stereoselective synthesis of C- and. P-stereogenic organophosphorus compounds. 2. Highly diastereoselective addition to alkenes and alkynes (dr ≥90:10). 3. Highly diastereoselective addition to imines. 4. Highly diastereoselective addition to C=O bond (de ≥90%). 5. Good stereo-directing properties.	 126-128 and 144 125-127 143, 145-146 137

1. The general difficulties associated with constructing carbon stereocenters, particularly quaternary stereocenters, include issues such as the low reactivity of precursors and challenges in distinguishing enantiofacial orientation.
2. The prominent influence of the less active phosphonate (or phosphine oxide) on the equilibrium in phosphonate-phosphite (or phosphine oxide and phosphinous acid) tautomerism.
3. The inevitable occurrence of retro-hydrophosphonylation and phospha-Brook rearrangement in Pudovik reactions.

A potential solution to these challenges could involve employing an appropriate *H*-phosphonate bound to a chiral auxiliary, accompanied by meticulous optimization of reaction conditions.

This approach aims to achieve the diastereoselective formation of the C-P bond across a broad spectrum of substrates containing a carbon-heteroatom double bond.

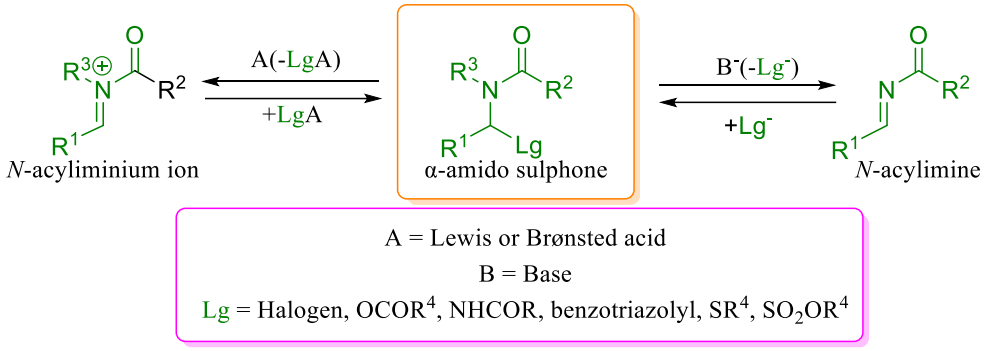
In subsequent chapters, I intend to present newly developed diastereoselective protocols that focus on the utilization of TADDOL derived *H*-phosphonate across various carbon-heteroatom substrates in the asymmetric synthesis of structurally diverse α-substituted organophosphorus compounds. In my research I have decided to select and focus on the use of TADDOL derived *H*-phosphonate since this compound is relatively easy to obtain (even on multigram scale) from optically pure esters of tartaric acids that are not expensive and commercially available in both enantiomerically pure forms. This chiral auxiliary is a bench stable, white solid, well soluble in a variety of organic solvents, moisture, and air resistant and can be stored for months without any signs of decomposition or racemisation. Surprisingly its use as chiral auxiliary is not well developed in the literature and therefore merits further investigations. Additionally, the use of TADDOL derived *H*-phosphonate avoids the formation of additional chiral center at the phosphorus atom and therefore facilitates the interpretation of the research results. Finally, the TADDOL part can be easily cleaved after the synthesis from pure single diasteroisomer of the product (leaving the phosphorus atom in the molecule) and leading to the α-substituted phosphonic acids in optically pure form. The cleavage can be done either classically using concentrated HCl or under milder reaction conditions using bromotrimethylsilane (BrTMS) and this approach is advantageous when labile, more fragile to strong acidic conditions substrates are considered.

Chapter One

Asymmectric hydrophosphonylation of α-amido sulphones

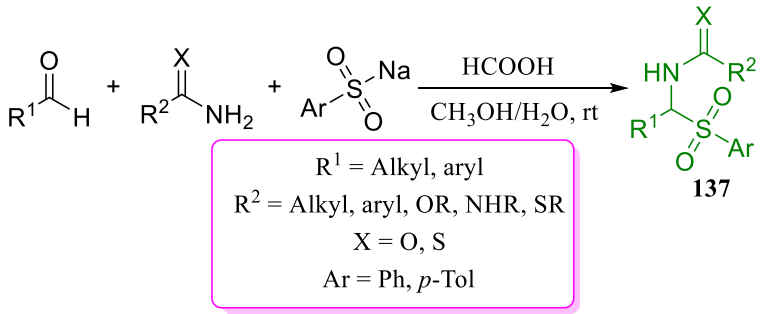
1.0. Introduction

N-Benyloxycarbonylamino sulphones, generally known as α-amido sulphones, are compounds characterized by the simultaneous presence of amide and sulphone functionalities in their structure. These compounds hold significant importance in organic chemistry due to their exceptional utility and stability as precursors of *N*-acylimines. Consequently, they have gained widespread recognition and found numerous applications in modern organic synthesis, particularly asymmetric synthesis, serving as valuable intermediates for the construction of complex molecular structures[148–150]. The remarkable utility of this class of compounds can be attributed to two key factors. Firstly, their facile conversion into reactive *N*-acylimine derivatives under either acidic or basic conditions enhances their versatility in various organic synthesis methodologies (Scheme 40).



Scheme 40. *Generation of N-acyliminium ion and N-acylimine from α-amido sulphones bearing a good leaving group (Lg).*

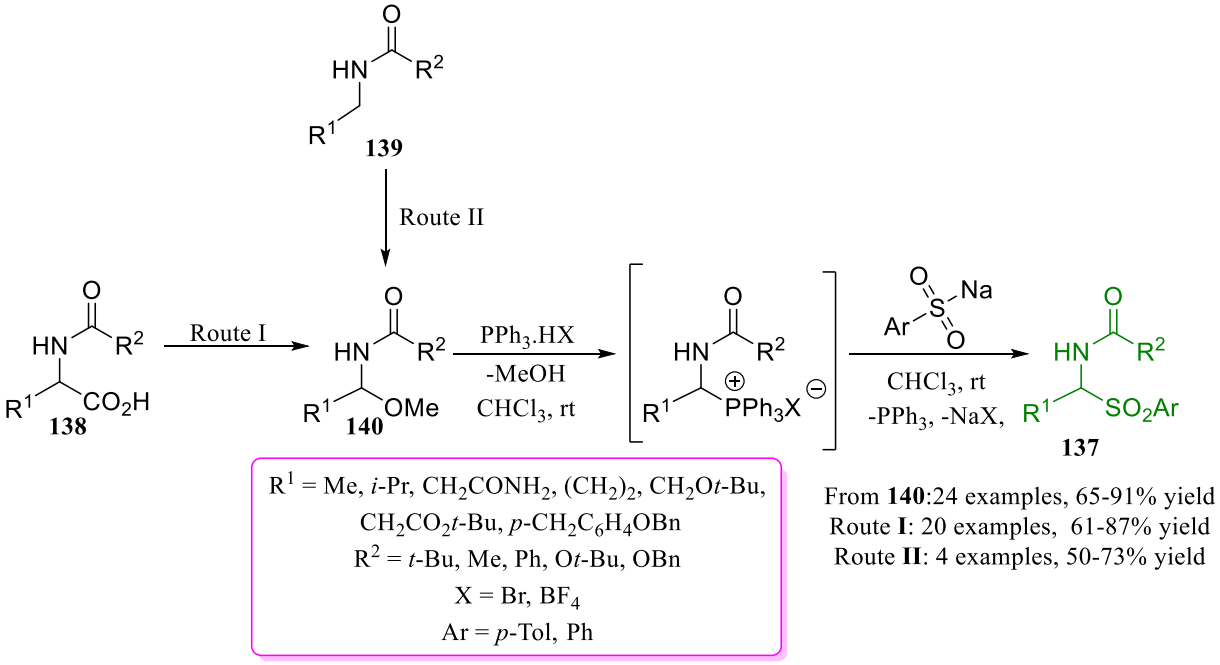
Secondly, their exceptional stability and straightforward method of preparation through a simple acid-promoted three-component reaction involving different aldehydes, sulphinates, and primary amides, carbamates, or carbamides (R^2 = R, OR or NHR)[148,151], make them easily accessible (Scheme 41).



Scheme 41. *The commonly used approach for the synthesis of α-amido sulphones.*

Adamek and coworkers successfully developed an effective protocol for synthesizing α-amido sulphones **137** with satisfactory yields (61-91%). This method involved the one-pot

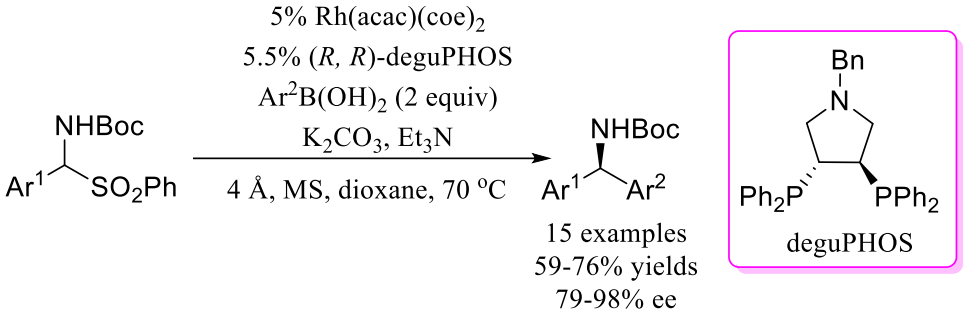
condensation of α-methoxy derivatives **140** with sodium aryl sulphinates in the presence of triphenylphosphonium tetrafluoroborate or bromide at room temperature (Scheme 42)[152]. The authors also presented alternative routes by incorporating their previous work on electrochemical decarboxylative α-methoxylation of *N*-acylamino acids **138** or amides /carbamates **139** to α-methoxy derivatives **140**[153] with this present reaction, enabling a convenient two-step transformation of *N*-acylamino acids **138** or amides/carbamate **139** to the corresponding α-amido sulphones **137** (Scheme 42). This methodology facilitates the synthesis of a wide range of structurally diverse α-amido sulphones, which could be challenging to obtain using the one-pot classical condensation described by Engberts and Strating[148,151]. As a result, this methodology significantly broadens the synthetic potential applications of this class of compounds.



Scheme 42. *Preparation of α-amido sulphones from α-methoxy derivatives **140**, derived from either acylamino acids **138**, or amides **139**. **Route I**: 7 mol% of 3-(1-piperidino)propylfunctionalized silica gel (SiO_2–Pip), MeOH, 10 °C. **Route II**: 1.7 mol% tetraethylammonium p-toluenesulfonate ($Et_4N^+TsO^-$), MeOH, 10 °C.*

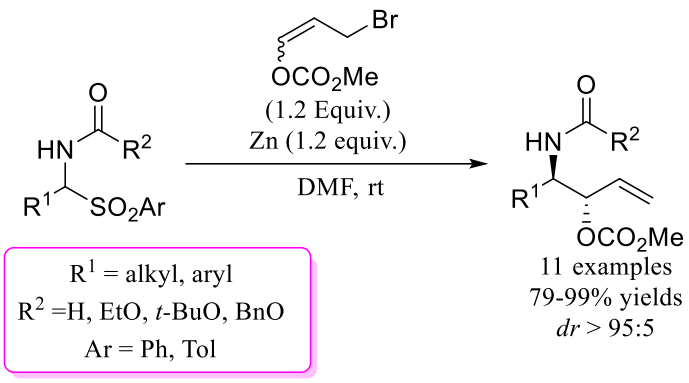
α-Amido sulphones have been employed as substrates in various protocols including reactions with organometallic reagents (for example lithium, magnesium, rhodium, and zinc organocatalyst) to generate *N*-acylimines needed for subsequent nucleophilic addition[154–157]. For example, Ellmann et al., reported the rhodium-catalyzed enantioselective reaction of *N*-Boc imines generated *in situ* from α-amido sulphones with arylboronic acids with different steric and electronic properties in the presence of catalytic amounts of (3*R*,4*R*)-bis(diohenylphos-phino)-1-benzylpyrrolidinen (deguPHOS) and 2-acetylacetonatobis(cyclooctene)rhodium. The

reaction led to the formation of *N*-Boc protected amine derivatives with high enantioselectivity (79-98% ee) and moderate yields (59-76%).



***Scheme 43**. Rhodium-catalyzed enantioselective addition of arylboronic acids to N-Boc imines generated in situ. Rh(acac)(coe) = 2-acetylacetonatobis(cyclooctene)rhodium; deguPHOS = (3R,4R)-Bis(diohenylphosphino)-1-benzylpyrrolidine.*

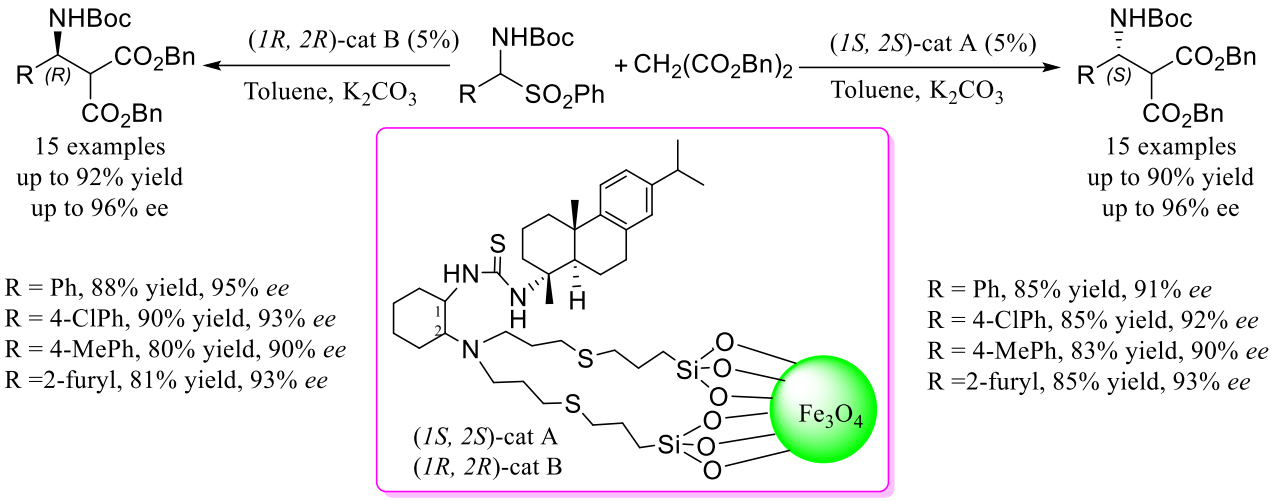
Additionally, the reactions of amido sulphones with allylating reagents led to the synthesis of homoallylamino derivatives[158,159]. A highly efficient approach for synthesizing *anti*-1,2-amino alcohols has been reported, utilizing the hydroxyallylation of α-amido sulphones with 3-bromo-propenyl methyl carbonate in the presence of zinc powder. The reaction was compatible with both aromatic and aliphatic sulphones to afford the products with good, isolated yields (79-99%) and excellent diastereoselectivity (>95:5 in all cases) (Scheme 44)[158].



***Scheme 44**. The diastereoselective reaction of α-amido sulphones with allylating reagent leading to homoallylamino derivatives.*

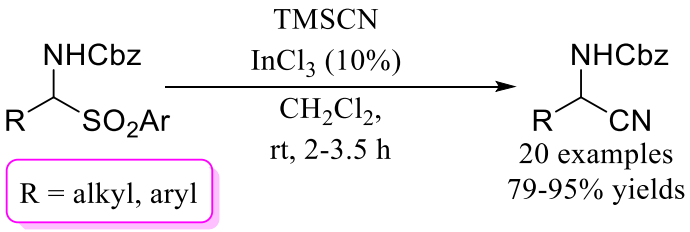
Further utility of α-amido sulphones involves reactions with malonate esters and related derivatives[160–162]. A convenient and environmentally friendly approach for the stereocontrolled synthesis of chiral β-amino acids, achieving high enantioselectivity (up to 96% ee) and yields (up to 92%), has been reported by Li's group[161]. The reaction employed the asymmetric Mannich protocol, wherein Boc imines were generated *in situ* from amido sulphones catalyzed by magnetic-nanoparticle-supported bifunctional rosin-derived tertiary amino thiourea

(Scheme 45). In this protocol, the configuration on the newly formed stereogenic β-carbon of the product is controlled by the stereochemistry of the catalyst.



Scheme 45. *Selected examples of enantioselective synthesis of chiral β-amino acids via the Mannich-type reactions of dibenzyl malonate with N-Boc-protected imines that are generated in situ from a-amido sulfones.*

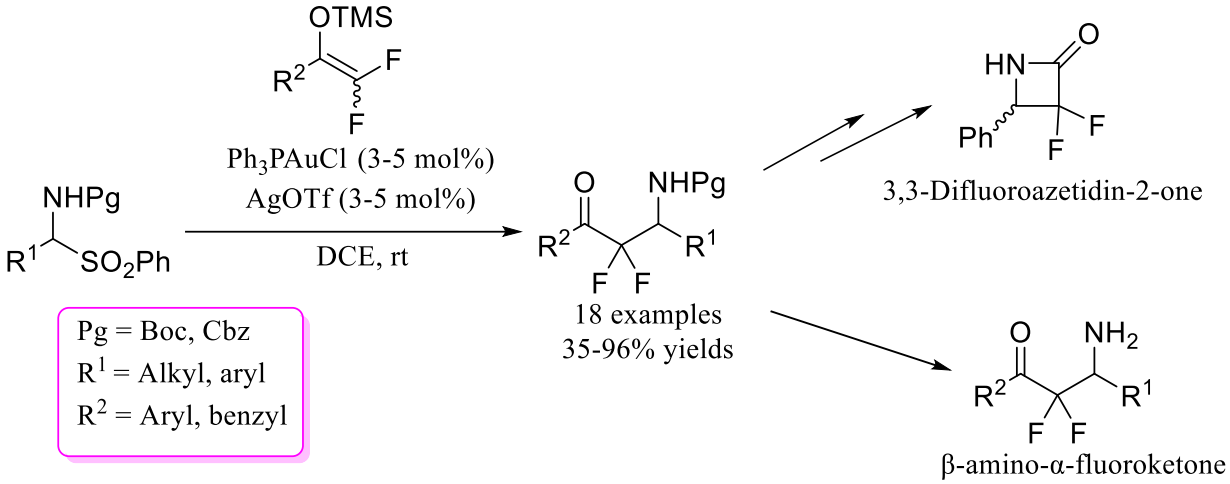
Another application of α-amido sulphones involved the reaction with cyanide ion to afford the α-amidonitriles (Scheme 46)[163–167]. Das et al. reported the application of α-amido sulphones (derived from aromatic and aliphatic aldehydes) in a Strecker reaction. This reaction employed trimethylsilyl cyanide (TMSCN) and indium (III) chloride catalyst under mild reaction conditions[166]. The resulting protected α-aminonitriles were obtained with substantial yields ranging from 79% to 95% (Scheme 46). Notably, this protocol addressed the challenges associated with previously established approaches[165,168,169], including prolonged reaction times, the requirement of costly reagents, and harsh reaction conditions.



Scheme 46*. Synthesis of α-aminonitriles via the Strecker reaction of α-amido sulphones with TMSCN using $InCl_3$ catalyst.*

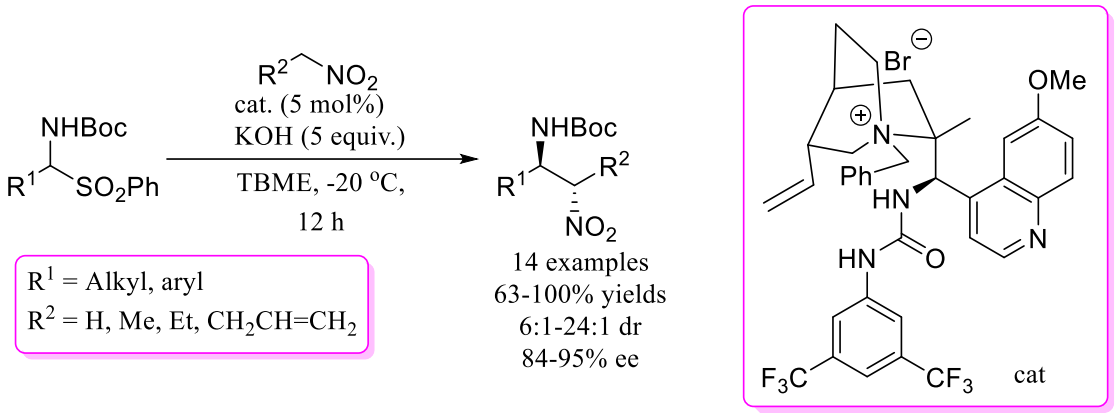
Further utility of sulphones is in the reaction with enolates derived from simple carbonyl derivatives (Scheme 47)[170–172]. By employing a catalytic amount of $Ph_3PAuOTf$ and AgOTf, the Mukaiyama-Mannich reaction was performed on aliphatic and aromatic α-amido sulphones together with fluorinated silyl enol ethers. This reaction gave the desired β-amino α-fluorinated ketones in moderate to high yields (35-96%) (Scheme 47). The products obtained serve as

valuable intermediates in the preparation of 3,3-difluoroazetidin-2-ones or β-amino-α-fluoroketone (Scheme 47)[173].



Scheme 47. *The synthesis of β-amino α-fluorinated ketone via Mukaiyama-Mannich of α-amido sulphones fluorinated silyl enol ethers. DCE- 1,2-dichloroethane*

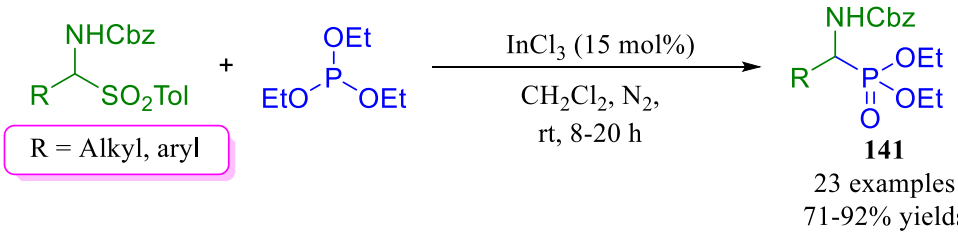
Finally, α-amido sulphones can react with nitronate anions, resulting in the formation of 2-nitroamine derivatives (Scheme 48)[174–176]. Dixon's group reported on the nitro-Mannich reaction, which involved amido sulphones derived from aromatic, heteroaromatic, and aliphatic aldehydes. In this reaction, *in-situ* generated imines were employed in the presence of a cinchona-derived dual functional H-donor phase transfer catalyst and KOH. The reactions resulted in the formation of products with moderate to quantitative yields (64-100%), accompanied by high diastereoselectivity (*dr* up to 24:1) and enantioselectivity (84-95% *ee*) (Scheme 48)[175]. This approach effectively tackled two common issues encountered in previous protocols. Firstly, it overcame the problem of low reactivity often observed when employing dual-functional Brønsted bases derived from cinchona alkaloids[177]. Secondly, it overcame the problem of significant loss of enantiofacial selectivity typically associated with asymmetric phase transfer (APT) catalysts[178]. The success of this method can be attributed to the distinctive structure of the newly developed dual-functional H-donor phase transfer catalyst, allowing for a smooth nitro-Mannich reaction with high reactivity and stereoselectivity[175].



Scheme 48. *Utility of α-amido sulphones in the nitro-Mannich reaction with nitronate anion using dual-functional H-donor phase transfer catalyst. TBME: tert-butyl methyl ether*

Despite the versatile applications of α-amido sulphones as substrates in the synthesis of a broad spectrum of structurally diverse compounds, it is surprising to observe the limited attention given in the existing literature to their use as imine precursors for synthesizing α-substituted aminophosphonates and their corresponding aminophosphonic acids. These compounds, serving as analogues of natural amino acids, constitute a significant class of molecules known for their remarkable biological activity[10,12,13,22,179], including their potential as enzyme inhibitors[29,31], drug candidates for antibiotics[39,180,181], antibacterial and antifungal agents[182], and other intriguing properties[19] (*as mentioned in the introductory part of this thesis*)

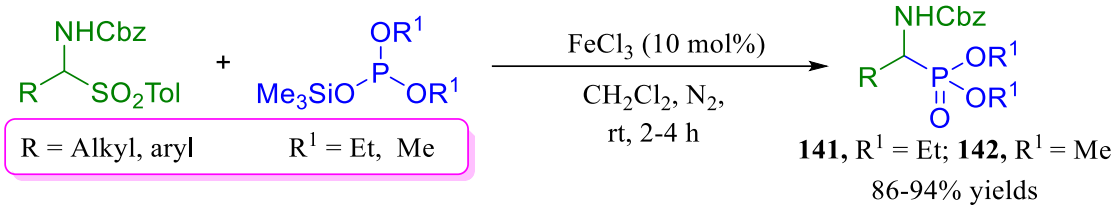
To the best of my knowledge, only three articles have been published thus far regarding the utilization of α-amido sulphones in the synthesis of α-substituted aminophosphonates. The first article, authored by Das et al., detailed their investigation of the reaction between α-amido sulphones and triethyl phosphite, catalyzed by indium (III) chloride, at room temperature. This reaction resulted in the formation of the corresponding protected α-aminophosphonates **141** with high yields ranging from 71% to 92% (Scheme 49)[167].



Scheme 49. *Preparation of α-aminophosphonates **141** from α-amido sulphones catalyzed by indium (III) chloride.*

Other Lewis acids, including $CeCl_3.7H_2O$, $ZrCl_4$, VCl_3, and $CuBr_2$, were utilized in the reaction system to obtain the product, albeit with low yields ranging from 10% to 45%. Testing the reaction with various *H*-phosphonates such as dimethyl-, diethyl-, and diphenyl *H*-

phosphonates gave just a trace of the product, whereas triethyl phosphite and triphenyl phosphite gave the product with acceptable yields. Subsequently, the same research group explored the use of dialkyl trimethyl silyl phosphites in reaction with α-amido sulphones in the presence of inexpensive, easily accessible, and highly reactive $FeCl_3$ catalyst, resulting in the formation of the α-aminophosphonates **141, 142** with acceptable yields (86-94%) (Scheme 50)[183]. Other catalysts, including $ZnCl_2$, $ZrCl_2$, $ZrCl_4$, CuCl, and $NiCl_2.6H_2O$, as well as $InCl_3$, demonstrated low reactivity in the reaction system. Furthermore, employing alternative phosphorus nucleophiles such as diethyl *H*-phosphonate and triethyl phosphite resulted in lower yields and longer reaction times when compared to using diethyl trimethyl silyl phosphite as the nucleophilic agent in the reaction.



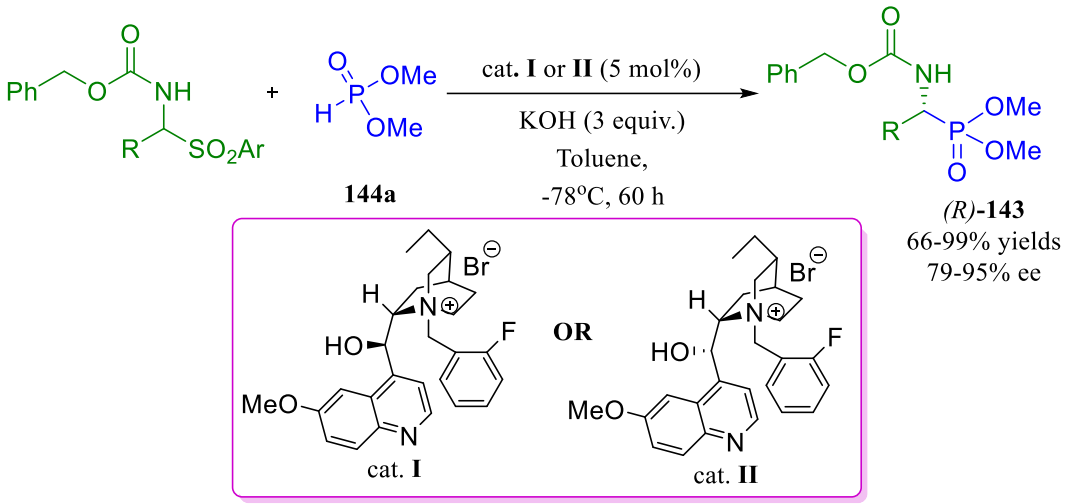
Scheme 50. *Preparation of α-aminophosphonates **141** and **142** from the reaction of α-amido sulphones with dialkyl trimethyl silyl phosphites catalyzed by iron (III) chloride.*

Both reactions (Schemes 49 and 50) follow a pathway involving the formation of an *N*-acyliuminium ion intermediate, leading to the preparation of the desired products as racemic mixtures. However, these protocols necessitate the utilization of a metallic Lewis acid catalyst and phosphorus nucleophiles that can be malodorous or not easily accessible. Furthermore, the reactions must be conducted under an inert atmosphere in dry conditions, employing a chlorinated solvent, and the purification of the final products entails a laborious process of column chromatography.

In the third publication, the authors present an exclusive method known to date for the asymmetric synthesis of enantiomerically α-aminophosphonic acid derivatives, utilizing α-amido sulphones. This procedure relies on activating the amido sulphones in the presence of a chiral quaternary ammonium salt catalyst under basic and phase-transfer catalysis conditions. This activation leads to the generation of an *in-situ N*-acylimine, which undergoes a subsequent reaction with dimethyl *H*-phosphonate **144a** to produce the desired optically active α-aminophosphonates with (*R*) configuration at the newly formed stereogenic carbon and with fairly good enantioselectivity (Table 2)[184]. To drive the reaction to completion, a higher excess of *H*-phosphonate was necessary when employing the Cbz group in the sulphone (3 equiv of *H*-phosphonate), as opposed to the Boc group (1.5 equiv of *H*-phosphonate). The authors

demonstrated a limited diversification of the substrate's scope, particularly for sulphones with aromatic substituents. Furthermore, a decrease in enantioselectivity was observed when utilizing the catalyst with the opposite configuration (cat **II**) in the reaction system, implying that the protocol is only effective for generating (*R*) configuration at the α-carbon attached to the phosphorus atom.

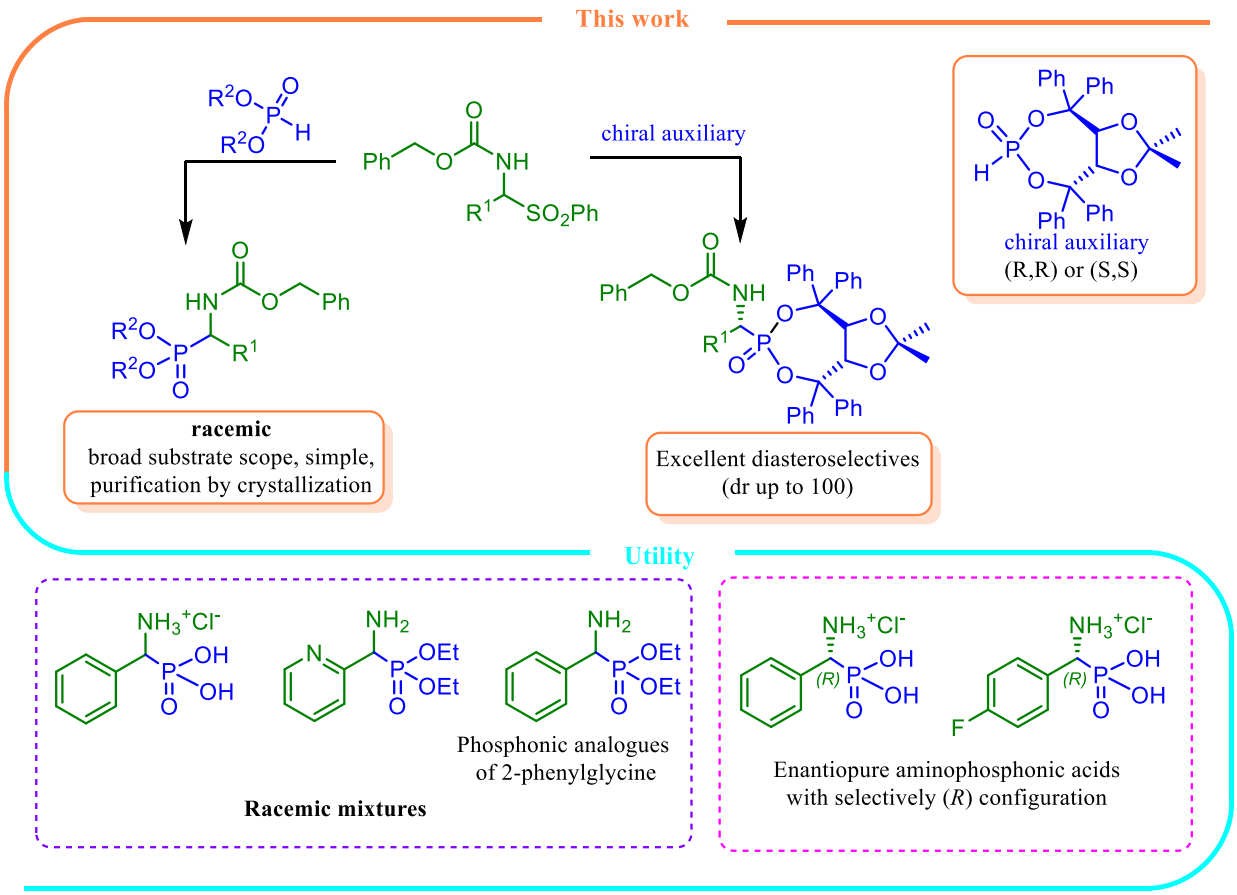
Table 2. Asymmetric synthesis α-aminophosphonic acid derivatives from α-amido sulphones using phase-transfer catalysis (PTC).



Entry	R	Ar	Pg	Product	Yield[a] (%)	ee[b] (%)
1	$Ph(CH_2)_2$	*p*-Tol	Boc	**143a**	94[c] (88)	88[c] (34)
2	$Ph(CH_2)_2$	*p*-Tol	Cbz	**143b**	95	84
3	*c*-C_6H_{11}	*p*-Tol	Boc	**143c**	94	82[d]
4	*c*-C_6H_{11}	Ph	Cbz	**143d**	93 (99)	89 (78)
5	$CH_3(CH_2)_5$	Ph	Boc	**143e**	84	87[d]
6	$CH_3(CH_2)_4$	Ph	Cbz	**143f**	97 (94)	95 (84)
7	CH_3	Ph	Cbz	**143g**	76	80

*[a]Isolated yield. [b]Determined by HPLC. [c]Larger reaction scale (1 mmol). [d]ee determined after the removal of the Boc protecting group. Results in parenthesis are for the opposite enantiomer of the catalyst (cat **II**).*

Considering the immense importance of α-aminophosphonates and their derivatives, research is still ongoing to develop novel methodologies for their preparation. During my Ph.D., I have developed a straightforward and efficient protocol that utilizes a stable and versatile intermediate, specifically α-amido sulphones, for the preparation α-aminophosphonates both as racemic mixtures and in an asymmetric fashion with excellent diastereoselectivity (Scheme 51). This achievement is attained through a one-pot approach that involves the *in-situ* generation of *N*-acylimines in the presence of a simple inorganic base, followed by their subsequent nucleophilic reaction with readily available chiral phosphorus nucleophiles serving as chiral auxiliary (Scheme 51).



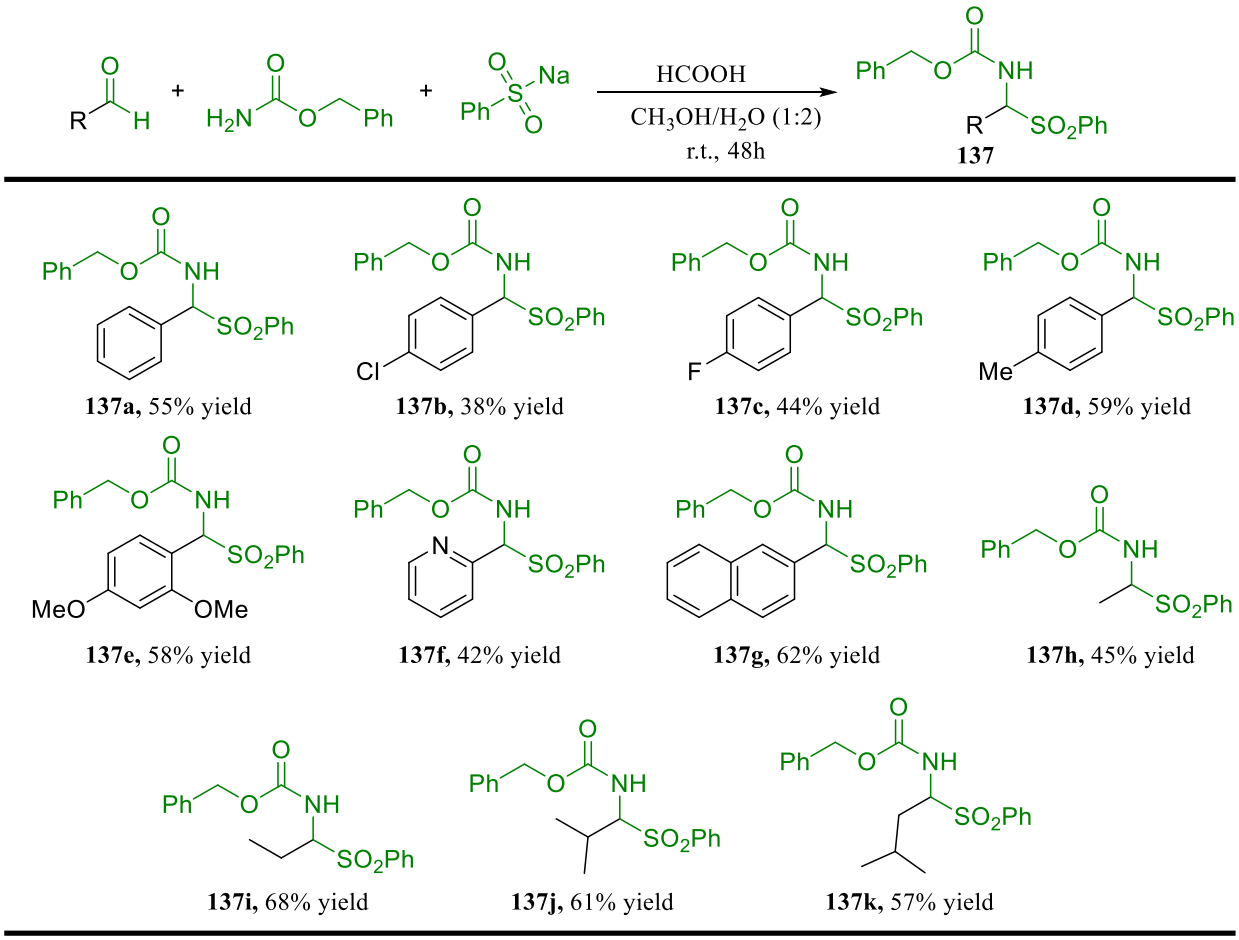
Scheme 51. *Utility of α-amido sulphones in the synthesis of α-substituted aminophosphonates.*

2.0 Results and Discussion

2.1. Synthesis of starting α-amido sulphones

Using a literature protocol[185], under mild reaction conditions and with vigorous stirring for 48 hours, a convenient one-pot, three-component coupling of aldehydes, benzyl carbamate, and benzenesulphinic acid sodium salt, promoted by formic acid in a mixture of CH_3OH and H_2O (1:2 ratio), resulted in the formation of the desired α-amido sulphones **137**. The subsequent washing of the obtained products with H_2O and diethyl ether afforded the pure products as a white solid that can be stored for a long time without any precautions, and with isolated yields ranging from 38% to 68% (Scheme 52). I have chosen to utilize this protocol due to its simplicity and the readily available starting materials and reagents. It is worth mentioning that the choice of benzyl carbamate as one of the starting materials in the synthesis of the sulphones was deliberate, as it can be easily removed through hydrogenation under neutral conditions while leaving the phosphonate moiety intact. This process allows the resulting free amine to be

utilized, for example in subsequent attachment to the peptide fragment or further structural modifications if necessary.



Scheme 52. *Synthesis of α-amido sulphones **137**, yields reported for isolated products.*

^{1}H, ^{13}C NMR, and mass spectroscopic analyses were carried out on each pure isolated sulphone to determine its structure. Figure 11 shows the NMR spectra of the α-amido sulphone **137b** as a representative example.

2.2. Optimizations of the reaction of α-amido sulphones with non-chiral *H*-phosphonates

For optimizing the hydrophosphonylation reaction system under basic conditions, α-amido sulphone **137a** and diethyl *H*-phosphonate **144b** were selected as the model substrates (Table 3). During the initial stage of optimizing the reaction, I swiftly discovered a significant challenge: the resulting *N*-acylimine **145a** was highly unstable upon isolation from the reaction mixture, leading to its decomposition back to the original benzaldehyde.

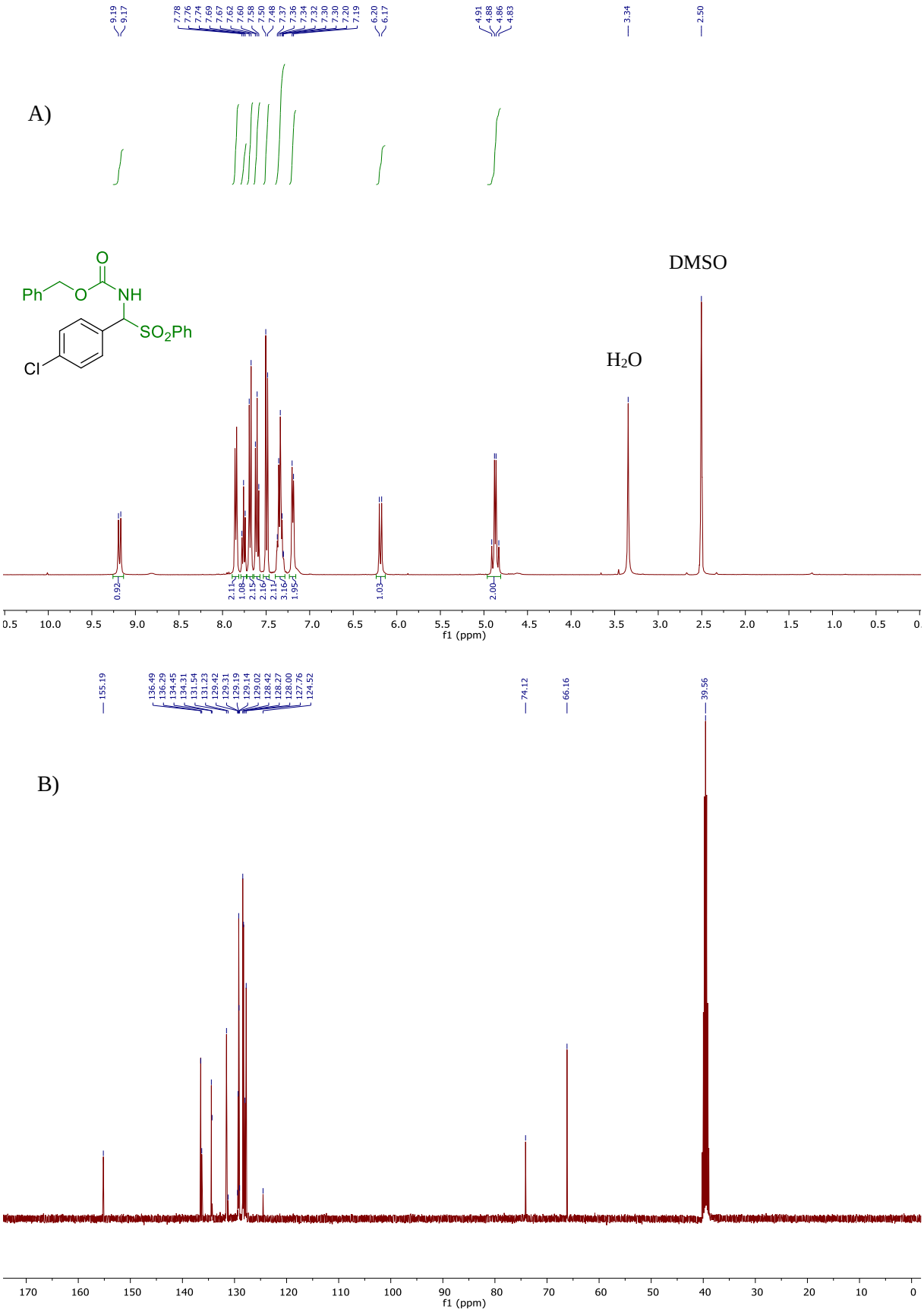
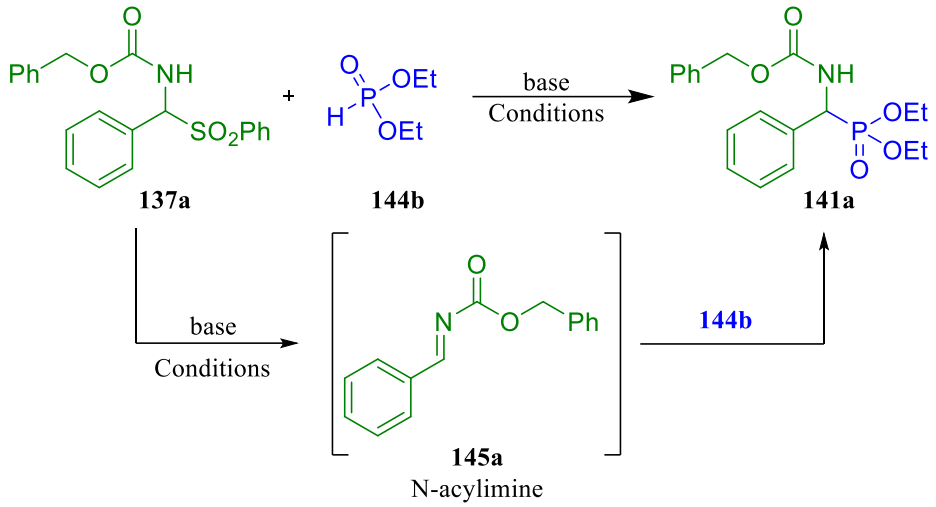


Figure 11. *α-Amido sulphone* ***137b*** *spectra registered using Jeol 400yh apparatus. A)* ^{1}H *NMR (400 MHz, DMSO-*d_6*). B)* ^{13}C *NMR (101 MHz, DMSO-*d_6*).*

To overcome this issue, it became evident that strict adherence to anhydrous conditions and an inert atmosphere of argon were crucial in preventing the undesired decomposition and ensuring the stability of *N*-acylimine **145a**.

As my focus was on developing a straightforward and reliable procedure, I decided to generate the imine in situ. As a result, all the reactions were carried out in one pot fashion by reacting the α-amido sulphone **137a**, diethyl *H*-phosphonate **144b**, suitable base and solvent under various conditions. This approach enhanced the simplicity and robustness of the protocol by eliminating the need for a separate step in isolating the *N*-acylimine **145a** (Table 3). In the control experiment, no reactivity was observed when the reaction was performed in the absence of a base (Table 3, entry 1). However, the presence of inorganic solid bases led to superior results (Table 3, entries 2, 3, 4, 5) compared to the utilization of organic (liquid) bases (entries 6, 7, 8, 9). This finding highlights the crucial significance of the base in the reaction system, stemming from its dual functionality. Firstly, it plays an essential role in the *in-situ* generation of *N*-acylimine, which serves as a crucial intermediate for the successful progression of the reaction. Secondly, the base acts as an activator, enhancing the nucleophilicity of the H-P species and enabling it to undergo a nucleophilic attack on the *N*-acylimine generated *in situ*. It is also noteworthy that the choice of the base significantly influences the efficiency of the reaction, with inorganic solid bases, particularly K_2CO_3, yielding the best outcome with 95% isolated yield after simple crystallization from diethyl ether (Table 2, entry 3). Additional experiments were carried out to investigate the influence of solvents on the system. The highest reactivity was observed in THF (entry 3). However, good reactivity was also observed in acetonitrile, 2-methyl-THF, and 1,4-dioxane, although with longer reaction times compared to THF (entries 10, 11, and 12). These solvents are known for their environmentally friendly nature and are classified as green solvents. Finally, the reactivity of the reaction was investigated by varying the K_2CO_3 amount. Increasing the amount of K_2CO_3 to 6 equiv. did not improve the conversion (entry 16). Conversely, a significant decrease in conversion was observed when 2 equiv. of K_2CO_3 was used (Table 3, entry 15).

Table 3. Hydrophoshonylation of α-amido sulphone **137a** with non-chiral *H*-phosphonate **144b**- optimizing the reaction conditions[a].



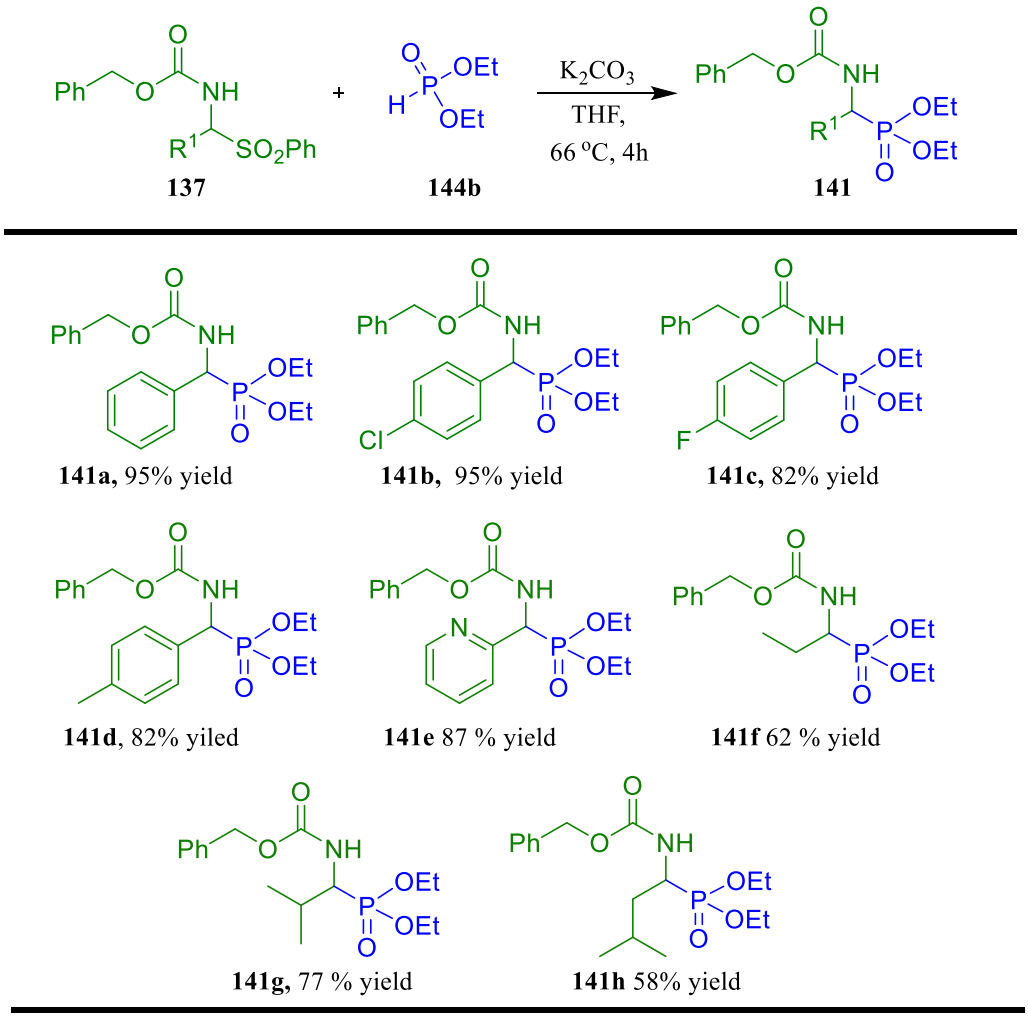
Entry	Base	Solvent	Temp (°C)	Time (h)	Conv. (%)[b]
1	-	THF	rt	24	0
2	K_2CO_3 (4 eq.)	THF	rt	24	30
3	K_2CO_3 (4 eq.)	THF	66	4	99 (95)[c]
4	Cs_2CO_3 (4 eq.)	THF	66	4	74
5	NaOH (4 eq.)	THF	66	4	81
6	Pyridine (4 eq.)	THF	66	4	0
7	Et_3N (4 eq.)	THF	66	4	0
8	Diisopropylamine (4 eq.)	THF	66	4	5
9	L-proline (4 eq.)	THF	66	4	0
10	K_2CO_3 (4 eq.)	2-methyl THF	80	4	66 (89)[d]
11	K_2CO_3 (4 eq.)	Acetonitrile	82	4	50 (94)[d]
12	K_2CO_3 (4 eq.)	1,4-Dioxane	101	4	54 (80)[d]
13	K_2CO_3 (4 eq.)	MeOH	64	4	0
14	K_2CO_3 (4 eq.)	EtOAc	77	4	42 (56)[d]
15	K_2CO_3 (2 eq.)	THF	66	4	60
16	K_2CO_3 (6 eq.)	THF	66	4	97

[a]*General reaction conditions (unless otherwise stated): α-amido sulphone **137a** (2.4 mmol), H-phosphonate **144b** (2.4 mmol), base (9.6 mmol, 4 equiv).* [b]*Conversion based on the ^{31}P NMR spectra of the crude reaction mixture.* [c]*Isolated yield.* [d]*Reaction time 8h.*

2.3. The scope of the reaction of α-amido sulphones with non-chiral *H*-phosphonates

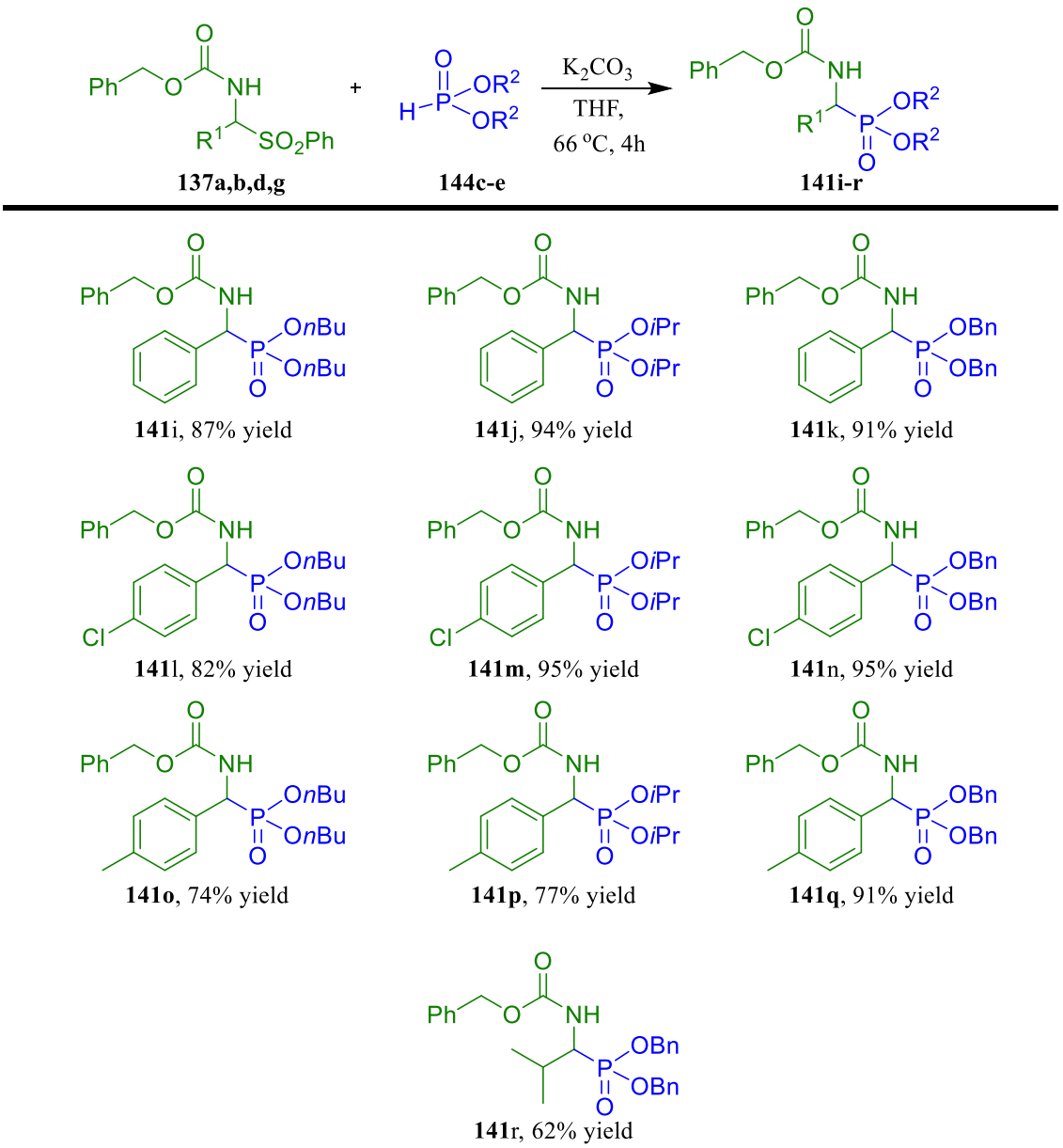
After successfully obtaining the optimized reaction conditions, I conducted further studies to explore the applicability of the methodology for the hydrophosphonylation of α-amido sulphones derived from different aldehydes with different non-chiral *H*-phosphonates **144**. The reaction proceeded smoothly, yielding various α-substituted aminophosphonates in good to excellent isolated yields of 58-95% (Scheme 53 and 54). It was gratifying to observe

that the reaction demonstrated excellent compatibility with a wide variety of substituted benzaldehyde-derived α-amido sulphones including compounds without substituent **141a**, electron-withdrawing groups **141b, c** as well as those with electron-donating groups **141d**. Furthermore, the methodology proved effective even with a heteroaromatic 2-pyridine-derived α-amido sulphone yielding the desired product **141e** (Scheme 53).



Scheme 53*. The scope of the hydrophoshonylation of α-amido sulphones derived from different aldehydes with diethyl phosphonate* ***144b.*** *Yields are given for the isolated products.*

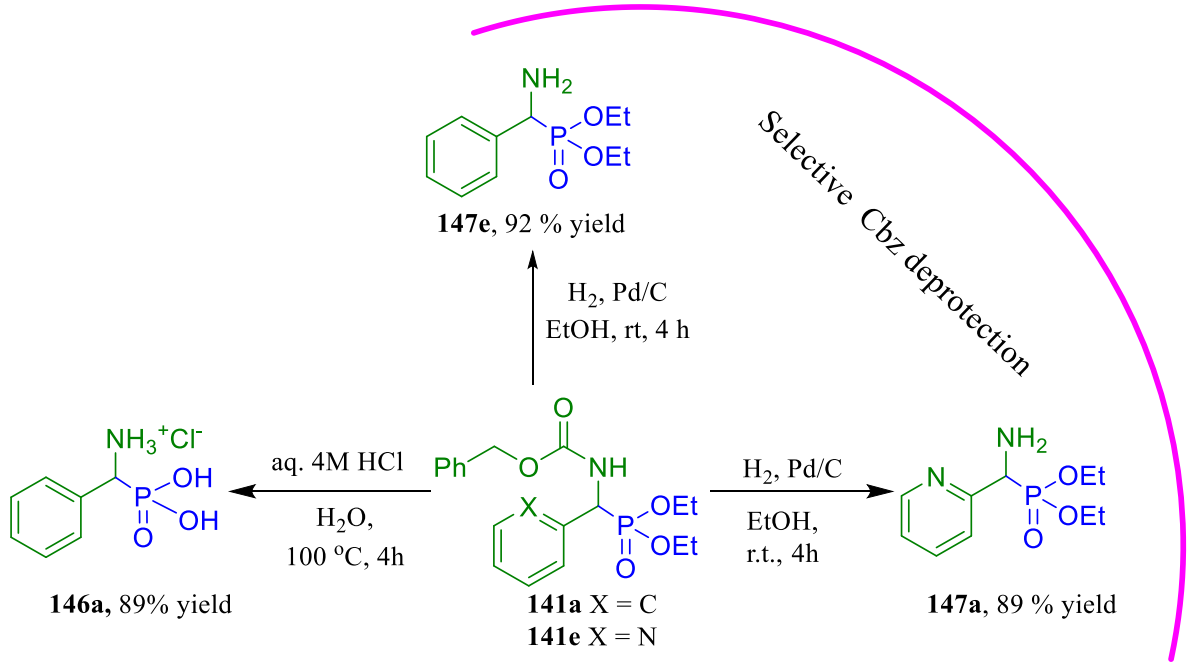
In all cases, the desired aromatic α-amino phosphonates were obtained in pure form as non-hygroscopic, highly stable white solids in high isolated yields (82–95%) after a simple crystallization process using diethyl ether. The synthesis of the aliphatic α-aminophosphonates **141f-h**, derived from the corresponding aliphatic α-amido-sulphones, also proceeded smoothly. However, the yields of the resulting products were slightly lower (58-77%) than those obtained with the aromatic derivatives. The aliphatic products **141f-h** were isolated as oily compounds by a simple purification method involving filtration through a pal of silica gel (Scheme 53).



Scheme 54*. The scope of the hydrophoshonylation of α-amido sulphones with various H- phosphonates* ***144c-e.*** *Yields are given for the isolated products.*

Similarly, by substituting diethyl *H*-phosphonate **144b** with various structurally diverse phosphonates, such as *n*-butyl *H*-phosphonate **144c**, *i*-propyl *H*-phosphonate **144d**, and the bulkier benzyl *H*-phosphonate **144e**, in reaction with different aromatic α-amido sulphones (**137a** without substituent, **137b** with an electron withdrawing group, **137d** with an electron donating group) and aliphatic α-amido sulphones **137j**, the system remained compatible. This compatibility led to the formation of the desired products **141i-r**, with yields ranging from 62% to 95% (Scheme 54).

To showcase the synthetic application of the produced α-aminophosphonates, a conventional acid hydrolysis was used to facilitate the simultaneous removal of both the nitrogen-protecting and the phosphonate ester groups from α-aminophosphonates **141a** to give racemic α-aminophosphonic acid salt **146a** with 89% isolated yield (Scheme 53). On the other hand, the presence of benzyl carbamate in the synthesized α-aminophosphonates **141a** and **141e** allows for the selective deprotection of the nitrogen atom when subjected to Pd/C and hydrogen gas in ethanol to give the deprotected α-aminophosphonate esters **147a** (89% isolated yield), a phosphonic analogue of 2-phenylglycine possessing a free amino group that is well-suited for further transformation, e.g in subsequent integration into a peptide sequence, and **147e** with 91% isolated yield (Scheme 55).



Scheme 55. *Synthetic utility of the obtained α-aminophosphonates.*

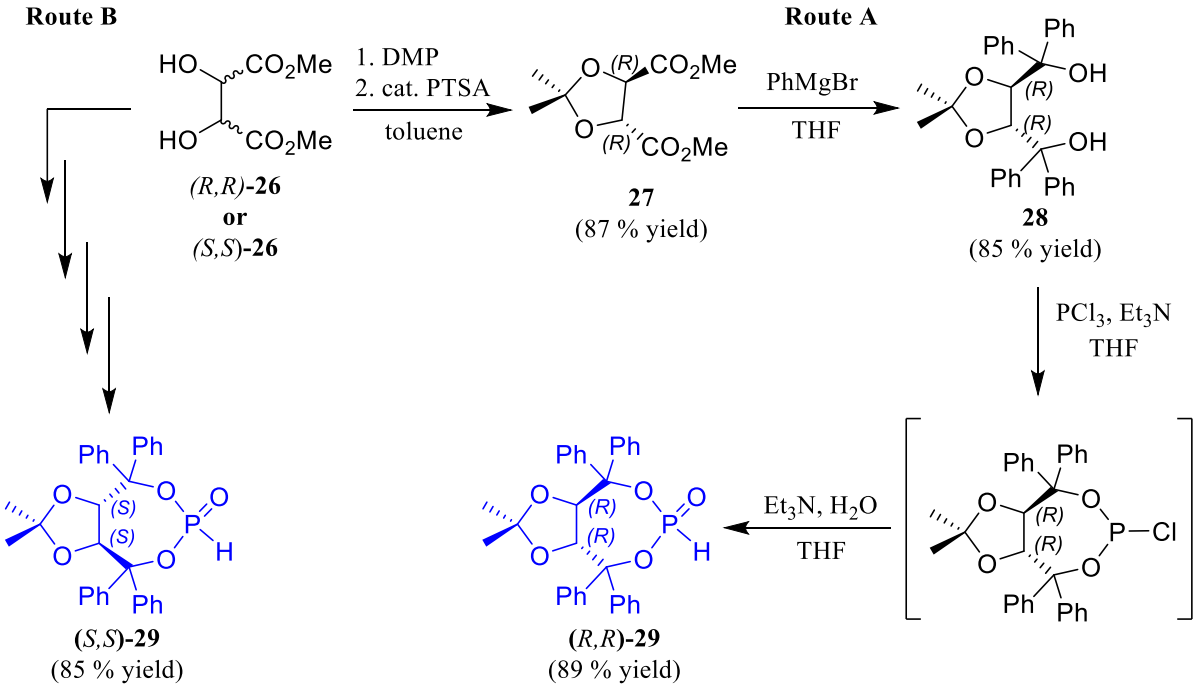
2.4. Reaction of α-amido sulphones with chiral TADDOL-derived *H*-phosphonate

2.4.1. Preparation of the chiral TADDOL derived *H*-phosphonate

Subsequently, my attention turned towards conducting the asymmetric hydrophosphonylation reaction of α-amido sulphones. To achieve this, I utilized the model sulphone **137a** in reaction with TADDOL-derived *H*-phosphonate **29** as a chiral auxiliary and phosphorus nucleophile The objective was to enhance the formation of the desired products in a diastereoselective fashion by capitalizing on the presence of the chiral phosphorus nucleophile (*R, R*)-**29**.

Firstly, I have mastered the preparation of (*R,R*)-**29** based on literature data starting from the easily accessible and cost-effective natural chiral source, tartaric acid dimethyl ester (*R,R*)-**26**,

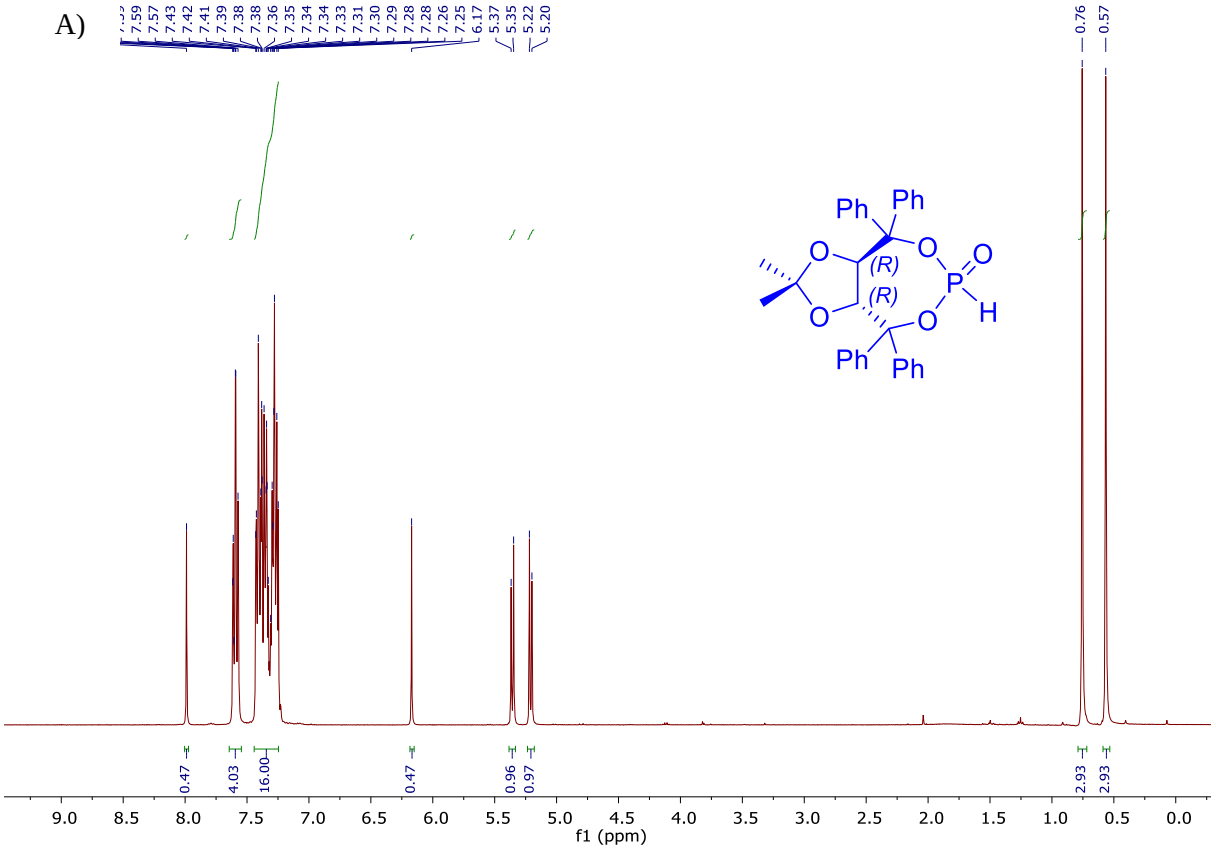
the synthesis of the TADDOL-derived *H*-phosphonate **29** involved a four-step transformation. In the first step, the two hydroxy groups in the dimethyl tartarate **26** were protected (in the form of isopropylidene ketal) with the use of 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to give dimethyl (2*R*,3*R*)-2-3-O-isopropylidene tartarate **27** in 87% yield. Subsequently, **27** underwent a reaction with phenyl magnesium bromide in THF, leading to the formation of (*R*,*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxalane **28** (TADDOL) which was crystallized from ethanol to give an isolated yield 85% yield (Scheme 56, route A)[186,187].



***Scheme 56**. Preparation of TADDOL-derived H-phosphonate **29** from tartaric acid dimethyl ester. DMP = 2,2-dimethoxypropane; PTSA = p-toluenesulfonic acid.*

Upon reacting **28** with PCl_3 in the presence of Et_3N, a corresponding chloride intermediate was generated. This intermediate subsequently underwent hydrolysis, leading to the synthesis of the TADDOL-derived *H*-phosphonate (*R*,*R*)-**29** which was purified through column chromatography (with the eluent mixture of hexane and ethyl acetate in the ratio of 5:1 to 3:1) to give an isolated yield of 89% (Scheme 56)[84,85]. This compound could be conveniently prepared even on a multigram scale, and it exists as an air- and moisture-stable white solid, requiring no special precautions for long-term storage. Similarly, utilizing the opposite enantiomer of tartaric acid dimethyl ester, namely (*S*,*S*)-**26**, resulted in the synthesis of the TADDOL-derived *H*-phosphonate **29** with (*S*,*S*) configuration with an 85% isolated yield (for the final synthetic stage). Figure 12 shows the ^{1}H, ^{31}P, ^{13}C NMR spectra recorded and used for characterization of TADDOL-derived *H*-phosphonate **29** with (*R*,*R*) configuration.

A)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7.43
7.42
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7.34
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7.30
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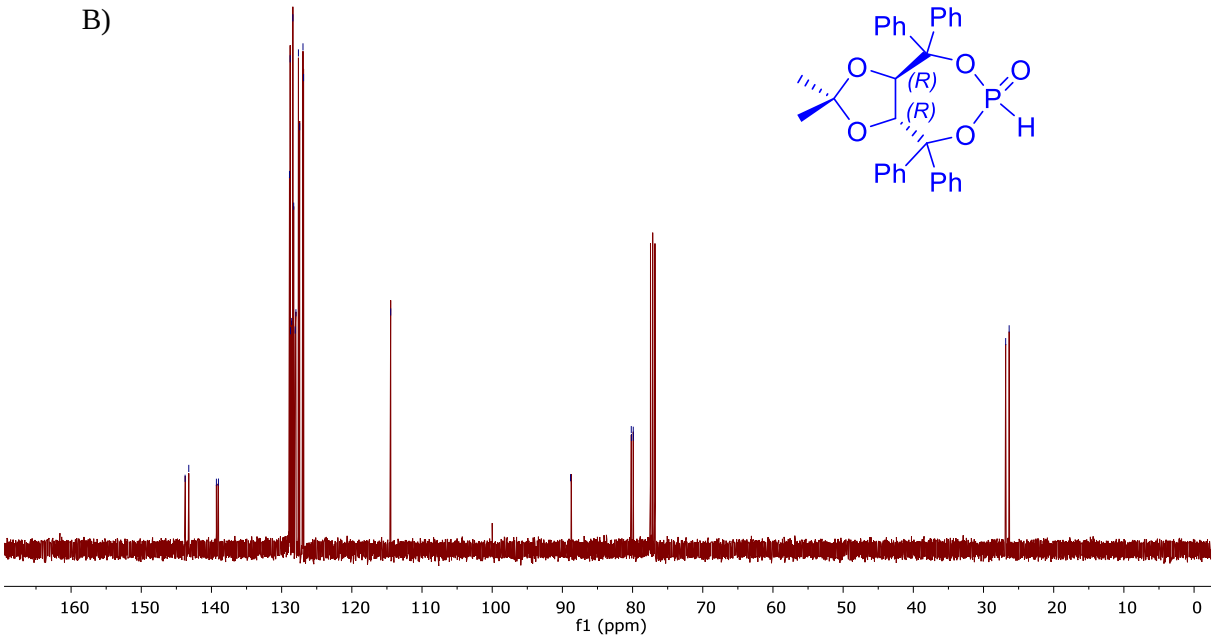
7.26
7.25
6.17
5.37
5.35
5.22
5.20
0.76
0.57
Ph
Ph
O
O
(R)
(R)
O
P
O
H
O
Ph
Ph
0.47
4.03
16.00
0.47
0.96
0.97
2.93
2.93
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


143.75
143.23
139.30
139.00
128.88
128.79
128.74
128.57
128.40
128.28
128.07
127.97
127.61
127.43
126.96
126.88
114.46
88.84
80.19
80.16
79.90
79.88
26.84
26.35

B)


Ph
Ph
O
O
(R)
(R)
O
P
O
H
O
Ph
Ph
160
150
140
130
120
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90
80
70
60
50
40
30
20
10
0
f1 (ppm)

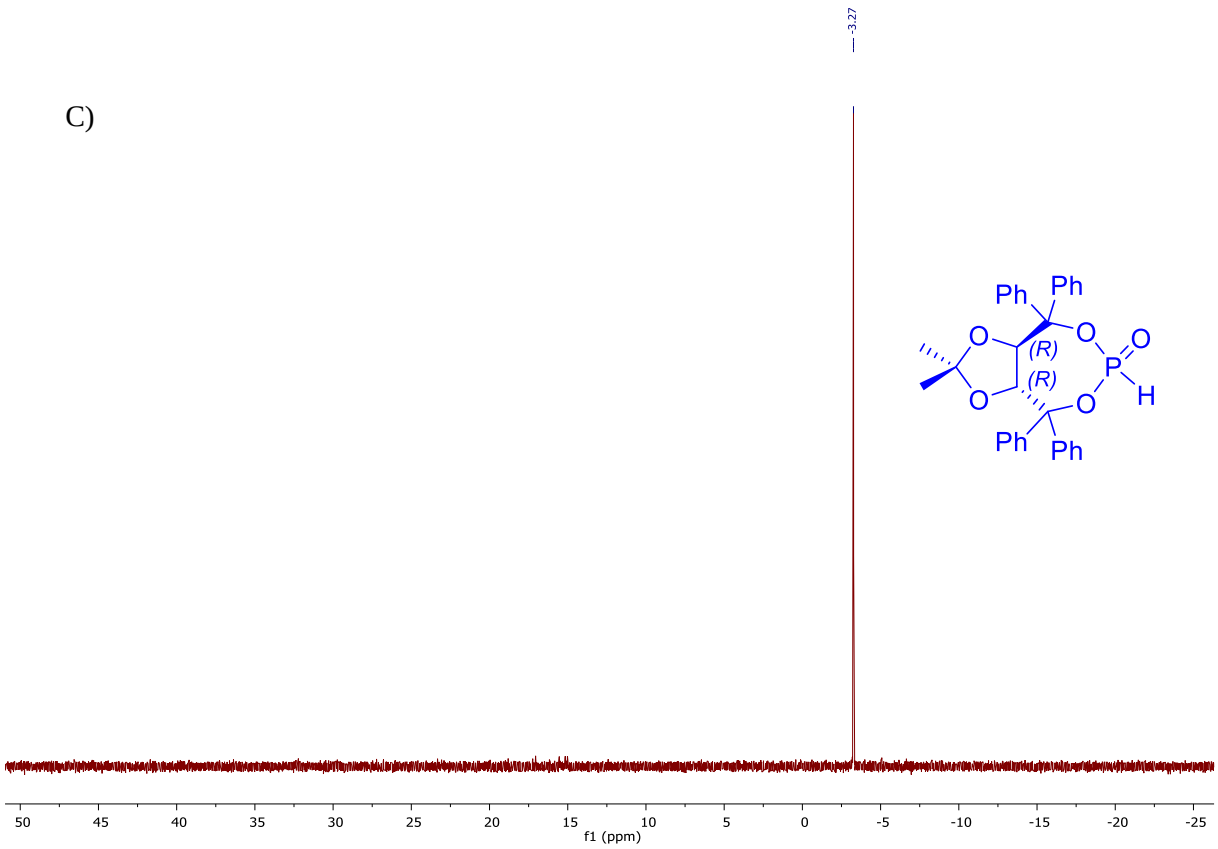


Figure 12. *TADDOL-derived H-phosphonate (R,R)-**29** spectra registerd using Jeol 400yh apparatus. A)* ^{1}H *NMR (400 MHz, $CDCl_3$), B)* ^{13}C *NMR (101 MHz, $CDCl_3$). C)* ^{31}P *NMR (162 MHz, $CDCl_3$)*

2.4.2. Optimizations of the reaction of α-amido sulphones with chiral TADDOL derived *H*-phosphonate

Under the optimized reaction conditions employed for the synthesis of racemic α-aminophosphonates **141**, I carried out the diastereoselective hydrophosphonylation addition of (*R, R*)-**29** to the model α-amido sulphone **137a** in the presence of K_2CO_3 in THF at 66 ^{o}C, which resulted in the formation of the product **148a** as a pair of diastereoisomers with 80% conversion**.** On the ^{31}P NMR spectra, the chemical shift of the signal corresponding to the starting TADDOL-derived *H*-phosphonate (*R,R*)-**29** (δ_P = -3.15 ppm, in $CDCl_3$) was significantly different from the chemical shift that corresponds to the reaction product (δ_{major} = 15.02 and δ_{minor} = 15.47 ppm, in $CDCl_3$) as shown in figure 13. This stark contrast in chemical shifts enabled me to establish the conversion of the reaction clearly. Also, as initially anticipated, two distinct signals were seen on the ^{31}P NMR spectrum of the crude reaction mixture corresponding to each diastereoisomer (Figure 13). This observation provided hope for an efficient and rapid evaluation of the diastereoselectivity of the reaction (Table 4, entry 1). Unfortunately, poor

diastereoselectivity (dr 35:65) was observed in the resulting product **148a** from Table 4, entry 1.

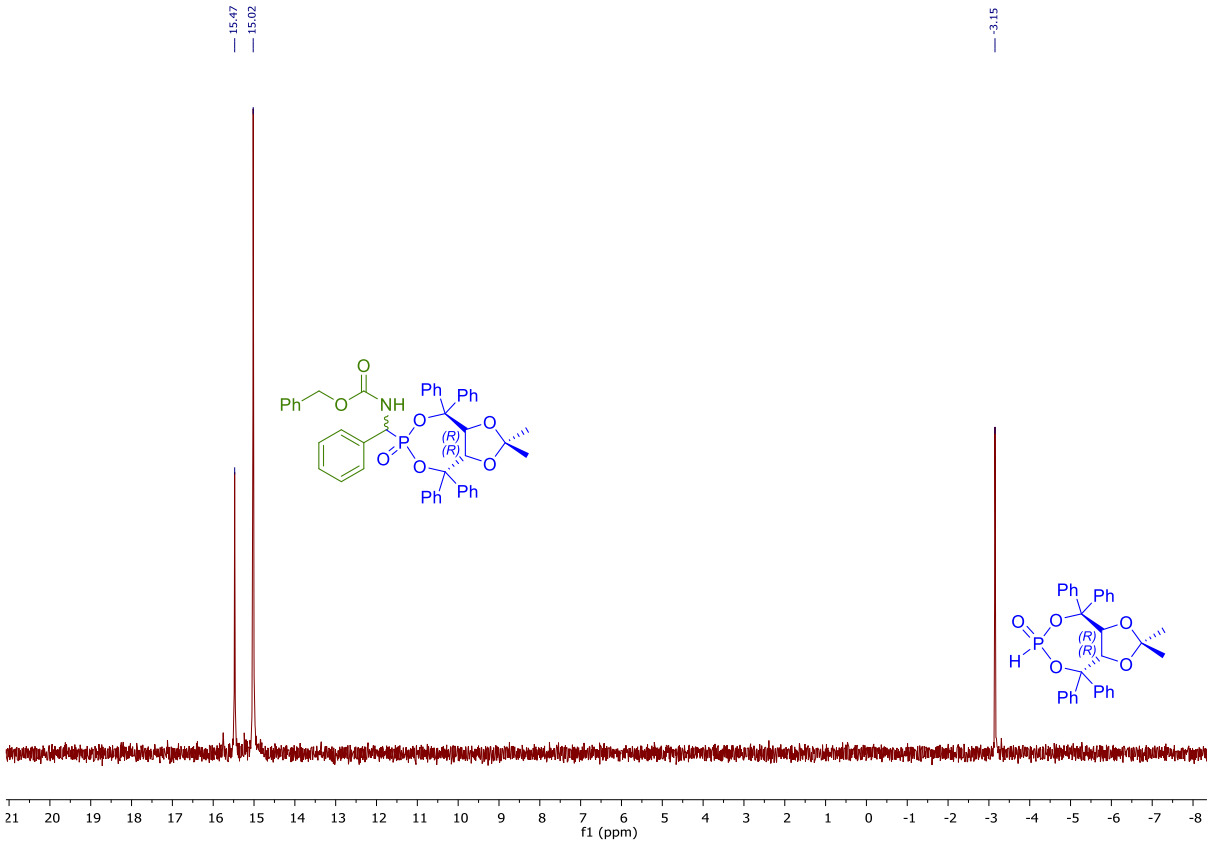


Figure 13. *^{31}P NMR (162MHz, $CDCl_3$) registered using Jeol 400yh apparatus showing the spectrum of the crude reaction mixture composed of unreacted (R,R)-**29** and the product obtained as pair of diastereoisomers from entry 1 Table 4.*

Consequently, I investigated the influence of the base on the diastereoselectivity of the reaction by testing different inorganic and organic bases under similar reaction conditions. However, these efforts once again led to disappointing results (Table 4, entries 2–6), with the best result obtained when Cs_2CO_3 was used (Table 4, entry 2). Initially, to my satisfaction, the ^{31}P NMR analysis of the reaction mixture using KOH as a base showed a single signal, suggesting the presence of either one diastereoisomer, but since the signal was rather broad, I also assumed the possibility of overlapping of two signals corresponding to the two diastereoisomers (Figure 14, A). To verify this, I performed a ^{13}C NMR analysis of the crude product, which revealed the presence of two diastereoisomers in an estimated diastereomeric ratio of approximately 30:70. The presence of two doublet signals (at a chemical shift in the region of δ_{major} = 53.85 and δ_{minor} = 53.50 ppm in $CDCl_3$ for ^{13}C NMR) was due to coupling between the α-carbon and the phosphorus atoms in the minor and major diastereoisomers. (Figure 14, B). Subsequently,

for any overlapping signals observed in the ^{31}P NMR, the diastereomeric ratios were estimated based on the ^{13}C NMR spectra.

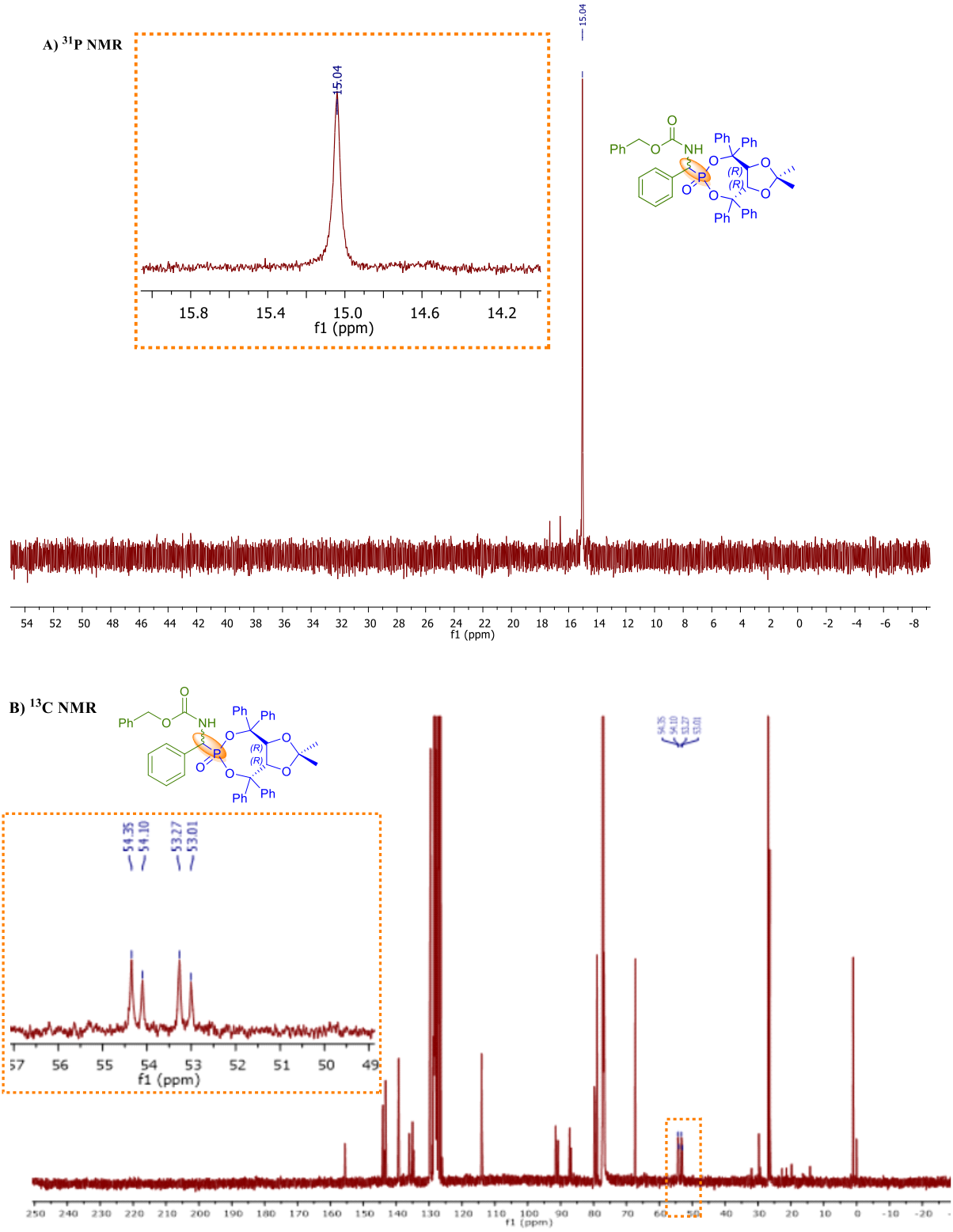
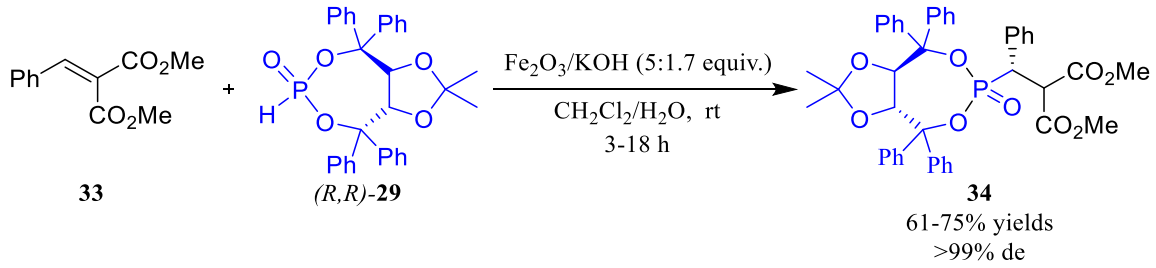


Figure 14. *Diastereomeric analysis of the crude product using ^{31}P NMR (162MHz, $CDCl_3$) and ^{13}C NMR (101MHz, $CDCl_3$) spetra registered using Jeol 400yh instrument.*

Additionally, I investigated the influence of different solvents on the diastereoselectivity of the reaction by employing Cs_2CO_3 as a base at the temperature that corresponds to the boiling point of the tested solvents. The reaction proceeded efficiently, demonstrating reasonable reactivity. However, the diastereoselectivity was found to be poor in all cases (Table 4, entries 7–9).

Next, I decided to evaluate the feasibility of performing the reaction under milder conditions. To achieve that, I got inspiration from the study conducted by Enders et al., in which they carried out the diastereoselective synthesis of β-phosphonomalonates via phospha-Michael addition of (*R, R*)-**29** to the C=C bond of unsaturated malonates using metal oxide in the presence of a solid base under heterogeneous conditions[89]. The influence of different metal oxides, including Al_2O_3, ZnO, Cu_2O, MnO_2, Fe_2O_3, and MgO, on the diastereoselectivity of the Michael addition was investigated in their study. The Fe_2O_3, in combination with KOH, emerged as the optimized solid support base utilized in the substrate's scope of the reaction. This combination afforded phosphonates with high diastereoselectivity (82-91% de of the crude products) and 61-75% yields (Scheme 57)[89].



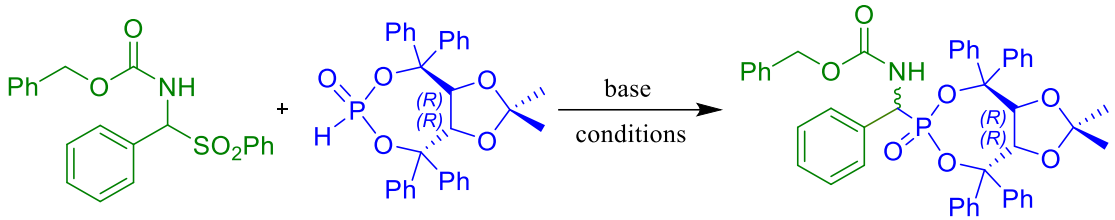
Scheme 57*. The phospha-Michael addition of (R, R)-**29** to α, β-unsaturated malonates using Fe_2O_3/KOH as a solid support base.*

The authors reported that the metal oxide played a crucial role in the success of the reaction by facilitating the activation of the P-H bond in (*R, R*)-**29** for subsequent deprotonation with a base. In my case, however, performing the hydrophosphonylation addition of (*R, R*)-**29** to the C=N bond of α-amido sulphones **137a** at room temperature in the presence of solid support, which was prepared from the combination of different metal oxides (Fe_2O_3, Al_2O_3, ZnO, or MgO) with inorganic solid bases (KOH, K_2CO_3, Cs_2CO_3, or NaOH) according to literature procedure[89], led to the formation of the desired product **148** with good conversion, but the diastereoselectivity was only moderate (Table 4, entries 10-16).

In continuation of this work, I decided to examine the influence of temperature on the diastereoselectivity of the reaction. In this approach, *N*-acylimine **145a** was first prepared in a separate flask by heating the sulphone in the presence of K_2CO_3 in THF at 66 °C (standard conditions) and then cooled under argon to -78 °C, followed by the addition of (*R, R*)-**29** and

the corresponding base. Such reactions performed with *n*-Buli or LDA did not produce the desired product **148a** (Table 4, entries 17 and 18).

Table 4. Asymmetric hydrophoshonylation of α-amido sulphone **137a** with chiral TADDOL derived *H*-phosphonate *(R,R)*-**29** – optimization of reaction conditions.[a]



137a (*R,R*)-**29** **148a**

Entry	Conditions	Diastereomeric ratio *dr* (%)[b] /Conversion [%][b]
1.	K_2CO_3 (4 equiv), 66°C, 4h, THF	35:65 [80]
2.	Cs_2CO_3 (4 equiv), 66°C, 4h, THF	33:67 [97]
3.	NaOH (4 equiv), 66°C, 4h, THF	36:64 [87][c]
4.	KOH (4 equiv), 66°C, 4h, THF	34:66 [100][c]
5.	Pyridine (4 equiv), 66°C, 4h, THF	-
6.	Et_3N (4 equiv), 66°C, 4h, THF	-
7.	Cs_2CO_3 (4 equiv), 80°C, 4h, 2-methyl THF	36:64 [89]
8.	Cs_2CO_3 (4 equiv), 110°C, 4h, toluene	65:35 [97]
9.	Cs_2CO_3 (4 equiv), 82°C, 4h, acetonitrile	45:55 [84]
10.	KOH (2.5 equiv), Fe_2O_3, r.t., 5 days, CH_2Cl_2	60:40 [80][d]
11.	KOH (2.5 equiv), Al_2O_3, r.t., 5 days, CH_2Cl_2	25:75 [89][d]
12.	KOH (2.5 equiv), ZnO, r.t., 5 days, CH_2Cl_2	30:70 [76][d]
13.	KOH (2.5 equiv), MgO, r.t., 5 days, CH_2Cl_2	35:65 [74][d]
14.	K_2CO_3 (2.5 equiv), Al_2O_3, r.t., 5 days, CH_2Cl_2	22:78 [98][d]
15	Cs_2CO_3 (2.5 equiv), Al_2O_3, r.t, 5 days, CH_2Cl_2	35:65 [79][d]
16.	NaOH (2.5 equiv), Al_2O_3, r.t., 5 days, CH_2Cl_2	40:60 [98][d]
17.	n-BuLi (1 equiv), -78°C, 12h THF	-[e]
18.	LDA (1 equiv), -78°C, 12h, THF	-[e]
19.	$ZnEt_2$ / (TMEDA) (1 equiv), -78°C, 12h, THF	100 [74][e]
20.	**KOH (3 equiv), -78°C, 4 days, THF**	**100 [95]**
21.	KOH (2 equiv), -78°C, 4 days, THF	100 [87]

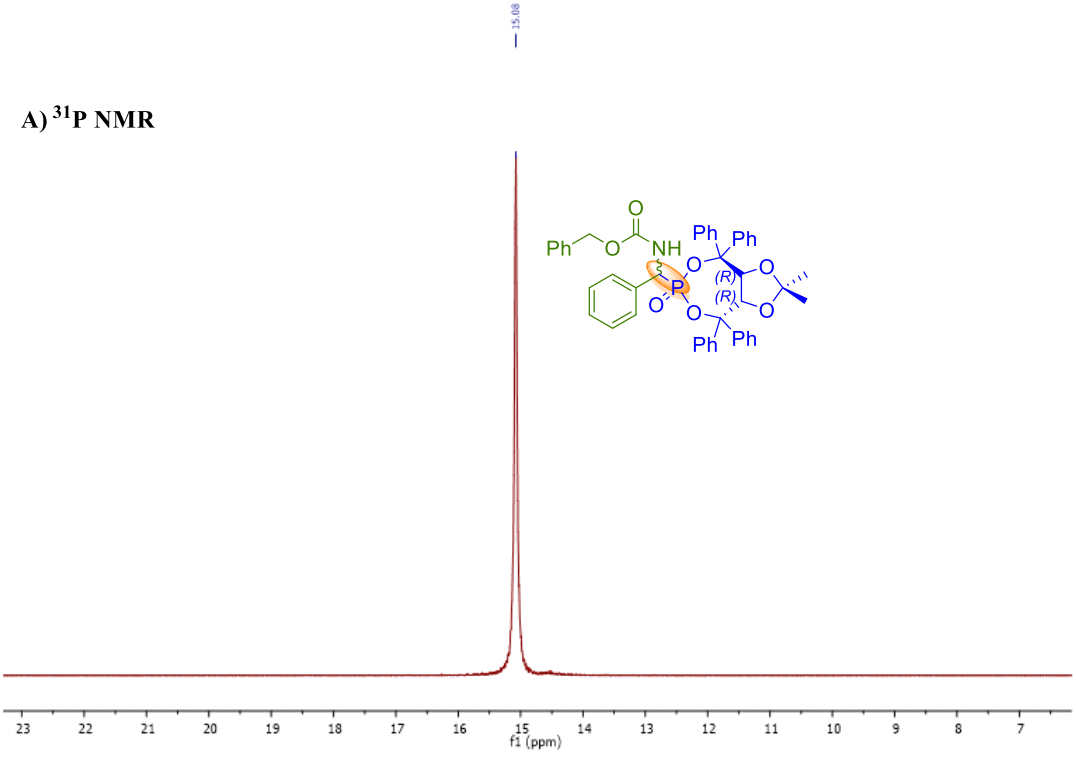
*[a]General reaction conditions (unless otherwise stated): α-amido sulphone **137a** (2.4 mmol), H-phosphonate (R,R)-**29** (2.4 mmol), base (9,6 mmol, 4 equiv). [b]Diastereoselectivity and conversion based on the ^{31}P NMR spectra of the crude reaction mixture. [c]Diastereoselectivity based on the ^{13}C NMR analysis of the crude product. – stands for No reaction. [d]For solid base (2.7 g of metal oxide containing 2.5 mmol of the base). [e]The imine was first generated by reacting **137a** with K_2CO_3 (2 equiv) at 66°C for 4h in THF and after filtration, the filtrate containing the imine was transferred to a separate flask and cooled to -78°C followed by the addition of appropriate base and (R,R)-**29**.*

However, the reaction of Et_2Zn and (*R*, *R*)-**29** resulted in an organozinc-phosphorus adduct that was highly insoluble at -78 °C, but the solubility was improved by the addition of *N*,*N*,*N*,*N*-tetramethylenediamine (TMEDA)[85,90], allowing the hydrophosphonylation reaction to proceed at such low temperatures to give the desired product **148a** as a single diastereoisomer but with a conversion of 74% (Table 4, entry 19). Inspired by this result and my effort to develop a simple protocol, I decided to perform the direct hydrophosphonylation of the α-amido sulphone **137a** with *(R,R)*-**29** employing KOH, a readily available solid inorganic base that was initially used in the synthesis of racemic α-aminophosphonates (Scheme 50 and 51).

I was extremely pleased to discover that, in this reaction, the *in-situ* generated *N*-acylimine **145a** subsequently underwent nucleophilic reaction with (*R*,*R*)-**29** to give the desired α-aminophosphonate **148a** as a single diastereoisomer and with high conversion (Table 4, entry 20). Finally, a decrease in reactivity was observed when the amount of KOH used in the reaction setup was reduced from 3 equiv. to 2 equiv. (Table 4, entry 21).

To confirm that the single signal observed in the ^{31}P NMR spectrum for the product of the reaction described in Table 4, entry 20 corresponds to a single diastereoisomer rather than arising from the overlap of two diastereoisomers, I performed a ^{13}C NMR analysis on the crude product. The resulting analysis showed the presence of only one doublet (indicating coupling between the α-carbon and phosphorus atoms), which confirms the presence of a single diastereoisomer (Figure 15).

A) ^{31}P NMR



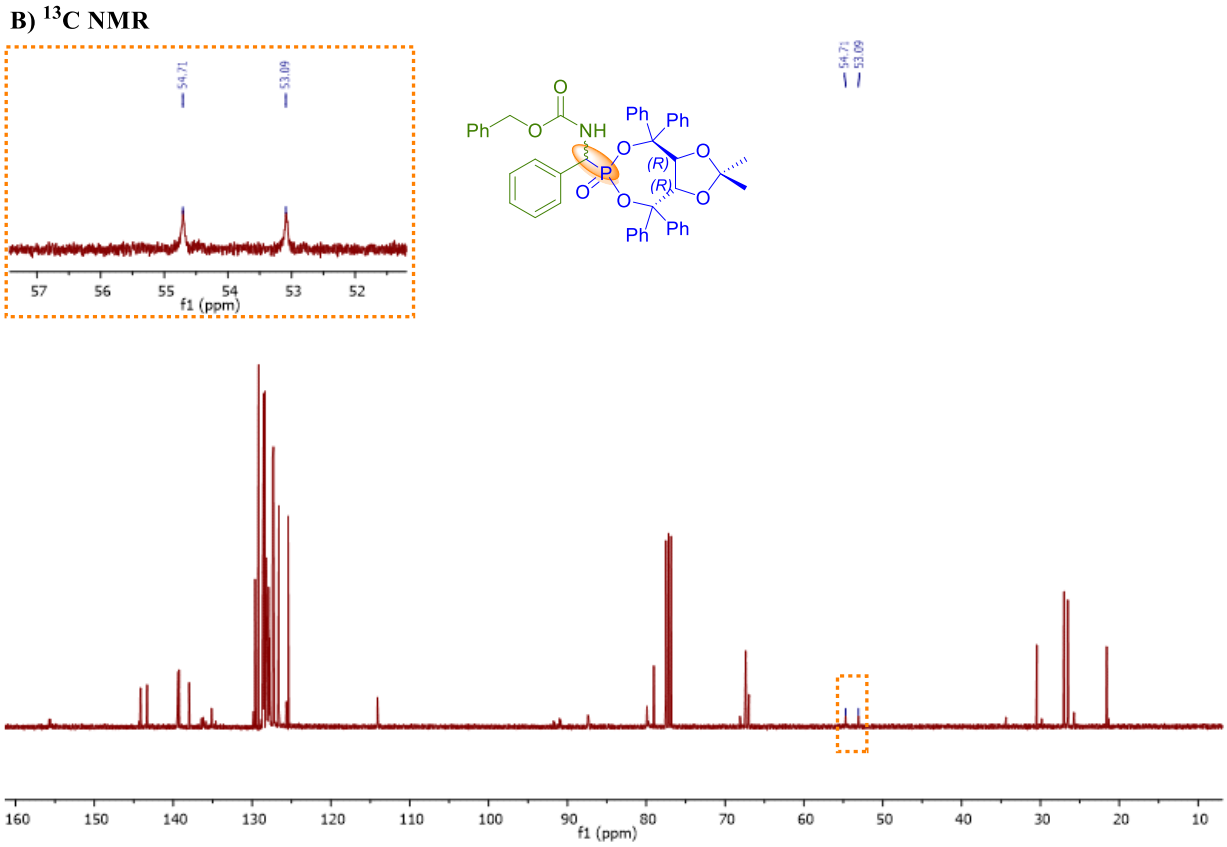
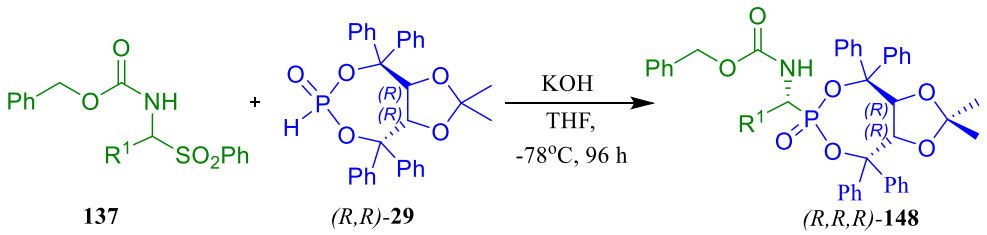


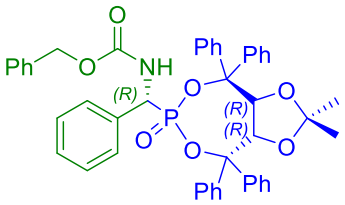
***Figure 15**. Confirmation of the presence of a single diastereoisomer in the crude product using ^{31}P NMR (162MHz, $CDCl_3$) and ^{13}C NMR (101MHz, $CDCl_3$) Analysis using Jeol 400yh instrument.*

2.4.3. The scope of the reaction of α-amido sulphones with TADDOL derived *H*-phosphonate

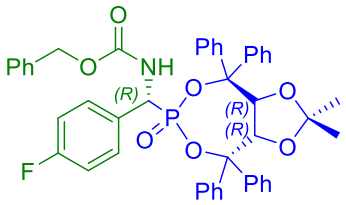
Under the optimized reaction conditions, I investigated a range of α-amido sulphones for the asymmetric hydrophosphonylation using (*R*,*R*)-**29** to demonstrate the applicability and limitations of the developed protocol (Scheme 58). The reaction proceeded smoothly for aromatic α-amido sulphones, yielding the desired α-aminophosphonates **148a–f** as single diastereoisomers with good, isolated yields (85–95%). The diastereoselectivity of the reaction was unaffected by the presence of electron-donating groups in the para-position **148d**, both ortho and para-positions **148e** or electron-withdrawing groups in the para-position **148b**, **c**, even with a bulkier group **148f**. Furthermore, poor diastereoselectivity was observed in the product **148g** when the reaction was attempted with sulphone-bearing heteroaromatic moiety. Finally, when utilizing aliphatic α-amido sulphones, the reaction yielded the products **148h-i** with diastereomeric ratios of 9:1 and lower yields (65-75%). The decrease in yields can be attributed to the lower reactivity of these aliphatic substrates.



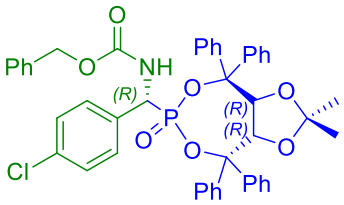
137 *(R,R)*-**29** *(R,R,R)*-**148**



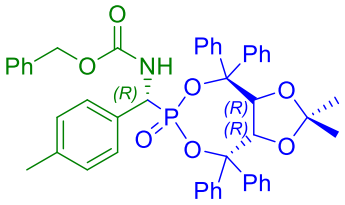
(R,R,R)-**148a**
dr 100, 85% yield



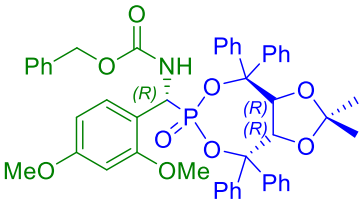
(R,R,R)-**148b**
dr 100**,** 93% yield



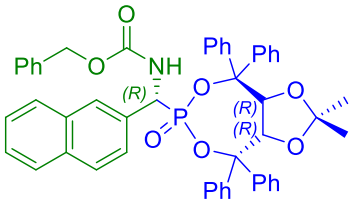
(R,R,R)-**148c**
dr 100, 95% yield



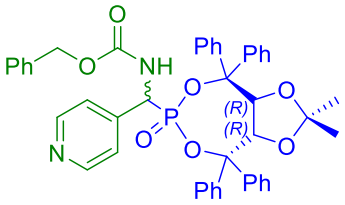
(R,R,R)-**148d**
dr 100, 91% yield



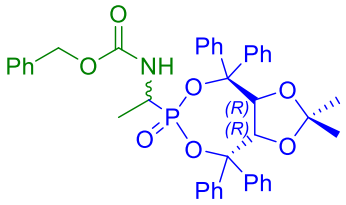
(R,R,R)-**148e**
dr 100, 89% yield



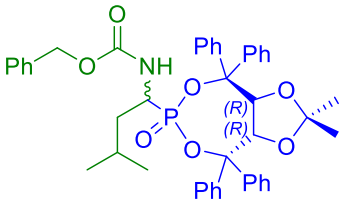
(R,R,R)-**148f**
dr 100, 90% yield



(R,R,R)-**148g**
dr 68:32, 76% yield



148h
dr 90:10, 65% yield



148i
dr 90:10, 75% yield

Scheme 58. *The scope of asymmetric hydrophoshonylation of α-amido sulphones with chiral TADDOL derived H-phosphonate (R,R)-**29**. Yields are reported for isolated products. dr was determined based on ^{31}P NMR.*

The X-ray analysis of the crystal from the α-aminophosphonate **148a** revealed an absolute configuration of (*R*) at the newly formed α-stereogenic carbon atom (Figure 16A). Therefore, the (*R,R,R*) configuration was assumable for all the pure single diastereoisomers **148a-i** obtained from the hydrophosphonylation reaction of the α-amido sulphones with (*R,R*)-**29**.

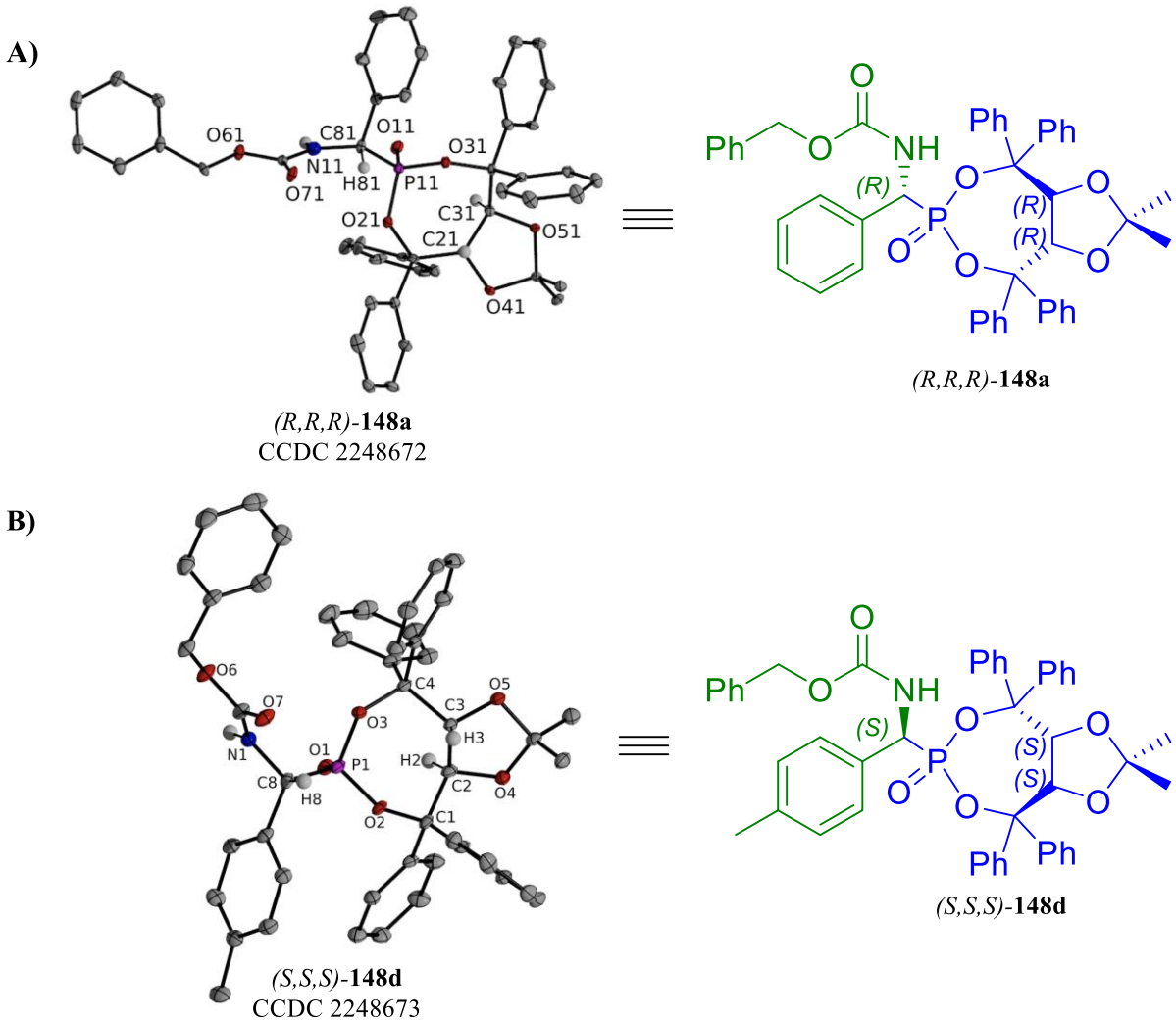
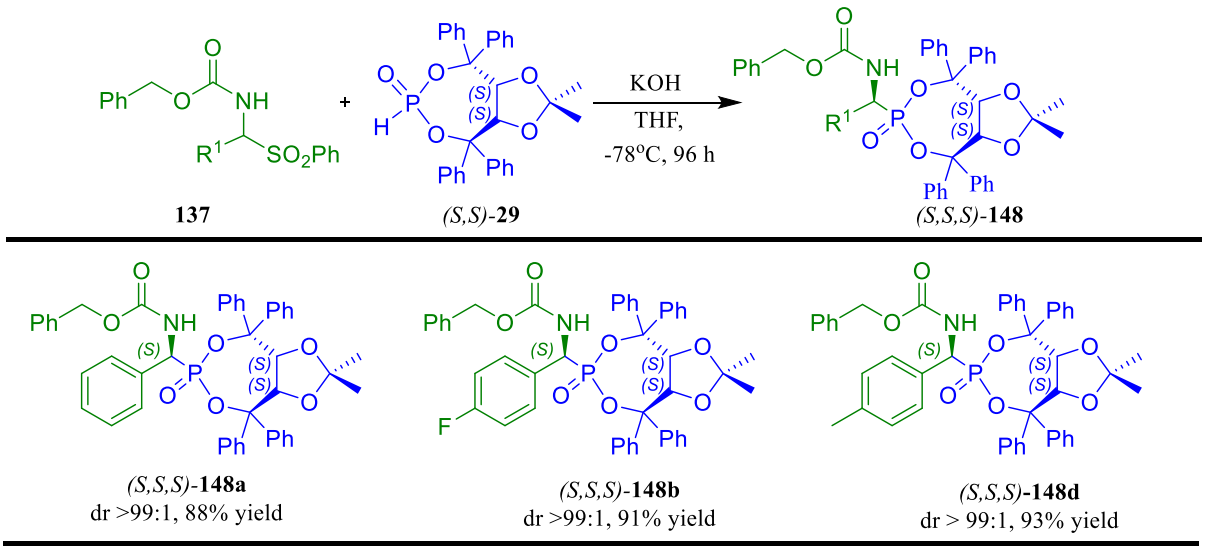


Figure 16. *The absolute configuration of the crystals* ***148a*** *and* ***148d*** *as determined from X-ray analysis.*

A fascinating observation arose when the enantiomerically opposite form of the chiral phosphorus auxiliary, specifically (*S*,*S*)-**29**, was employed under optimized reaction conditions, resulted in the formation α-amininophosphonates **148a,b,d** in high yield and excellent diastereoselectivity (Scheme 59). As I envisioned, this led to a reversal in the absolute configuration at the newly formed asymmetric α-carbon center, resulting in an (*S*) configuration, as unambiguously confirmed by the X-ray analysis of the crystals of compound (*S*,*S*,*S*)-**148d** (Figure 16B)**.** Hence, for all pure single diastereoisomers (*S*,*S*,*S*)-**148a,b**, obtained from the hydrophosphonylation reaction, the (*S*,*S*,*S*) configuration was assumed.



***Scheme 59**. The scope of asymmetric hydrophoshonylation of α-amido sulphones with chiral TADDOL derived H-phosphonate (S, S)-**29**. Yields are reported for isolated products. dr was determined based on ^{31}P NMR.*

To further investigate the enantiomeric nature of the compounds (*R, R, R*)-**148d** and (*S, S, S*)-**148d**, circular dichroism (CD) measurements were also conducted (Figure 17). The CD spectra obtained for the solutions of these compounds showed that (*R,R,R*)-**148d** and (*S,S,S*)-**148d** exhibited a mirror image relationship, indicating that the two compounds are indeed enantiomers, confirming the results of the X-ray analysis.

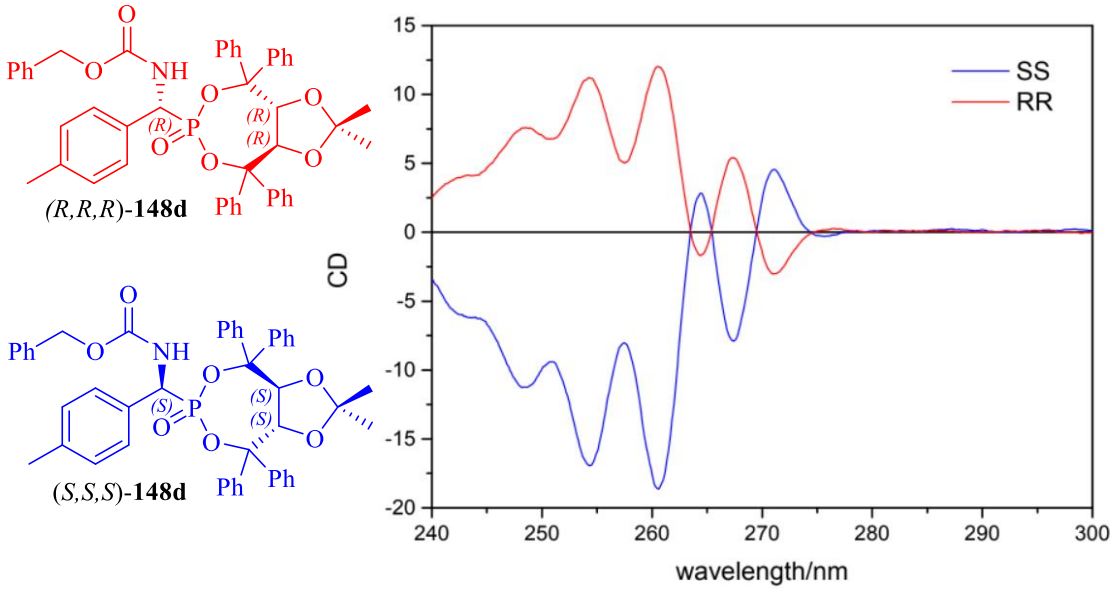
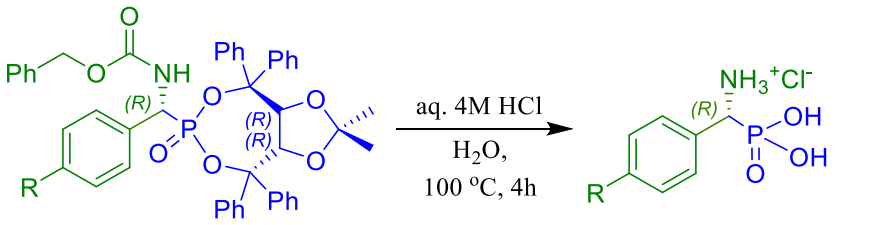


***Figure 17**. Confirmation of enantiomeric nature of (R,R,R)-**148d** and (S,S,S)-**148d** through circular dichroism measurements. ECD spectra were recorded in the 240–300 nm range with a Jasco J-1500 1500 spectropolarimeter (Jasco Inc, USA). Before use, the optical chamber of the CD spectrometer was deoxygenated with dry nitrogen and was held under a nitrogen atmosphere during the measurements. All optical measurements were performed in quartz cell cuvettes with conventional path lengths of 10 mm. The sample solutions in CH_2Cl_2 were of concentration 1.10-5 M.*

This developed methodology offers a notable advantage in the selective preparation of both enantiomers of α-aminophosphonates, which stems from the straightforward utilization of either of the two readily accessible enantiomers of the chiral auxiliary, (*R, R*)-**29** or (*S, S*)-**29**. The ability to selectively produce the desired enantiomer highlights the significant influence exerted by the chiral auxiliary on the diastereoselectivity of the hydrophosphonylation reaction involving α-amido sulphones.

To demonstrate the utility of the obtained diastereoisomers of α-substituted aminophosphonates **148** in the synthesis of enantiomers of α-substituted aminophosphonic acids. The phosphonate ester and the benzyl carbamate (Cbz) protecting groups were simultaneously removed from the pure diastereoisomers of α-aminophosphonates (*R,R*)-**148a, b** through classical acid hydrolysis to give enantiomerically pure α-aminophosphonic acids (*R*)-**146a** (90% yield) and (*R*)-**146b** (87% yield) without racemization (Scheme 60). The determination of the absolute configuration of the enantiomerically pure α-aminophosphonic acids was achieved through measurements of the specific rotation $[\alpha]_D^{20}$ of the obtained enantiomerically pure α-aminophosphonic acids **146a,b**. These obtained values were then compared with those reported in the literature for reference[90].



(*R,R,R*)-**148a** R = H
(*R,R,R*)-**148b** R = F

(*R*)-**146a** R = H (90% yield)
(*R*)-**146b** R = F (87% yield)

Scheme 60*. Transformation of α-substituted aminophosphonates to optically active α-aminophosphonic acids.*

3.0. Conclusions

I have demonstrated that the α-amido sulphones are readily accessible as stable substitutes for imines and serve as valuable substrates for synthesizing a range of α-aminophosphonates and α-aminophosphonic acids.

The developed protocol relies on the *in-situ* formation of imine via a one-pot reaction involving α-amido-sulphones, *H*-phosphonates, and a suitable base under optimized conditions. The *in-situ* generated imines underwent hydrophosphonylation with different *H*-phosphonates in the presence of K_2CO_3 as a base at the boiling point of THF for 4 h to afford the racemic α-aminophosphonates in high yields. In this way I have synthesized 18 racemic α-aminophosphonates. The products were purified either by crystallization or simple filtration through a pad of silica gel.

Furthermore, I have optimized an asymmetric variant of the hydrophosphonylation of α-amido sulphones using chiral *H*-phosphonate derived from readily accessible TADDOL as phosphorus nucleophile. Under optimized reaction conditions, hydrophosphonylation at -78°C, KOH, 96h in THF afforded the desired α-aminophosphonates with excellent diastereoselectivity (dr up to 100). In this way I have synthesized 12 α-aminophosphonates. The stereochemistry of the newly generated α-carbon atom could be precisely controlled during the asymmetric synthesis, depending on the enantiomer of the chiral TADDOL-derived *H*-phosphonate used. The use of (*R,R)*-TADDOL derived *H*-phosphonate resulted in the formation of (*R,R,R*)- α-aminophosphonates and (*S,S)*-TADDOL derived *H*-phosphonate resulted in the formation of (*S,S,S*)-α-aminophosphonates. The absolute configuration was confirmed by X-ray measurements.

Finally, the obtained α-aminophosphonates (racemic and pure diastereoisomers) underwent a selective deprotection process facilitated by the benzyl carbamate moiety present in their structure. This process resulted in the formation of α-aminophosphonate esters, while acid hydrolysis resulted in racemic α-aminophosphonic acids (with the asymmetric version yielding enantiomerically pure α-aminophosphonic acids). The obtained compounds possess significant value as versatile building blocks in the fields of organic synthesis and medicinal chemistry.

Chapter Two

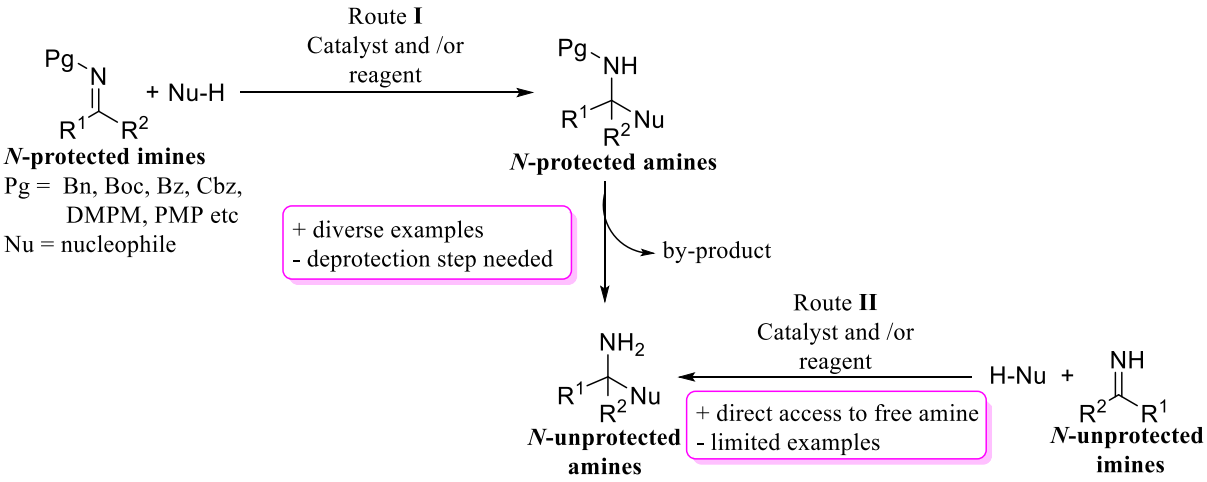
Asymmetric hydrophosphonylation of imines

1.0. Introduction

Schiff bases, more commonly known as imines, are a highly versatile and valuable group of compounds that have found a wide range of applications in organic chemistry. These compounds are commonly derived from the condensation reaction of aldehydes or ketones with primary amines, forming a carbon-nitrogen double bond (C=N). The inherent C=N bond gives imines remarkable reactivity, making them highly reactive intermediates in the synthesis of various organic compounds with a wide range of applications[188–191].

In many organic reactions, imines, which serve as precursors, can be categorized into two groups. The first group consists of the commonly used *N*-protected (substituted) imines (Scheme 61, route I), where the correct choice of the protective group or the substituent on the nitrogen plays a crucial role in achieving the desired reactivity and selectivity of the reaction. To obtain the free amine, it becomes necessary to remove the *N*-protecting group from the products[192]. Unfortunately, this process is not atom-economic and potentially limits the functional group compatibility of the system[193,194].

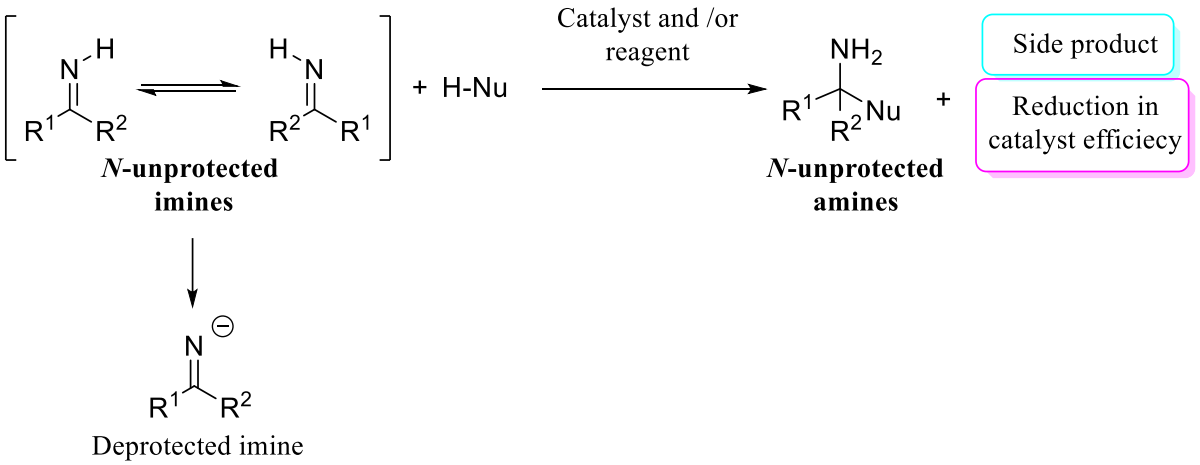
To overcome the challenges associated with *N*-protected imines, the second category comes into play; the *N*-unprotected (unsubstituted) imines. These imines offer a direct route to free amines by eliminating an unnecessary deprotection step, thanks to the absence of a protecting group in the structure. As a result, they provide a more atom-economical strategy for obtaining the desired products without any by-products (Scheme 61, route II).



Scheme 61. *Types of imines employed in addition reactions. Pg = protecting group; Bn = benzyl, Boc = tert-butyloxycarbonyl, Bz = benzoyl, Cbz = benzyloxycarbonyl, PMP = p-methoxybenzyl, DMPM = 3,4-dimethoxybenzyl.*

However, despite the advantages of using *N*-unsubstituted imines, there are few reports in the literature on their addition reactions compared to *N*-substituted imines, which could be due to several difficulties associated with their use such as:

- firstly, the instability of *N*-unsubstituted imines[195,196], combined with the observed potential for catalyst poisoning by *N*-unsubstituted amine products, can lead to unwanted by-products[197,198] and reduced catalyst efficiency, thus obstructing the desired reaction pathway;
- secondly, the absence of a protective group attached to the iminic nitrogen atom makes it difficult to modify the reactivity and selectivity of the *N*-unsubstituted imines[199–202];
- thirdly, the development of protocols with high stereoselectivity becomes challenging due to the presence of E/Z isomers in *N*-unsubstituted imines[203,204];
- furthermore, deprotonation of the proton attached to the nitrogen atom can also hinder the desired addition reactions under basic conditions (Scheme 62)[191].



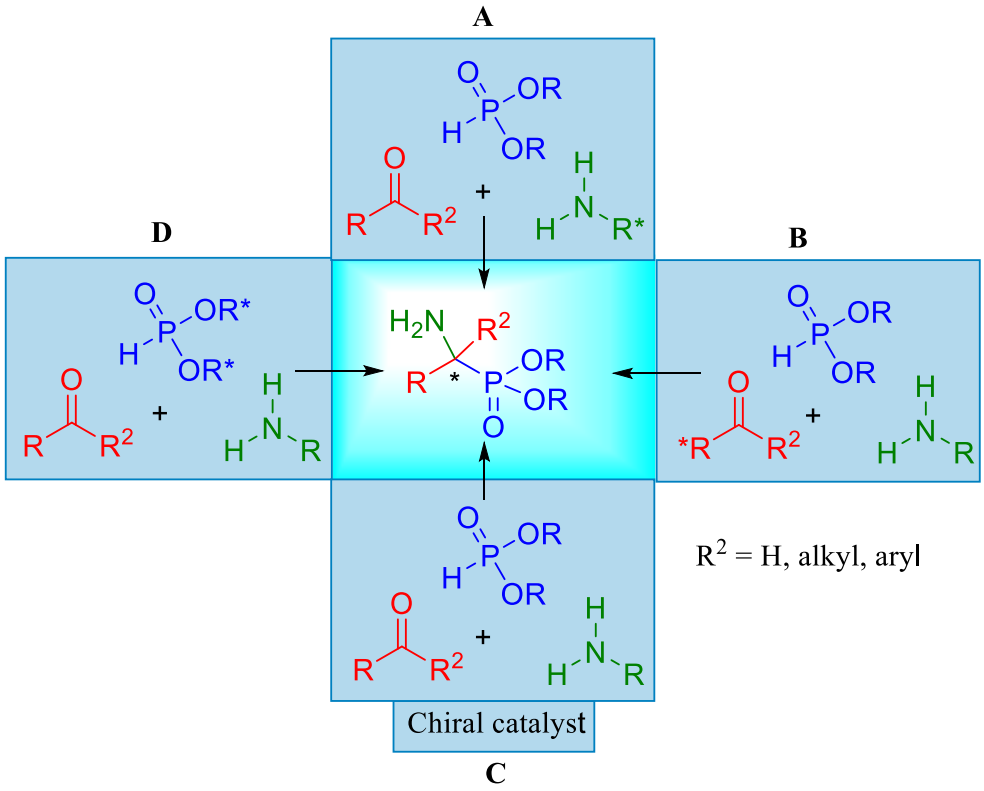
Scheme 62. *Challenges with N-unprotected imines.*

In this chapter, despite the above-stated challenges regarding addition reactions to *N*-unprotected imines, I will provide a concise review of recent advances in nucleophilic additions of P-nucleophiles to both *N*-protected and *N*-unprotected imines as a route in the synthesis of α-aminophosphonates and their derivatives. As earlier mentioned in the introduction (see introductory part, section 2.1 of the present dissertation for more details), these compounds have interesting biological properties that have attracted the attention of the scientific community. In recent years, numerous methods have been developed by several research groups for the preparation of enantiomerically pure α-aminophosphonic acids, α-aminophosphonates and their derivatives with remarkable stereoselectivity[24,26,205,206]. Among the most employed

synthetic routes leading to α-aminophosphonates and their derivatives are the Kabachnik-Fields and the aza-Pudovik condensation reactions.

1.1. The C-P bond formation via Kabachnik-Fields reaction

The Kabachnik-Fields reaction is a classic and possible most widely used method for the preparation of both racemic and optically active α-aminophosphonates, which can easily be transformed to α-aminophosphonic acids by the cleavage of the ester functionality, for example by hydrogenolysis or hydrolysis. The reaction involves the one-pot, three-component condensation of aldehydes or ketones with primary amines and a phosphite ester under various reaction conditions. The induction of stereochemistry in α-aminophosphonates can be achieved through various means, such as incorporating chirality in the starting amine (A), the carbonyl compound (B), utilizing a chiral catalyst (C), or phosphorus-containing chiral auxiliary (D) (Scheme 63).



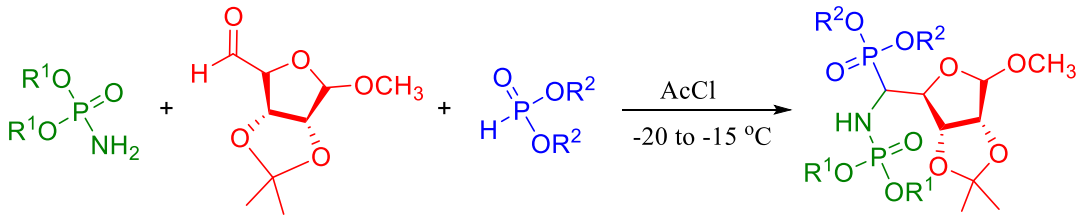
Scheme 63*. Stereoselective synthesis of α-aminophosphonates via Kabachnik-Fields protocol. R* in* ***D*** *= chiral auxiliary*

There are several review articles that discuss the Kabachnik-Fields reaction in detail[26,205–208], and I would like to present some selected, specific examples of these approaches used in the synthesis of α-aminophosphonates with significant asymmetric induction.

1.1.1. Kabachnik-Fields reaction using carbonyl substrates containing stereogenic centres

In a study conducted by Miao's group, the authors utilized the Kabachnik-Fields protocol to synthesize *N*-protected α-aminophosphonates **151**. This involved the reaction of dialkyl phosphoramidate **149** with methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside **150** and dialkyl *H*-phosphonate **144**, in the presence of acetyl chloride, resulting in moderate yields and diastereoselectivity (Table 5)[209]. The authors postulated that the acceleration of the intramolecular dehydration of an unstable adduct, formed through the addition of **149** to **150**, leading to the corresponding imine intermediate, was facilitated by the presence of acetyl chloride as a dehydrating agent. This imine intermediates further underwent nucleophilic addition, ultimately resulting in the formation of products **151.** No attempt was made to obtain the corresponding aminophosphonic acids, nor was the absolute configuration of product **151** determined.

Table 5. Diastereoselective synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-O-isopropylidene-β-D-ribofuranosides **151**.



149 **150** **144** **151a-j**

R^1	144/R^2	Products	yield (%)[a]/dr[b]
n-C_3H_7	**a**/CH_3	**151a**	49/69:31
n-C_3H_7	**b**/C_2H_5	**151b**	56/72:28
n-C_3H_7	**c**/*n*-C_3H_7	**151c**	47/68:32
n-C_3H_7	**d**/*i*-C_3H_7	**151d**	45/70:30
n-C_3H_7	**e**/*n*-C_4H_9	**151e**	50/84:16
C_2H_5	**a**/CH_3	**151f**	50/63:37
C_2H_5	**b**/C_2H_5	**151g**	53/75:25
C_2H_5	**c**/n-C_3H_7	**151h**	49/77:23
C_2H_5	**d**/*i*-C_3H_7	**151i**	48/78:22
C_2H_5	**e**/*n*-C_4H_9	**151j**	51/73:27

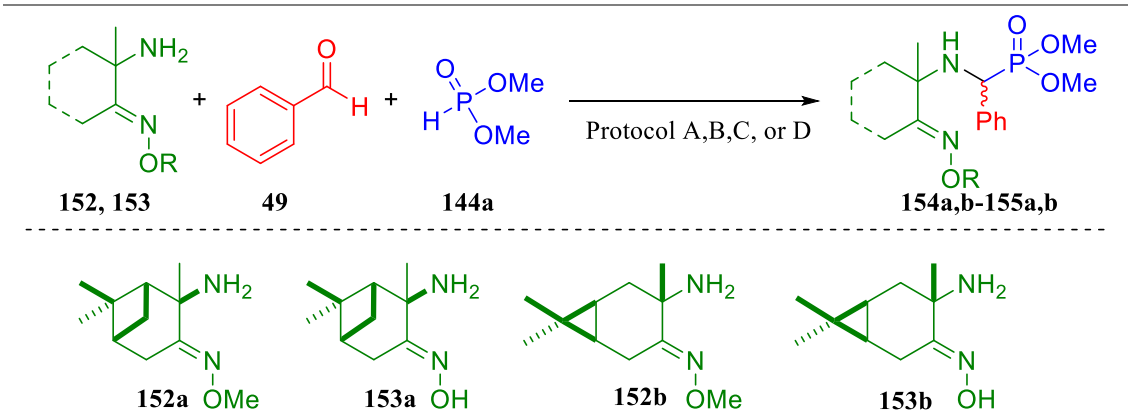
[a]Isolated yield of major diastereoisomer. [b]dr was established based on ^{31}P NMR spectra of the crude reaction.

1.1.2. Kabachnik-Fields reaction with amines containing stereogenic centre

In a different approach, the stereoselective formation of α-aminophosphonates was achieved by condensation of chiral terpenic α-amino oximes **152** or **153** with aldehydes and dimethyl *H*-phosphonate **144a** using the one-pot, three-component Kabachnik-Fields protocol (Table 6)[210]. The catalyst used ($SnCl_2x2H_2O$, SiO_2, or Al_2O_3-H^+) and the heating method

(conventional or microwave) influenced the diastereoselectivity of the reaction, with the most favourable results observed when microwave irradiation was accompanied by simultaneous cooling. It is worth noting that the condensation of compound **152b** with benzaldehyde using protocol B and SiO_2 as catalyst gave a pure stereoisomer **154b**. However, the authors acknowledged that the obtained low yield of the product (8%) prevented a conclusive assessment of stereoselectivity. Poor to moderate yields and diastereoselectivities were obtained for the synthesized α-aminophosphonates.

Table 6. Selected examples of the Kabachnik-Fields condensation of chiral amino oximes **152** or **153** with aldehyde and dimethyl *H*-phosphonate **144a**.

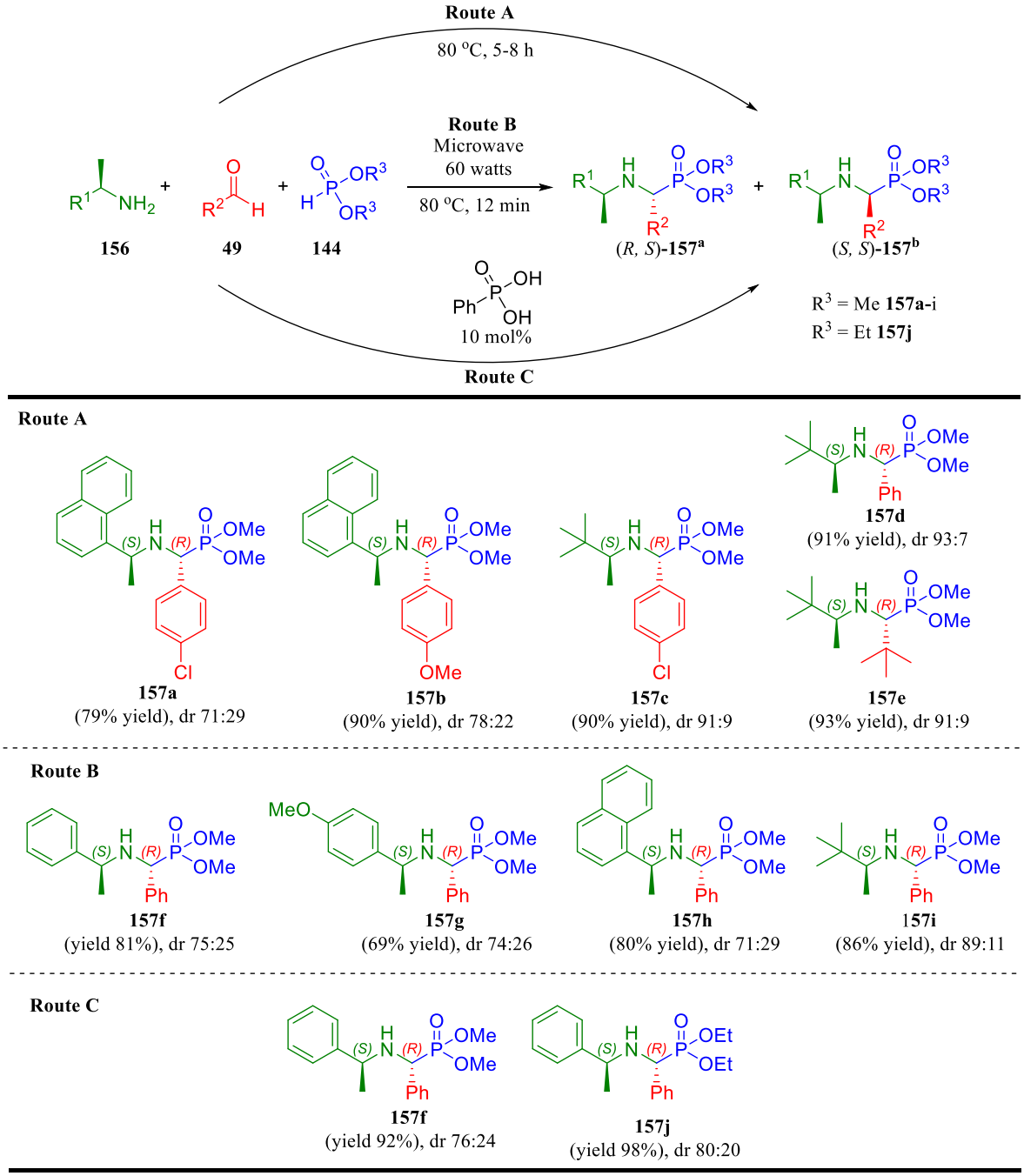


Amine	Protocol[a]	Catalyst	Products	Yield[b] (%)	dr[c]
152a	A	$SnCl_2x2H_2O$	**154a/a'**	14	40:60
152a	B	SiO_2	**154a/a'**	80	80:20
152b	A	$SnCl_2x2H_2O$	**154b/b'**	54	60:40
152b	B	SiO_2	**154b/b'**	8	100:0
153a	C	$Al_2O_3(H^+)$	**155a/a'**	47	66:34
153b	C	$Al_2O_3(H^+)$	**155a/a'**	traces	-
152a	C	$Al_2O_3(H^+)$	**154a/a'**	27	50:50
152b	C	$Al_2O_3(H^+)$	**154b/b'**	45	67:33
153a	D	$Al_2O_3(H^+)$	**155a/a'**	traces	-
153b	D	$Al_2O_3(H^+)$	**155b/b'**	28	80:20
152a	D	$Al_2O_3(H^+)$	**154a/a'**	85	71:29
152b	D	$Al_2O_3(H^+)$	**154b/b'**	80	67:33

*[a]Protocol **A**: $SnCl_2x2H_2O$, 14 days, rt; **B**: SiO_2, 14 days, rt; **C**: $Al_2O_3(H^+)$, 45 min, Microwave, 75 °C; **D**: $Al_2O_3(H^+)$, 3 h Microwave, refrigerator cooling to 0°C. [b]Preparative yields. [c]dr determined based on ^1H NMR.*

Ordoñez's group reported the diastereoselective synthesis of α-aminophosphonates **157a-e** through a one-pot, three-component Kabachnik-Fields condensation that involved the reaction of aldehydes (aryl or alkyl) **49**, (*S*)-α-methylamines **156**, and dimethyl *H*-phosphonate **144a** under a catalyst- and solvent-free approach (Scheme 64, route A)[211]. Under mild conditions, the reactions proceeded smoothly with high efficiency to give the products with satisfactory

yields and good diastereoselectivities. By employing chiral (*S*)-3,3-dimethyl-2-butylamine in the condensation reaction, the diastereoselectivity improved significantly (dr ranging from 80:20 to 93:7). In contrast, the use of (S)-1-(1-naphthyl)ethylamine resulted in lower diastereoselectivity (with a dr of 78:22 in the best case).



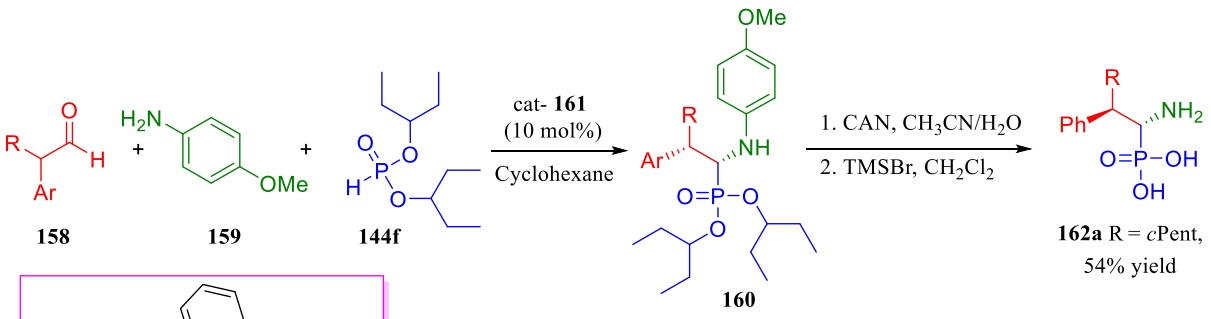
Scheme 64. *Selected example of one-pot three-component preparation of α-aminophosphonates* ***157*** *under microwave irradiation.* [a]*major diastereoisomer.* [b]*minor diastereoisomer. dr determined based on* ^{31}P *NMR of the crude product.*

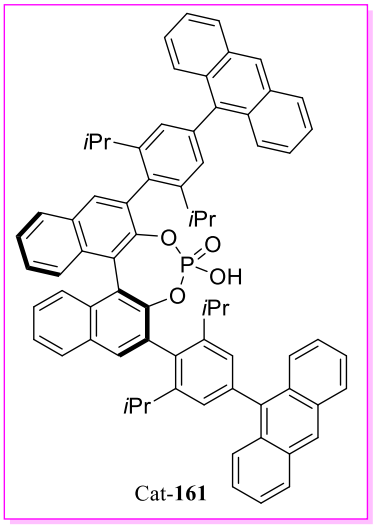
Apart from its environmentally friendly nature, this approach offers an additional advantage by enabling the large-scale synthesis of various α-aminophosphonates.

Using microwave irradiation as a source of heat, an alternative diastereoselective method for the preparation of α-aminophosphonates was developed. This method involved a one-pot, uncatalyzed, and solvent-free three-component reaction of aldehydes **49** with either (*S*)-α-methylbenzylamine or (*S*)-3,3-dimethyl-2-butylamine **156** and dimethyl *H*-phosphonate **144a**. As a result, α-aminophosphonates **157f-i** were produced with good yield and moderate diastereoselectivity, with the major diastereoisomer having an (*R, S*) configuration (Scheme 64, route B)[212]. This reaction proceeded with high reactivity under mild conditions and could also be applied in the multigram preparation of the different α-aminophosphonates. In continuation of their study, the same research group reported a solvent-free Kabachnik-Fields type reaction of one-pot, three-component condensation of benzaldehyde **49** and (S)-α-methylbenzylamine **156** with dimethyl- or diethyl *H*-phosphonate in the presence of phenylphosphonic acid as catalyst (10 mol%) at 80 ^{o}C. The α-aminophosphonates (*R, S*)-**157f** and (*R, S*)-**157j** were obtained in high yields and with moderate diastereoselectivities (Scheme 64, route C)[213]. The uniqueness of this protocol lies in the ability of the catalyst to be reused multiple times without loss of yield to afford the α-aminophosphonates on a multigram scale.

1.1.3. Kabachnik-Fields reaction catalyzed by chiral catalyst

Benjamin List et al. pioneered and reported the first catalytic asymmetric three-component Kabachnik-Fields reaction involving aryl aldehydes **158**, *p*-anisidine **159**, and di(3-pentyl) *H*-phosphonate **144f** catalysed by a *p*-anthracenyl-substituted TRIP (3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) analogue **161** in cyclo-hexane to afford the α-aminophosphonates (*R,R*)-**160** with moderate to high diastereoselectivity and enantioselectivity (Scheme 65)[214]. It is worth mentioning that the simultaneous generation of an additional stereogenic center enables the procedure to incorporate a dynamic kinetic resolution but unfortunately, a significant decrease in stereoselectivity was seen when alkyl acetaldehydes were employed. The authors further cleaved the *p*-methoxyphenyl and phosphonate groups in α-aminophosphonates **160a** using cerium ammonium nitrate (CAN) and bromotrimethylsilane (TMSBr) to furnish the corresponding α-aminophosphonic acid **162a** in 54% yield (Scheme 65). However, the configuration of the obtained acid **162a** wasn't mentioned by the authors.

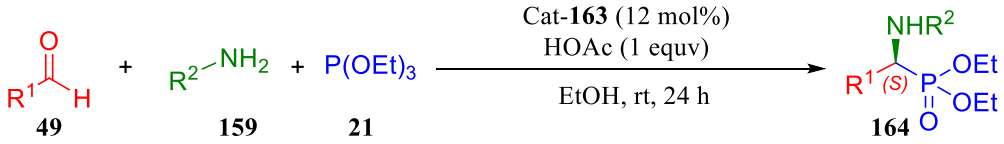


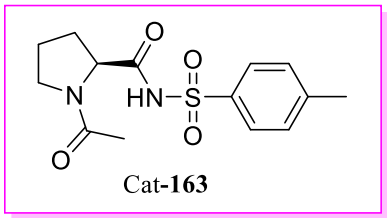


160a R = *c*Pent, Ar = C_6H_5, 86% yield, dr 16:1, er 96:4
160b R = *c*Pent, Ar =4-MeC_6H_4, 85% yield, dr 22:1, er 96:4
160c R = *c*Pent, Ar =4-MeOC_6H_4, 89% yield, dr 19:1, er 96:4
160d R = *c*Pent, Ar =3-MeOC_6H_4, 74% yield, dr 16:1, er 98:2
160e R = *c*Pent, Ar =4-ClC_6H_4, 83% yield, dr 20:1, er 94:6
160f R = *c*Pent, Ar = 3-ClC_6H_4, 80% yield, dr 28:1, er 94:6
160g R = *c*Pent, Ar = 2-naphthyl, 64% yield, dr 17:1, er 92:8
160h R = Me, Ar = C_6H_5, 63% yield, dr 3:2, er 51:49
160i R = Et, Ar = C_6H_5, 84% yield, dr 3:1, er 86:14
160j R = *i*Pr, Ar = C_6H_5, 86% yield, dr 16:1, er 95:5

***Scheme 65**. Representative examples of direct catalytic asymmetric Kabachnik–Fields reaction. dr and er were established by chiral-HPLC.*

In an unconventional Kabachnik-Fields reaction, Bhusare et al. introduced a distinct approach by employing trialkyl phosphite instead of dialkyl *H*-phosphonate[215]. This three-component, one-pot reaction involved aryl aldehydes and amines in the presence of triethyl phosphite **21**, catalyzed by (*S*)-1-acetyl-N-tosylpyrrolidine-2-carboxamide **163** (Scheme 66). The reaction proceeded under mild conditions, resulting in high yields of (*S*)-α-aminophoshonates **164** (71–90%) and with high enantioselectivity (73–92% ee).



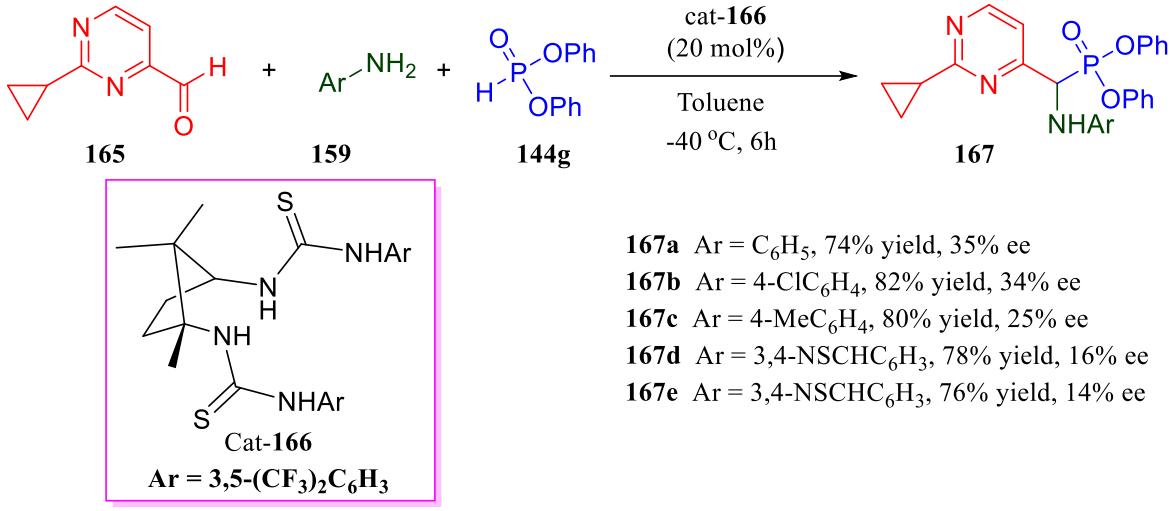


164a R^1 = C_6H_5, R^2 = C_6H_5, 88% yield, 89% ee
164b R^1 = 4-$NO_2C_6H_4$, R^2 = C_6H_5, 90% yield, 90% ee
164c R^1 = 4-MeOC_6H_4, R^2 = C_6H_5, 84% yield, 83% ee
164d R^1 = 4-OHC_6H_4, R^2 = 4-ClC_6H_4, 77% yield, 77% ee
164f R^1 = 4-MeOC_6H_4, R^2 = 4-ClC_6H_4, 78% yield, 75% ee

***Scheme 66**. Representative examples of one-pot enantioselective synthesis of α-aminophosphonates **164** with the use of cat-**163**. The ee determined by chiral HPLC, yields reported for isolated products.*

In turn, camphor-derived thiourea organocatalyst **166**, designed and synthesized by Reddy's group, was employed as a chiral catalyst in the condensation reaction of 2-

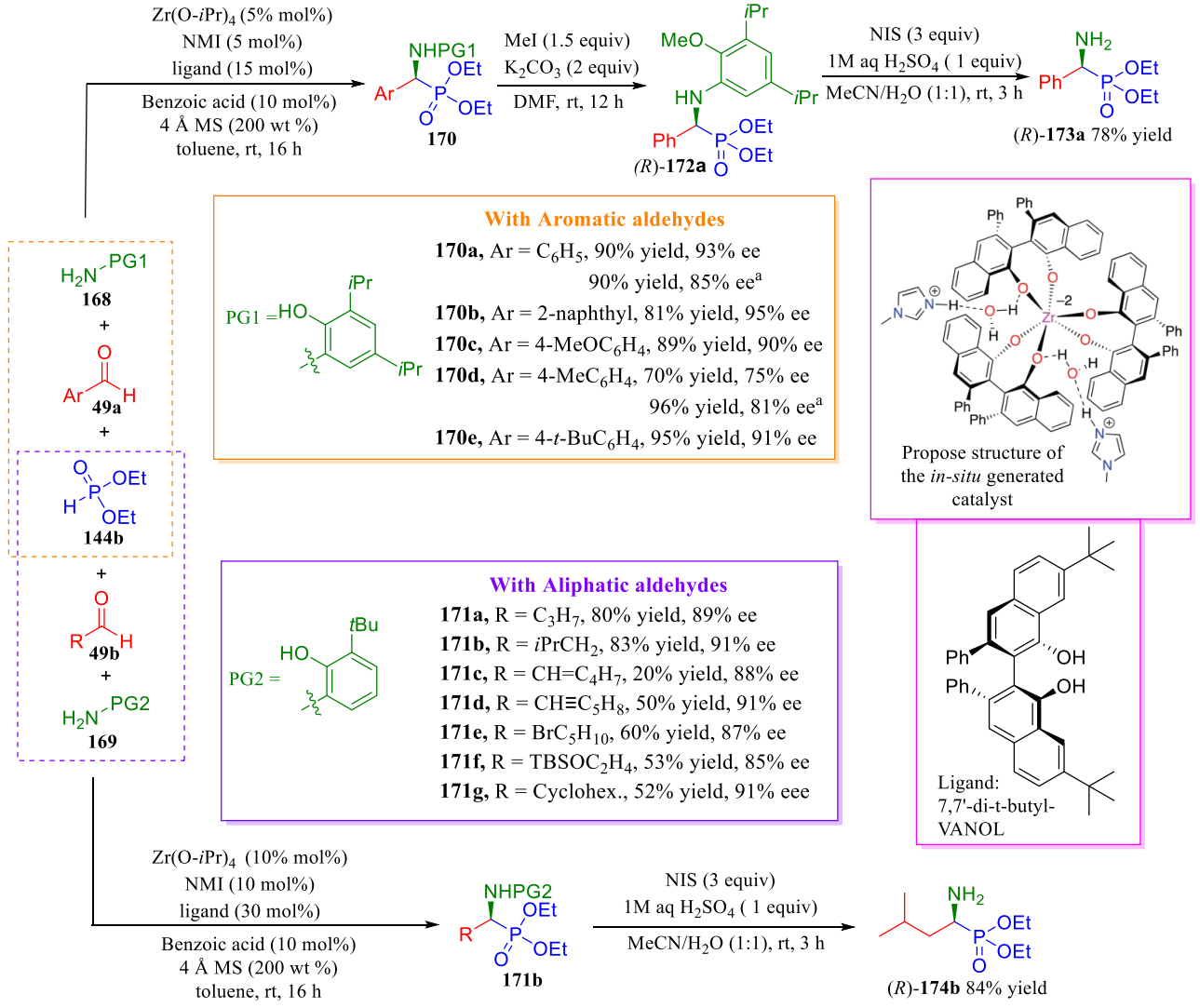
cyclopropylpyrimidin-4-carbaldehyde **165** with different amines **159** and diphenyl *H*-phosphonate **144g** to form α-aminophosphonates **167a-e** in 74–82% yields albeit with low enantioselectivities (14–35% ee) (Scheme 67)[216]. No information was given regarding the absolute configuration of product **167**.



***Scheme 67**. Kabachnik–Fields reaction catalyzed by chiral thiourea derivative **166**. Yield reported for the isolated product. The ee of the product was determined by chiral HPLC analysis.*

In a recent publication, Wulff et al. demonstrated catalyzed asymmetric Kabachnik-Fields three-component reaction of aldehydes (aryl and alkyl), amines, and dialkyl *H*-phosphonate[217]. This elegant approach involved the *in-situ* generation of the catalyst by reacting zirconium tetraisopropoxide and *N*-methylimidazole (NMI) with the ligand 7,7'-di-t-butyl-VANOL in an optimal ratio of 1:1:3. The resulting catalyst facilitated the reaction of the three components, leading to the formation of α-aminophosphonates with high asymmetric induction and satisfactory yields (Scheme 68). By increasing the addition of benzoic acid from 5 mol% to 10 mol%, the authors noted a positive effect on both the yields and, in some cases, the enantioselectivity of the products **170**. Regarding the reaction setup, 3,5-diisopropyl-2-hydroxyaniline **168** was discovered to be the optimal amine for aromatic aldehydes, whereas 3-t-butyl-2-hydroxyaniline **169** was identified as the preferred amine for aliphatic aldehydes, with diethyl *H*-phosphonate **144b** being the optimal P-nucleophile for both reaction systems. It is worth noting that the enantioselectivity observed for aliphatic α-aminophosphonates **171**, with an average of 90% ee, was comparable to that observed for aromatic α-aminophosphonates **170**, with an average of 91% ee. Nevertheless, it is paramount to highlight that the yields achieved in the former were relatively lower when compared to the latter. Upon employing the (*S*)-catalyst, the absolute configuration of both aromatic and aliphatic α-aminophosphonates was

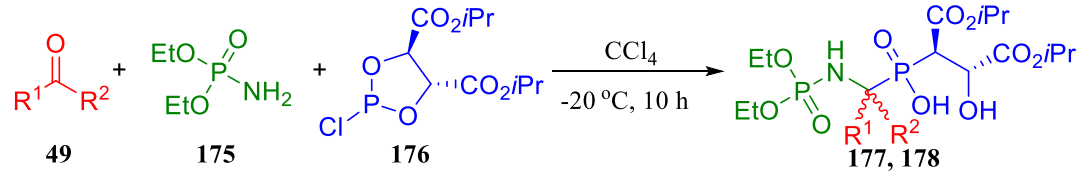
ascertained to be (*S*) at the newly formed stereogenic carbon following the deprotection to the free amine. It was presumed that this configuration remained consistent for all other aromatic and aliphatic aminophosphonates. In a two-step process, the deprotected aromatic aminophosphonate ester **173a** was successfully obtained with a yield of 78%. Firstly, the phenol functionality in aminophosphonate **170a** was methylated, resulting in the methyl ether (*R*)-**172**. Subsequently, oxidative deprotection using *N*-iodosuccinimide (NIS) was carried out, leading to the generation of the free amine product with an (*R*) configuration. Likewise, by directly treating aliphatic aminophosphonate **171b** with NIS, phospholeucine diethyl ester (*R*)-**174b** was generated, achieving a yield of 84% (Scheme 68)[217].



Scheme 68. *Selected example of the synthesis of α-aminophosphonates and their derivatives via the zirconium-catalyzed asymmetric Kabachnik–Fields reactions of aromatic and aliphatic aldehydes. [a]Reaction with 5 mol% benzoic acid. NMI-N:methylimidazole.*

1.1.4. Kabachnik-Fields reactions with phosphorus-containing compounds having a stereogenic center

The *N*-(diethoxyphosphinyl)-substituted α-aminophosphonates **177** were prepared in moderate to good yields but with poor diastereoselectivity through the direct condensation of aldehydes, diethyl phosphoramidate **175**, and chiral dioxaphospholane **176** at 20 °C in tetrachloromethane (Scheme 69)[218]. When acetophenone was used as a carbonyl component, a quaternary α-aminophosphonate **178** was obtained with a diastereomeric ratio of 67:33 and a yield of 62% (Scheme 69). Despite their efforts, the authors faced challenges in determining the absolute configuration of the products, as they were unable to successfully isolate the major diastereomer in its pure form.



49 **175** **176** **177, 178**

177a $R^1 = C_6H_5$, $R^2 = H$
85% yield, dr 64:36

177b $R^1 = 4\text{-}NO_2C_6H_4$, $R^2 = H$
84% yield, dr 58:42

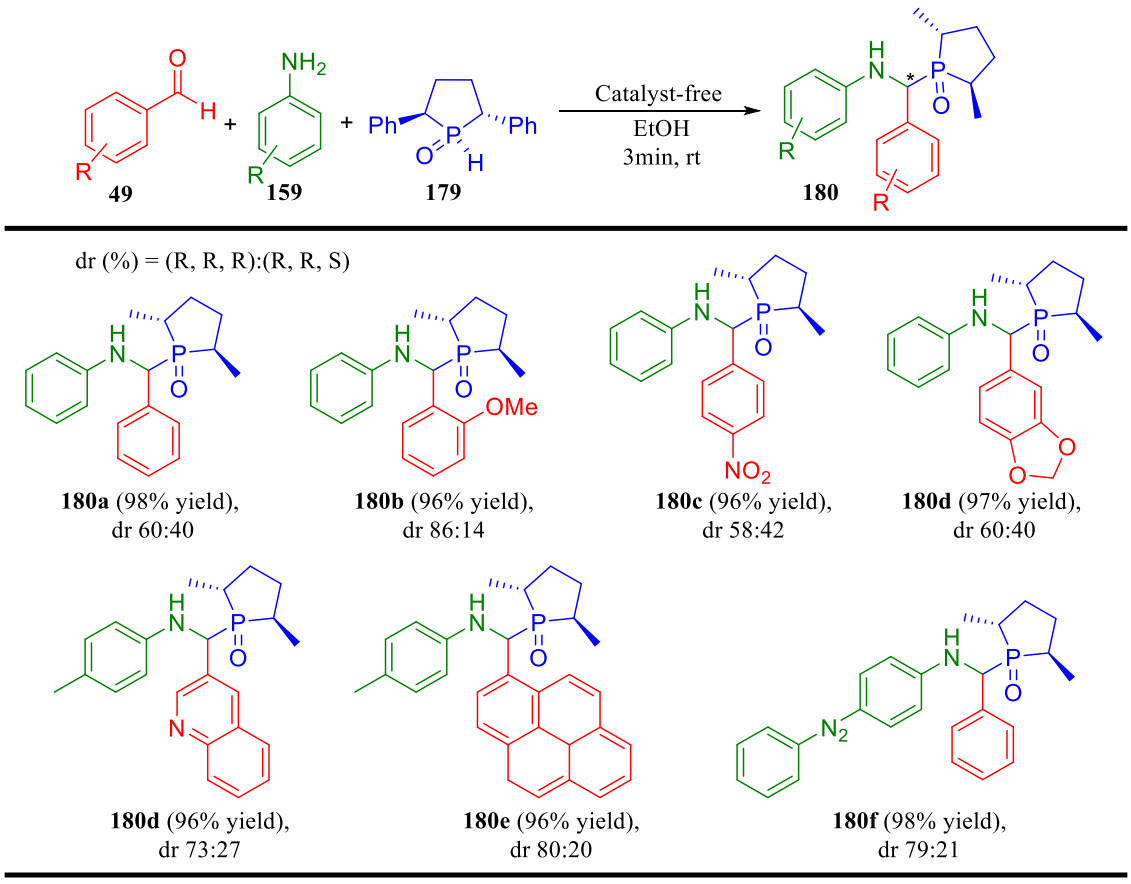
177c $R^1 = 4\text{-}MeC_6H_4$, $R^2 = H$
85% yield, dr 62:38

178 $R^1 = C_6H_5$, $R^2 = Me$
62% yield, dr 67:33

***Scheme 69**. Representative examples of asymmetric synthesis of N-phosphinyl α-aminophosphonic acid monoesters **177** and **178** via on-pot three-component reaction. Yields are reported for isolated products. The dr was determined based on the ^{31}P NMR of the crude product.*

Lakoud's et al. reported the first utility of enantiopure 1-*r*-oxo-2-*c*,5-*t*-diphenylphospholane **179** as a nucleophile in the synthesis of aminophospholane oxides **180** via the Kabachnik-Fields reaction under catalyst-free conditions[219]. Under greener and environmentally friendly conditions, the reaction between aromatic aldehydes **49** and anilines **159** utilizing (*R*,*R*)-**179** showed remarkable reactivity, yielding chiral products **180** with quantitative yields (up to 98%) but low diastereoselectivity (Scheme 70). X-ray analysis of the diastereoisomer of 2,5-diphenyl-1-oxo-1-[phenyl (phenylamino)-methyl] phospholane **180a** revealed an (*R*,*R*,*R*) configuration. This protocol has several advantages, including its atom-economic nature and

the absence of a catalyst, the use of green solvents, short reaction time and mild conditions. In addition, the products were easily isolated by a simple crystallisation process.



***Scheme 70**. Representative examples of Kabachnik-Fields reaction employing enantiopure phospholane oxide **179** under catalyst-free conditions. The yields were given for isolated products after crystallization.*

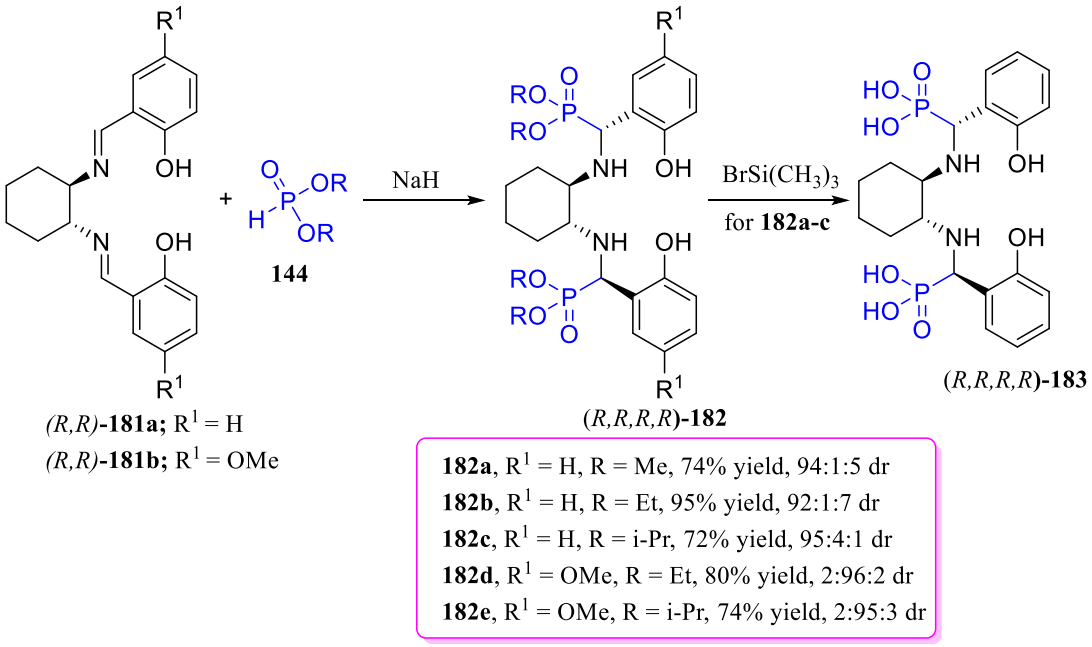
1.2. The C-P bond formation via aza-Pudovik reaction

The aza-Pudovik reaction, known as the hydrophosphonylation of aldimines or ketimines, offers a convenient approach for obtaining α-aminophosphonates. It involves the nucleophilic addition of phosphorus-containing agents (such as dialkyl *H*-phosphonates, diaryl *H*-phosphonates, phosphine oxides, or in general phosphorus nucleophiles containing chiral auxiliaries) to imines derived from the condensation of carbonyl compounds with amines[26,207,220]. This method plays a crucial role in synthesizing α-aminophosphonates, which serve as essential intermediates in producing amino acid analogues, namely aminophosphonic acids, either in a racemic[205], diastereomerically or enantiomerically pure form[26,207]. Several scientific reviews have covered the aza-Pudovik reactions in detail [26,208,221,222], but in this context, I would like to present only a few selected, specific examples of these methods used in the synthesis of stereoselective α-aminophosphonates and I would like to limit this review to

the use of H-P species bearing a chiral auxiliary attached to a phosphorus atom as a source of asymmetric induction in the desired product.

1.2.1. Aza-Pudovik reaction with chiral imines

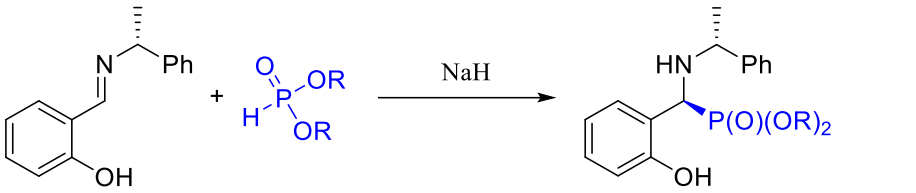
The aza-Pudovik type reaction of *N,N'*-disalicylidene-1,2-diaminocyclohexane imines **181** with diakyl P-nucleophiles (dimethyl-, diethyl-, and diisopropyl *H*-phosphonates) in the presence of sodium hydride, resulted in the preparation of bis-α-aminophosphonates **183** with (*R,R,R,R*) configuration. The reaction produced the products **182** in high diastereomeric ratios and satisfactory yields (72–90%). Subsequently, the dealkylation of the phosphonic acid ester groups in **182a-c** with trimethylsilyl bromide (TMSBr) led to the formation of the corresponding bis-α-aminophosphonic acids **183** while retaining the (*R,R,R,R*) configuration (Scheme 71)[223].



***Scheme 71**. Stereoselective synthesis of di(aminophosphonates) **182** and the corresponding aminophosphonic acids **183**.*

Similarly, the use of (*R*)-salicylaldimines **184**, which contain the methylbenzylamine moiety known to offer limited chiral support (as previously reported by the group, with a diastereomeric ratio of 75:25 in the best case[224,225]), along with diethyl or diisopropyl *H*-phosphonate in the presence of NaH in anhydrous ether, resulted in the formation of (*R,S*)-α-aminophosphonates **185a**, with a yield of 63% and a diastereomeric ratio of 93:7, as well as **185b** with a yield of 71% and a diastereomeric ratio of 86:14 (Scheme 72)[223]. The reason for the high diastereoselectivity observed in the hydrosphosphonylation of salicylaldimines (*R,R*)-

181 and (*R*)-**184**, as stated by the authors, was the stabilization of the sodium salt through intermolecular coordination of the sodium cation by the phenolic oxygen and the azomethine nitrogen. This stabilization effect also resulted in the predominant formation of the (*R*,*R*,*R*,*R*)-**182** and (*R*,*S*)-**185** isomers of their respective α-aminophosphonates[223]. The applicability of this protocol is limited to salicylaldehyde derivatives. Attempting the addition of the P-nucleophiles to (*R*,*R*)-*N*,*N'*-bis(benzylidene)-1,2-cyclohexanediamine or (*R*,*R*)-*N*,*N'*-bis(4-hydroxybenzylidene)-1,2-cyclohexanediamine in the presence of NaH resulted in the formation of α-aminophosphonates with very low yields, ranging from 15% to 20%.

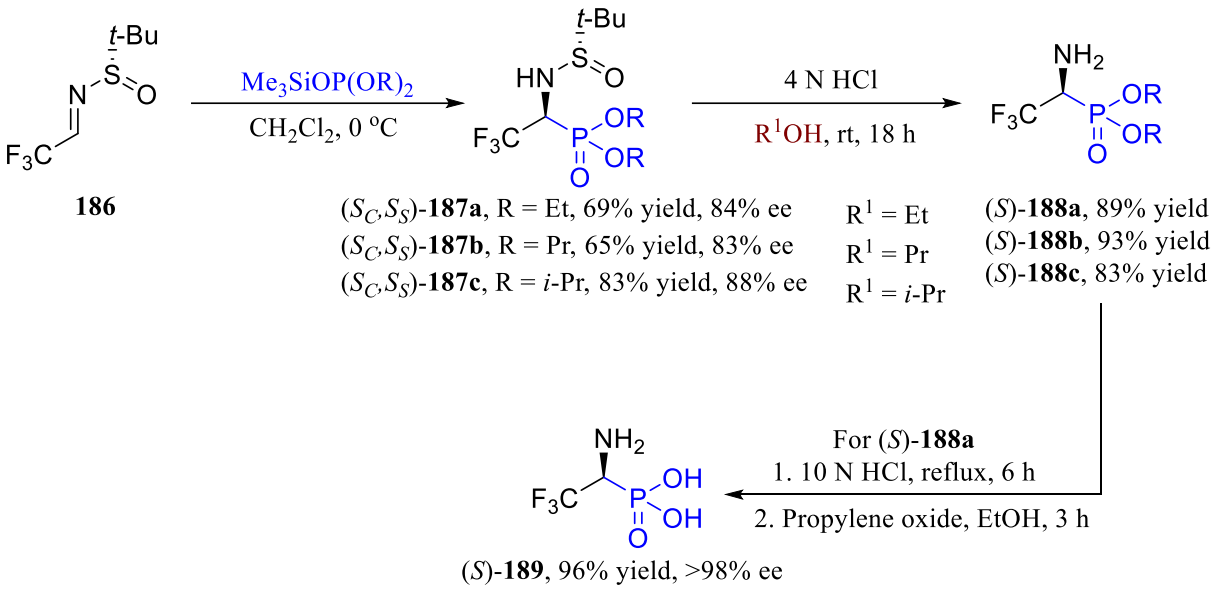


184 **144**

185a, R = Et, 63% yield, 93:7 dr
185b, R = i-Pr, 71% yield, 86:14 dr

***Scheme 72**: Diastereoselective synthesis of aminophosphonates **185** using chiral salicylaldimine **184**.*

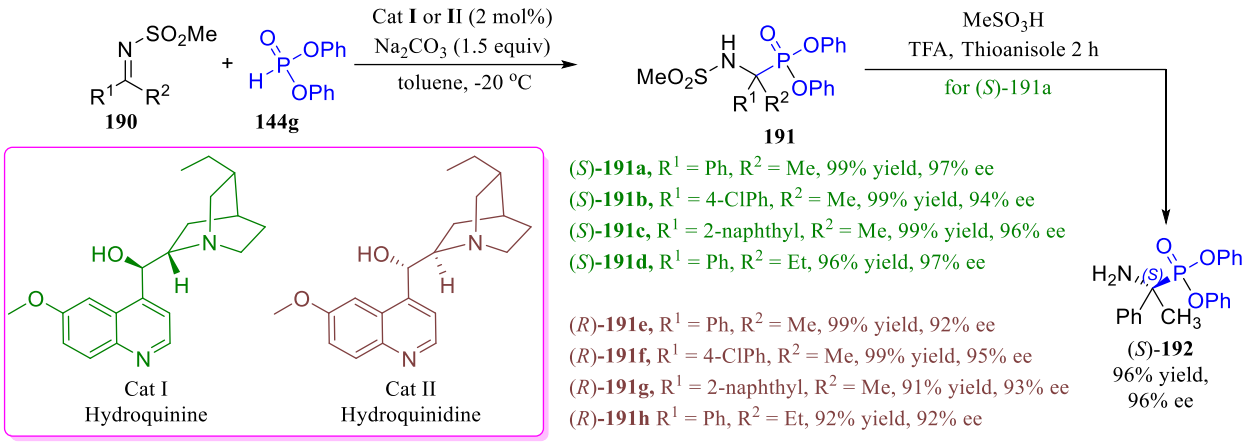
Various dialkyl trimethylsilyl phosphites were employed as efficient nucleophilic agents in the hydrophosphonylation reaction of *N*-tert-butylsulfinyl imine **186** in CH_2Cl_2 at 0°C. This reaction yielded (S_C,S_S)-*N*-*tert*-butylsulfinyl α-aminophosphonates **187a-c** in good yields, ranging from 69% to 83%, with enantiomeric excess values between 83% and 88% (Scheme 73)[226]. The subsequent selective deprotection of the iminic nitrogen of compounds **187a-c** with 4N HCl in alcohol resulted in the formation of α-aminophosphonic acid esters **188a-c**, achieving high yields ranging from 83% to 93%. Further hydrolysis of **188a** with 10 N HCl under reflux, followed by treatment with propylene oxide and EtOH, facilitated the synthesis of enantiopure (*S*)-phosphonotrifluoroalanine **189** with an excellent yield of 96% and an enantiomeric excess of 98% (Scheme 73)[226]. The use of *N*-*tert*-butanesulfinyl imine in the aza-Pudovik reaction offers several advantages. Firstly, it exhibits excellent diastereocontrol during the nucleophilic addition across the carbon-nitrogen double bond, leading to the formation of products with high selectivity[227,228]. Secondly, the group attached to the iminic nitrogen can be easily cleaved under mild reaction conditions, facilitating further functionalization of the synthesized products. Furthermore, *N*-*tert*-butylsulfinyl imine is stable under an inert atmosphere, making it suitable for handling and manipulation in synthetic processes[229].



***Scheme 73**. Asymmetric preparation of phosphonotrifluoroalanine **187** and its derivatives using N-tert-butylsulfinyl imine **186**.*

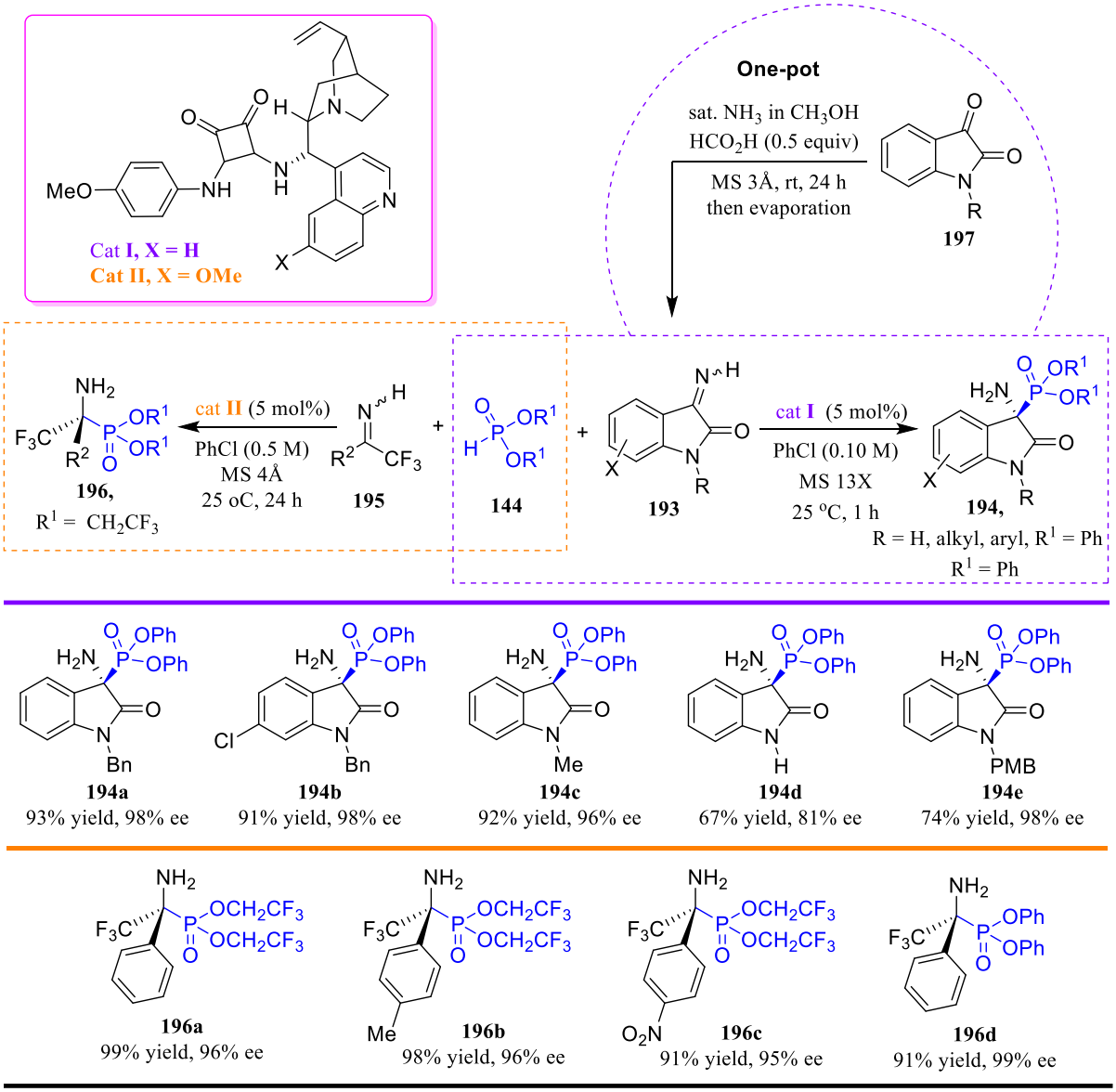
1.2.2. Aza-Pudovik reaction performed with chiral catalysts

A highly enantioselective aza-Pudovik reaction of ketimines, catalyzed by cinchona alkaloid was reported[230]. The reaction involves the enantioselective addition of diphenyl *H*-phosphonate **144g** to various ketimines **190**, in the presence of a catalytic amount of hydroquinine and 1.5 equiv. of Na_2CO_3 in toluene. As a result, the reaction yields the quaternary (*S*)-α-aminophosphonates **191** with excellent yields (93-99%) and enantioselectivity ranging from 55% to 97% *ee*. Substituting hydroquinine with hydroquinidine leads to the opposite enantiomers, namely quaternary (*R*)-α-aminophosphonates **191**, obtained with high yields (86-99%) and enantiomeric excess from 52% to 95% (Scheme 74). Furthermore, (*S*)-**191a** underwent desulfonylation upon treatment with methanesulfonic acid in TFA at room temperature. This resulted in the deprotection of the nitrogen atom, to give quaternary (*S*)-α-aminophosphonate **192** with high enantioselectivity (96% *ee*) and a yield of 96% (Scheme 74). By employing either of the organocatalysts, this protocol offered excellent stereocontrol, and the products were purified using a straightforward crystallization process[230].



***Scheme 74**. Selected examples of enantioselective aza-Pudovik reaction of ketimines catalyzed by cinchona alkaloids. TFA = trifluoroacetic acid, $MeSO_3H$ = methanesulfonic acid.*

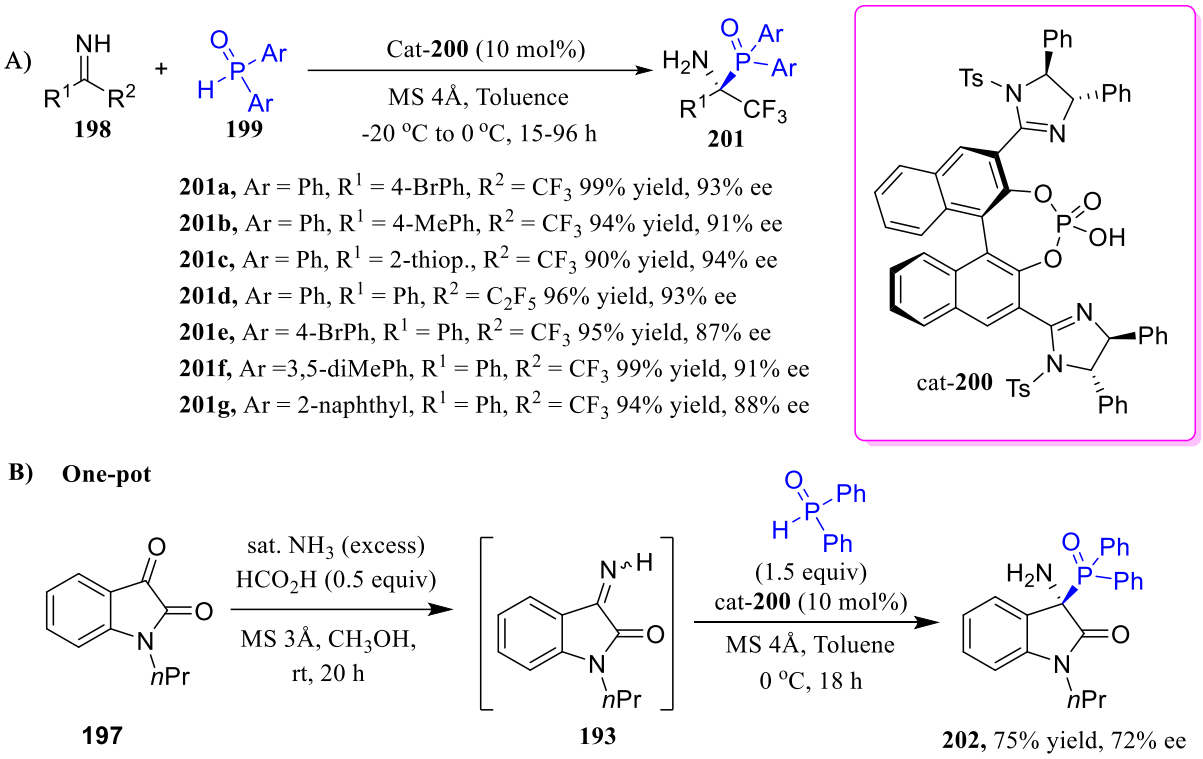
Recently, the direct organocatalytic enantioselective aza-Pudovik type reaction that involved the nucleophilic addition of diphenyl *H*-phosphonate to *N*-unsubstituted ketimines **193**, utilizing dual-functional squaramide catalyst **I** in chlorobenzene, was reported[231]. This reaction produced the *N*-unprotected tetrasubstituted (*R*)-α-aminophosphonates **194** in good yields (up to 93%) and high enantioselectivity (up to 99% *ee*) (Scheme 75). The authors also demonstrated a one-pot reaction where *N*-unsubstituted ketimine **193a** was formed *in situ* through the condensation of isatin **197** with ammonia, followed by the nucleophilic addition of diphenyl H-phosphonate under similar reaction conditions. The (*R*)-α-aminophosphonate **194a** was obtained in 84% yield and 98% enantiomeric excess. Furthermore, the scope of the protocol was expanded by conducting the hydrophosphonylation reaction of *N*-unsubstituted trifluoromethyl ketimines **195** with bis(2,2,2-trifluoroethyl) *H*-phosphonate, utilizing catalyst **II**. This transformation yielded quaternary (*R*)-α-aminophosphonates **196** in outstanding yields (90%-99%) and high enantioselectivity (89%-99% *ee*). When diphenyl *H*-phosphonate was employed as the P-nucleophile, adduct (*R*)-**196d** was also obtained with a yield of 91% and an enantiomeric excess of 99% (Scheme 75)[231]. The developed protocol demonstrated remarkable reactivity, allowing the reaction to proceed smoothly, even when reducing the catalyst loading to as low as 0.5 mol%. This modification still resulted in the synthesis of adduct **196a** with an 85% yield and an enantiomeric excess of 93%. Moreover, the products obtained from this reaction can be further transformed into other valuable intermediates[232], adding to the versatility of the methodology.



Scheme 75. *Synthesis of α-aminophosphonates via the enantioselective hydrophosphonylation of N-unsubstituted ketimines. PMB = p-methoxybenzyl ether.*

Nakamura et al. reported on enantioselective hydrophosphonylation of *N*-unprotected ketimines **198** with diphenyl phosphine oxide **199** catalyzed by bis(imidazoline)phosphoric acid cat-**200** to give the quarternary (*R*)-α-aminophosphine oxides **201** with yields ranging from 40% to 99% and enantiomeric excesses ranging from 78% to 95% (Scheme 76A)[220]. To expand the practicability of the protocol, the authors carried out a one-pot reaction involving the *in-situ* generation of the ketimine **193a** derived from isatin **197,** which subsequently reacted with diphenyl phosphine oxide **199** in the presence of bis(imidazoline)- phosphoric acid catalyst (Scheme 76B). The adduct (*R*)-**202a** was obtained with a yield of 75% and an *ee* of 72%. The utilization of *N*-unprotected ketimines in the reaction setup proved to be atom-economical and cost-effective since the reactions proceeded without the need for a deprotection

step, leading directly to the formation of free amine products. Furthermore, this protocol successfully addressed the challenges commonly encountered in asymmetric reactions involving *N*-unprotected imines, such as low reactivity and selectivity[191,233].



***Scheme 76**. A) Selected examples of catalytic enantioselective synthesis of α-aminophosphine oxides **201** through the reaction of ketimine **198** with phosphine oxides **199**. B) One-pot enantioselective synthesis of α-aminophosphine oxides **202**.*

1.2.3. Aza-Pudovik reaction with H-P nucleophiles containing chiral auxiliary

In the introductory part, section 4.1 of this dissertation, I discussed in detail the application of H-P nucleophiles containing chiral auxiliaries in the asymmetric hydrophosphonylation of imines (the aza-Pudovik reaction). Indeed, this approach has effectively demonstrated the significant impact and potential of these auxiliaries in transforming imines into valuable phosphorus-containing products.

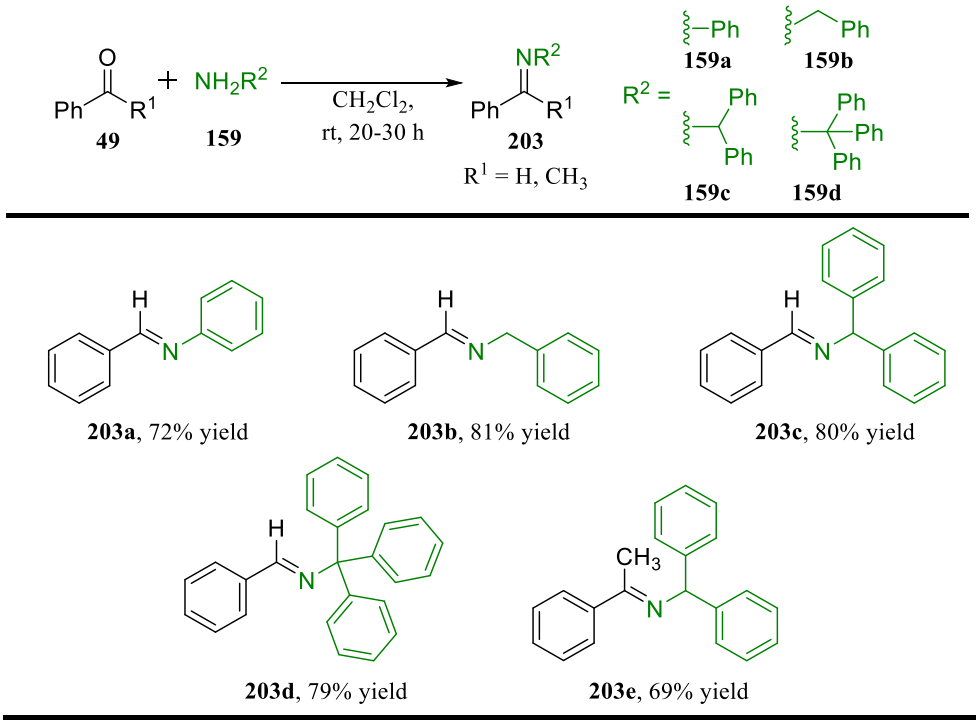
Due to the significant importance of imines as starting materials in the synthesis of α-aminophosphonates and their derivatives, researchers worldwide continue to investigate and develop new methods for transforming imines into α-aminophosphonates and their derivatives with a high degree of asymmetric induction. During my Ph.D., I have made an effort in developing a diastereoselective protocol for synthesizing α-aminophosphonates via the nucleophilic addition of chiral phosphorus nucleophile (*R*,*R*)-**29** (TADDOL-derived *H*-phosphonate) to carbon-nitrogen bond of aldimines or ketimines. The basic concept of this

approach was based on the need to use simple, inexpensive starting materials and chiral phosphorus nucleophile as the only source of chirality. I envisioned that the size of the substituents on the iminic nitrogen atom might play a crucial role in controlling or inducing the high diastereoselectivity of such a reaction. To test this hypothesis, I used primary amines with different substituents of varied sizes on the nitrogen atom, including aniline, benzylamine, benzhydryl amine, and tritylamine, to synthesize the corresponding *N*-substituted imines. These simple and easy to obtain imines were subsequently subjected to hydrophosphonylation reaction with (*R,R*)-**29** under various conditions.

2.0. Results and Discussion.

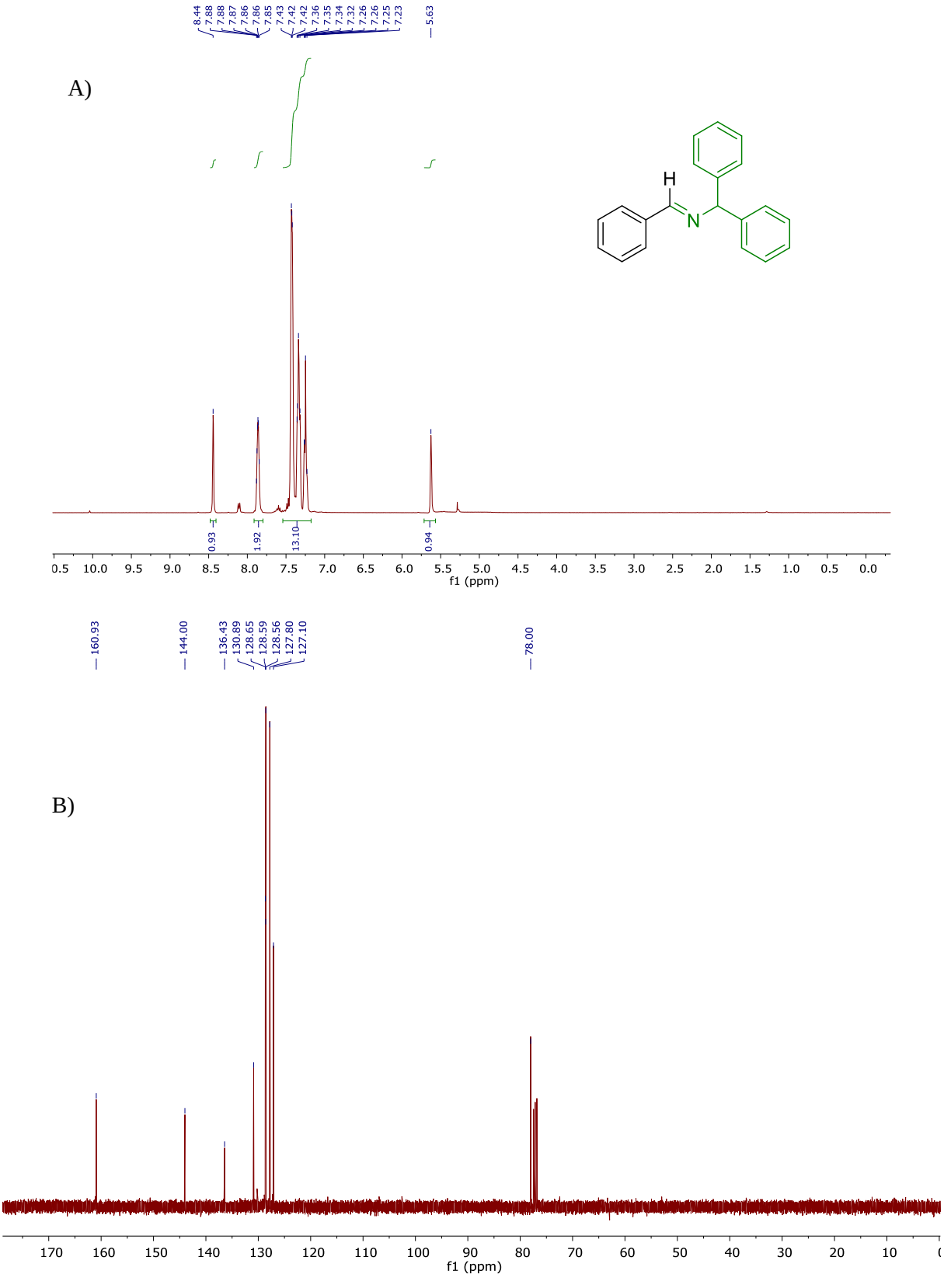
2.1. Synthesis of the starting imines

By employing the literature protocol with slight modifications[234,235], I carried out the synthesis of the imines that were subsequently used in the hydrophosphonylation reactions, involving the condensation of carbonyl compounds (aldehyde or ketone) with various primary amines (such as aniline, benzyl amine, benzhydryl amine, and trityl amine) in CH_2Cl_2 under mild conditions (Scheme 77). The resulting pure products **203** were obtained by crystallization using diethyl ether with moderate to high yields (69-80%). It should be noted that the reaction with ketone took longer time because of its low reactivity.



***Scheme 77**: Synthesis of aldimines and ketimines **203** from carbonyl compounds and primary amines*

For each pure isolated imine, the structural analysis was performed using ^{1}H and ^{13}C NMR. As a representative example, Figure 18 shows the NMR spectra of the *N*-substituted aldimine **203c** (A and B) and ketimine **203e** (C and D).



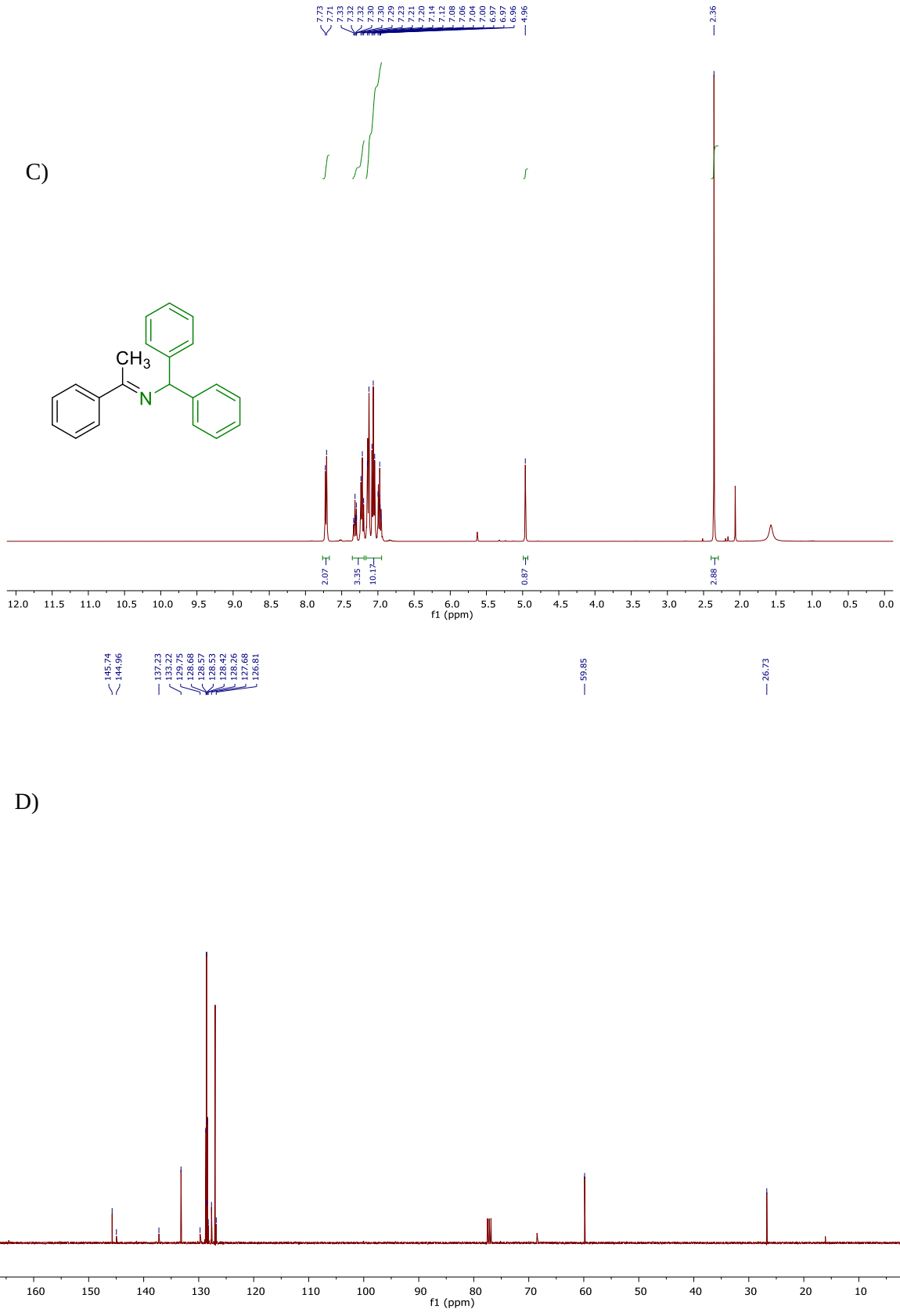
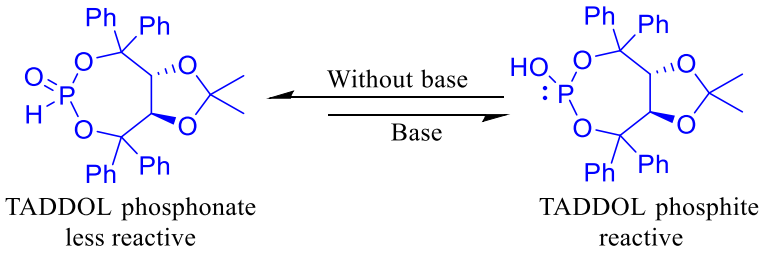


***Figure 18**. N-substituted imine **203c** spectra registered using Jeol 400yh apparatus. A) ^{1}H NMR (400 MHz, $CDCl_3$). B) ^{13}C NMR (101 MHz, $CDCl_3$) C) ^{1}H NMR (400 MHz, $CDCl_3$). D) ^{13}C NMR (101 MHz, $CDCl_3$)*

2.2. Optimization of the hydrophosphonylation reactions using imines 203 and TADDOL-derived H-phosphonate 29

In the first chapter, I effectively used TADDOL-derived *H*-phosphonate **29** with either (*R*,*R*) or (*S*,*S*)-configuration in the hydrophosphonylation of α-amido sulphones, which successfully led to the generation of α-aminophosphonates with satisfactory yields and excellent diastereoselectivity (resulting in a single diastereoisomer in the majority of cases). To broaden the applicability of the (*R*,*R*)-**29** as a phosphorus-containing chiral auxiliary (*R*,*R*)-**29**, I proceeded to evaluate its effectiveness in the asymmetric hydrophosphonylation of *N*-substituted model aldimines **203a-d** in the absence of a base and in dichloromethane. Unfortunately, no reactivity was observed in any of the aldimines tested under these conditions (Table 7, entries 1-4). However, the introduction of Cs_2CO_3 as a base in the reaction setup led to the desired α-aminophosphonates, albeit in moderate yields and with poor diastereoselectivity (Table 7, entries 5-7). It is widely agreed that the *H*-phosphonate nucleophilic species undergo phosphite-phosphonate tautomerization under neutral conditions, leading to the predominance of the less reactive phosphonate form (Scheme 78)[236,237]. This observation explains the lack of reactivity observed when the reaction was carried out without a base. However, when a base is present, it activates the phosphonate form, shifting the equilibrium towards the reactive phosphite. This activation is beneficial in enhancing the overall reactivity of the reaction system.



***Scheme 78**: Equilibrium between the less reactive TADDOL H-phosphonate and reactive TADDOL phosphite*.

Consequently, the activation of the TADDOL-derived *H*-phosphonate facilitates the nucleophilic attack on the electrophilic carbon of the imine, resulting in the formation of the α-aminophosphonates. This mechanistic understanding accounts for the experimental results obtained (Table 7, entries 5-8). It is noteworthy that the diastereoselectivity improves as the size of the substituent on the iminic nitrogen atom increases; however, this improvement comes at the expense of decreased reactivity of the imine. Among the tested imines, imine **203c** demonstrated the most promising outcome in terms of both diastereoselectivity and conversion (Table 7, entry 7). I was able to quickly determine the conversion and diastereoselectivity of

the reactions by registering and examining the ^{31}P NMR spectra of the crude reaction mixtures. The chemical shift of the starting TADDOL-derived *H*-phosphonate (R,R)-**29** (δ_P = -2.90 ppm, in $CDCl_3$) was significantly different from the chemical shifts of the other two signals observed in the ^{31}P NMR spectrum of the crude reaction mixture and corresponding to the reaction product (mixture of two diastereoisomers) (Figure 19). These two signals were assigned to the two diastereoisomers (δ_{major} = 19.31 and δ_{minor} = 18.02 ppm, in $CDCl_3$) of the desired aminophosphonate.

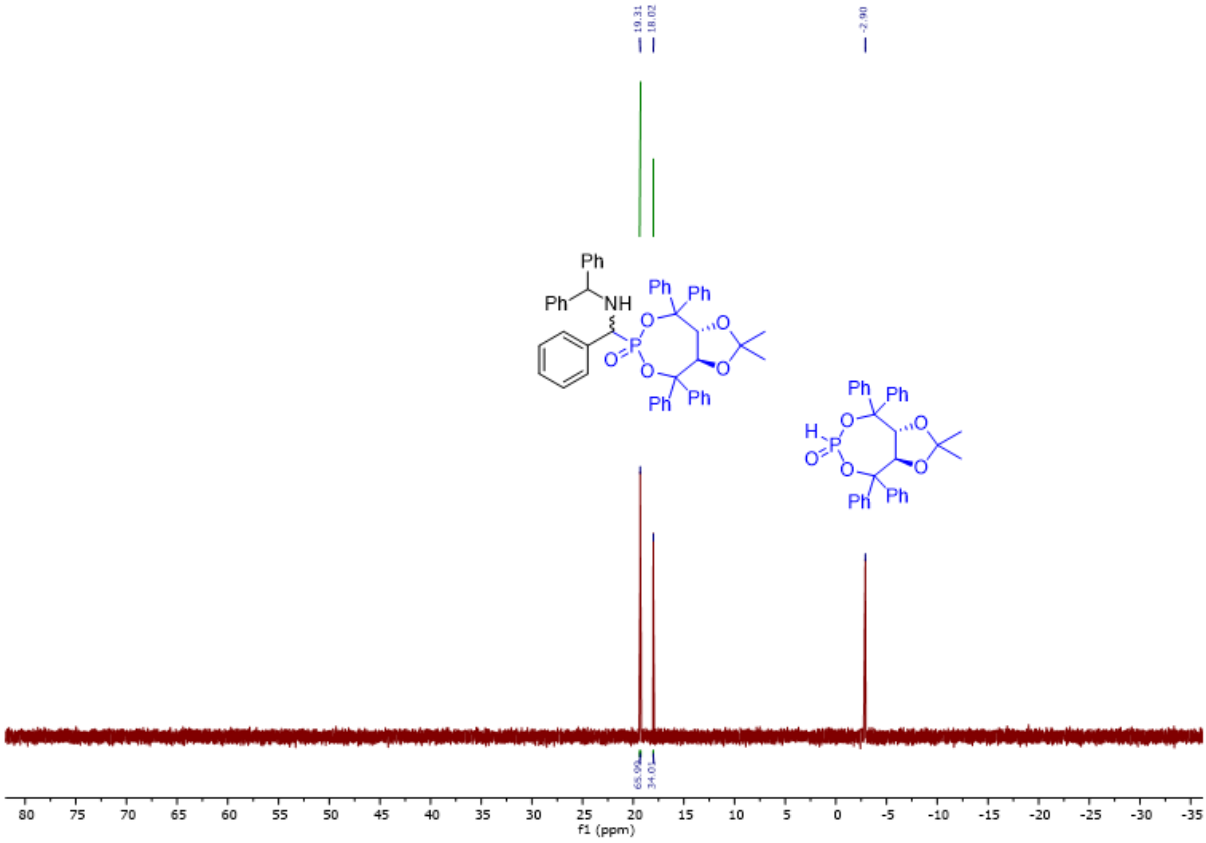
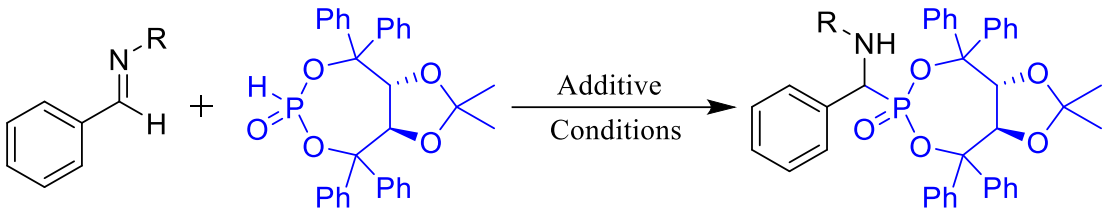


Figure 19. *The ^{31}P NMR (162MHz, $CDCl_3$, Jeol 400yh apparatus) spectrum showing the signal corresponding to the (R, R)-**29** and the obtained pair of diastereoisomers of the desired aminophosphonate (crude reaction mixture from entry 7, Table 7).*

Based on the most promising result, I chose imine **203c** as the model substrate for subsequent optimization of the reaction conditions. I tested different solvents for the reaction, each of which gave reasonable conversion rates. However, the diastereoselectivity remained moderate across all the solvents (Table 7, entries 9-12). Notably, the best result was obtained when toluene and dichloromethane were employed (Table, 7, entries 7 and 12). Subsequently, I thoroughly investigated the effect of various organic bases (Et_3N, pyridine, and quinine) and inorganic bases (K_2CO_3, KOH, and Cs_2CO_3) on the reaction system.

Table 7: Optimization of hydrophosphonylation of aldimines with TADDOL-derived *H*-phosphonate (*R,R*)-**29**.



203 (*R,R*)-**29** **204**

Entry	R	Solvent[a]	Additive[b]	Temp (°C)	Time (h)	Conv[c]. (%)	dr[c] (%)
1	Ph	CH_2Cl_2	-	rt	24	NR	-
2	CH_2Ph	CH_2Cl_2	-	rt	24	NR	-
3	$CH(Ph)_2$	CH_2Cl_2	-	rt	24	NR	-
4	$C(Ph)_3$	CH_2Cl_2	-	rt	24	NR	-
5	Ph	CH_2Cl_2	Cs_2CO_3	rt	24	61	63:37
6	CH_2Ph	CH_2Cl_2	Cs_2CO_3	rt	24	69	62:38
7	$CH(Ph)_2$	CH_2Cl_2	Cs_2CO_3	rt	24	57	66:34
8	$C(Ph)_3$	CH_2Cl_2	Cs_2CO_3	rt	48	18	74:26
9	$CH(Ph)_2$	THF	Cs_2CO_3	rt	24	51	53:47
10	$CH(Ph)_2$	EtOAc	Cs_2CO_3	rt	24	51	53:47
11	$CH(Ph)_2$	CH_3CN	Cs_2CO_3	rt	24	44	50:50
12	$CH(Ph)_2$	Toluene	Cs_2CO_3	rt	24	66	69:31
13	$CH(Ph)_2$	Toluene	K_2CO_3	rt	24	63	64:36
14	$CH(Ph)_2$	Toluene	KOH	rt	24	54	61:39
15	$CH(Ph)_2$	Toluene	Quinine (20 mol%)	rt	24	trace	Nd
16	$CH(Ph)_2$	Toluene	Quinine (20 mol%)	110	10	42	61:39
17	$CH(Ph)_2$	Toluene	Quinine (20 mol%)/Cs_2CO_3	rt	24	75	66:34
18	$CH(Ph)_2$	Toluene	Pyridine	rt	24	NR	-
19	$CH(Ph)_2$	Toluene	Et_3N	rt	24	63	60:40
20	$CH(Ph)_2$	Toluene	Cs_2CO_3	100	10	100	58:42
21	$CH(Ph)_2$	Toluene	Cs_2CO_3	0	72	24	70:30
22	$CH(Ph)_2$	Toluene	$BF_3.EtO_2$	rt	24	33	60:40
23	$CH(Ph)_2$	Toluene	$BF_3.EtO_2$	0 to rt	24	25	64:36
24	$CH(Ph)_2$	Toluene	CuCl	0 to rt	24	trace	nd
25	$CH(Ph)_2$	Toluene	$CuCl_2$	0 to rt	24	trace	nd
26	$CH(Ph)_2$	Toluene	CuI	0 to rt	24	trace	nd

*[a]Gineral conditions: the reaction was performed in 0.80 mL of the solvent on a 0.10 mmol scale of **203** and 0.10 mmol of (R,R)-**29**.[b]The 1.0 equivalent of the additive was used [c]The dr and conversion were determined based on ^{31}P NMR analysis of the crude reaction mixture.*

However, none of these bases improved the diastereoselectivity and the results remained unsatisfactory (Table 7, entries 12-19). In an effort to enhance the diastereoselectivity, I performed the hydrophosphonylation reaction in the presence of Cs_2CO_3 and a catalytic amount of quinine. This modification led to improved reactivity, although the diastereomeric ratio obtained was only moderate (Table 7, entry 17). I have carried out additional experiments to explore the influence of temperature on the reaction outcome. When the reaction was conducted at 100 °C, a 100% conversion was achieved, whereas, at 0 °C, the conversion was lower, with only a 24% conversion. However, regardless of the temperature variation, the diastereoselectivity did not show any significant improvement (Table 7, entries 20–21).

Inspired by the work of Miao's research group, who successfully employed the optically pure enantiomer of P-chiral (−)-O-(1R,2S,5R)-menthyl phenylphosphinate (R_P)-**87** in the presence of boron trifloride etherate ($BF_3.EtO_2$) in the addition reaction to *O*-pivaloylated N-galactosylimines **110**, to afford α-aminophosphinates **111** with high diastereoselectivities (up to >95:5 dr) and yields reaching up to 91% (Scheme 31)[134]. The authors stated that due to the low nucleophilicity of the P-H species and the moderate electrophilicity of the imines, Lewis acid is needed to activate these compounds and facilitate the completion of the reaction. In my case however the use $BF_3.EtO_2$ resulted in lower yields and moderate diastereoselectivity (Table 7, entries 22-23). Additionally, I screened other Lewis acids such as copper II chloride ($CuCl_2$), copper I chloride (CuCl), and copper I iodide (CuI) in the hydrophosphonylation reaction. Regrettably, this approach resulted in the product with poor conversions (Table 7, entries 24-26). Finally, in an effort to improve the diastereomeric ratio in the reaction product, I carried out several attempts to enrich one of the diastereoisomers in the crude reaction mixture through methods such as recrystallization or column chromatography. However, my attempts proved to be only partially successful. As shown in the ^{31}P NMR spectral (Table 7, entry 20 with 100% conversion) where I was able to improve the dr from initial 58:42 to 62:38 through chromatography and repeated crystallization (Figure 20).

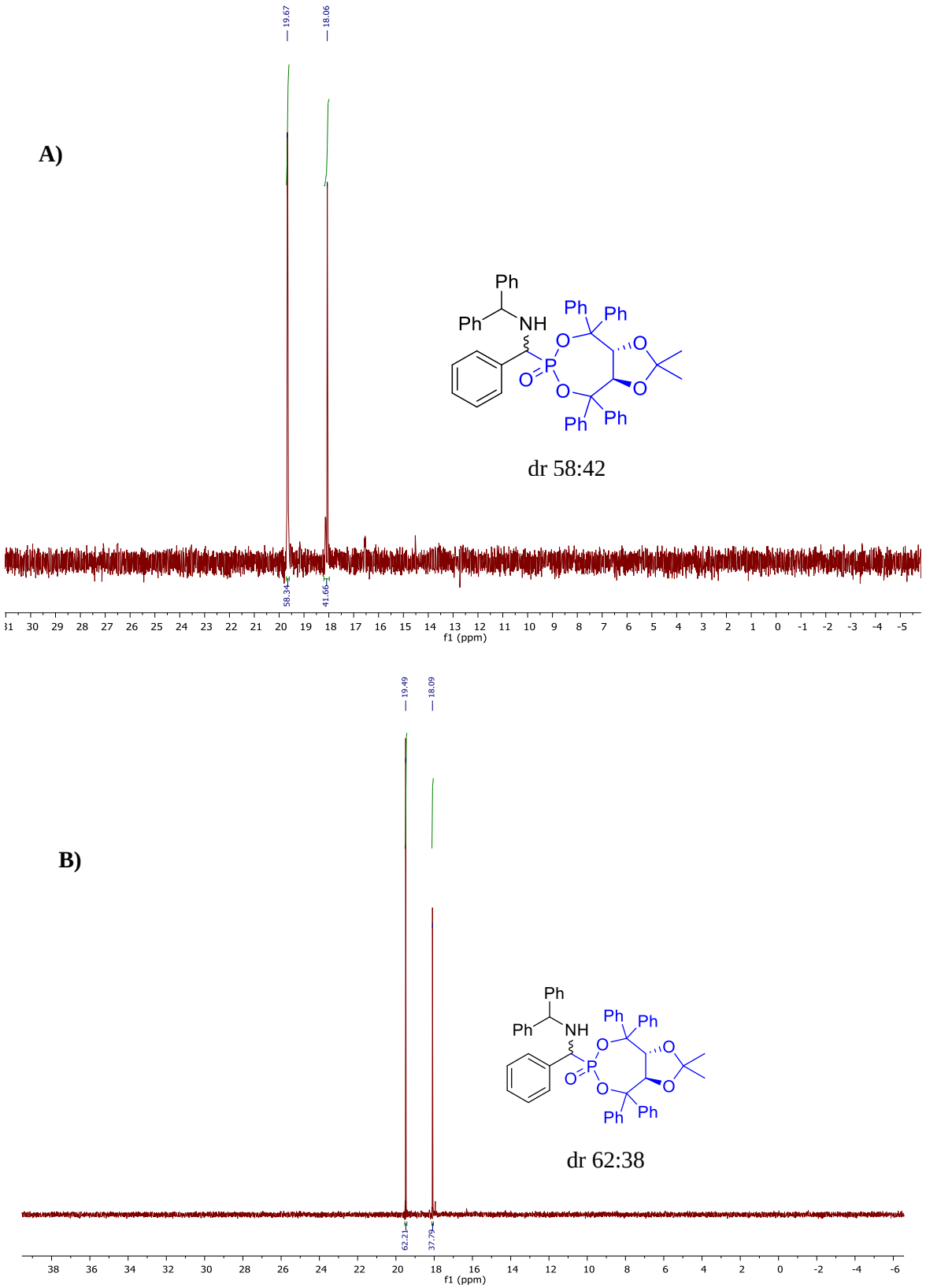
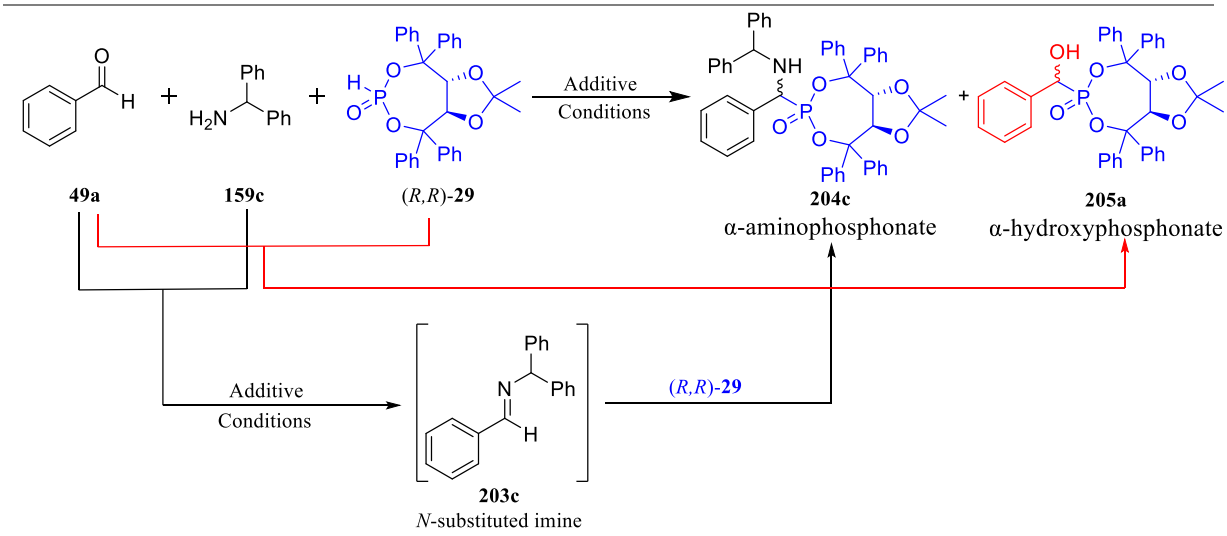


Figure 20. *^{31}P NMR (162MHz, $CDCl_3$) spectra as registered using Jeol 400yh apparatus showing A) crude reaction mixture B) The product after purification. entry 20 Table 7.*

In my continuous pursuit of enhancing the diastereoselectivity of the reaction system, I also explored a one-pot protocol involving the direct condensation of the aldehyde,

benzhydrylamine **159**, and TADDOL *H*-phosphonate **29**. The objective was to generate the *N*-substituted imine **203c** *in situ*, which would subsequently undergo hydrophosphonylation with (*R,R*)-**29** to give the α-aminophosphonate **204c** (Table 8). When the reaction was conducted without a base at 110°C in toluene, the product was obtained with moderate conversion but poor diastereoselectivity (Table 8, entry 1). Considering this, additives such as bases and Lewis acid were examined at the same temperature, and the reaction showed high reactivity with all the tested additives. However, the diastereoselectivity did not improve despite the increase in reactivity (Table 8, entries 2-4).

Table 8. Optimizations of one-pot three-component reaction of aldehyde, benzhydrylamine **159** and TADDOL derived H-phosphonate (*R,R*)-**29**.



Entry	Solvent	Additive[b]	Temp (°C)	Time (h)	Conv[c]. (%)	dr[c] 204c	dr[c] 205a
1	Toluene	-	110	8	84	50:50	0
2	Toluene	Cs_2CO_3	110	8	100	55:46	0
3	Toluene	Et_3N	110	8	100	57:43	0
4	Toluene	$BF_3.EtO_2$	110	8	99	56:46	0
5	Toluene	Quinine (20 mol%)	110	8	100	62:38	-
6	Toluene	-	rt	24	78	61:28	10:1
7	Toluene	-	-30	35	100	0	93:7
8	Toluene	Quinine (20 mol%)	rt	24	100	0	90:10

*[a]Reaction conditions: reactions were performed in 0.80 mL of the solvent on 0.10 mmol of **49**, 0.10 mmol of **159c,** and 0.10 mmol of (R,R)-**29**.[b]The 1.0 equivalent of the base (unless otherwise stated). [c]The dr and conversion were determined based on the analysis of the ^{31}P NMR spectra of the crude reaction mixture.*

I was hoping that at least the presence of chiral quinine could play a dual role as a catalyst and as a Brønsted base, thereby facilitating the attainment of high selectivity. Unfortunately, under

the same experimental conditions at 110 °C, the reaction proceeded with 100% conversion albeit with low diastereoselectivity (Table 8, entry 5 and Figure 21).

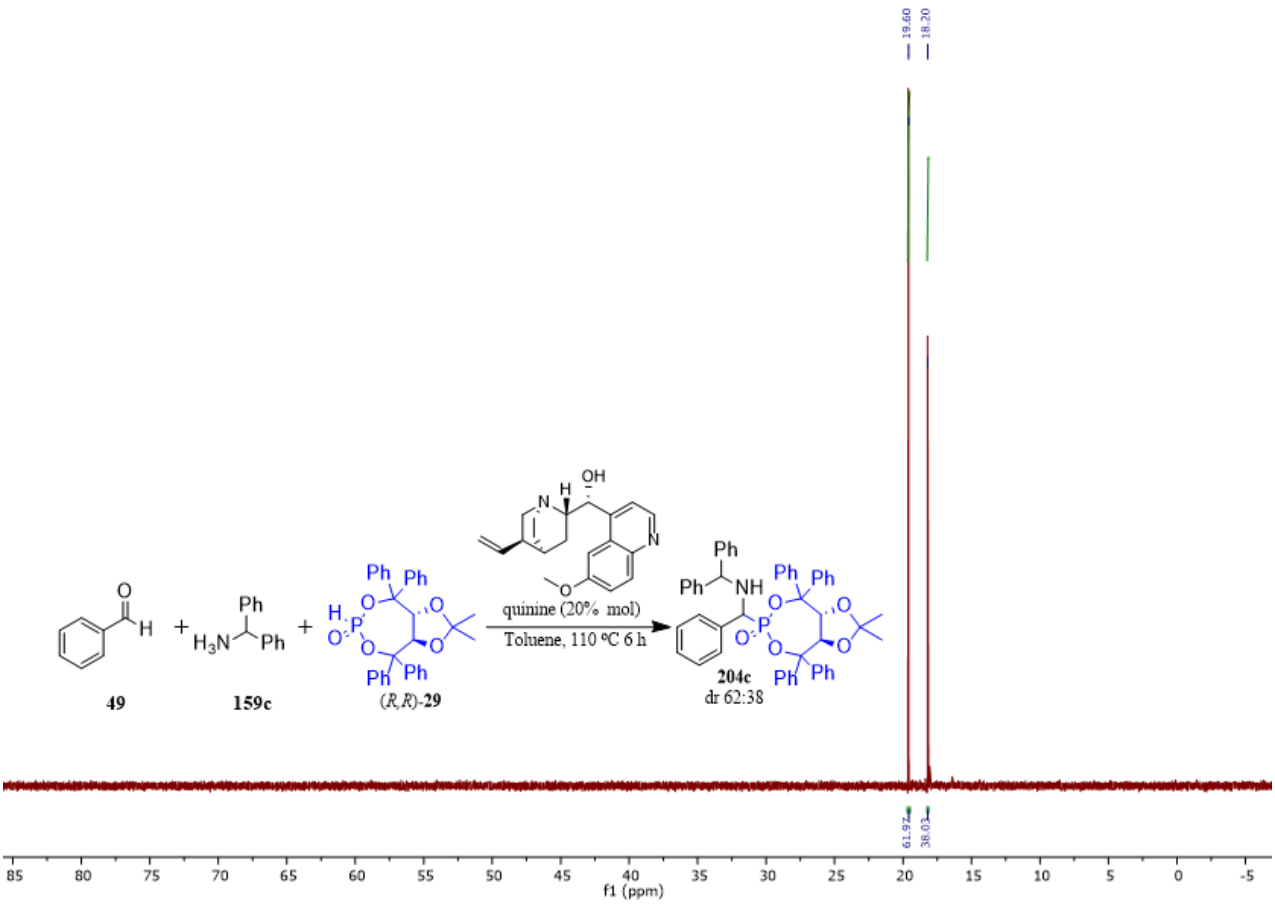


Figure 21. *^{31}P NMR (162MHz, $CDCl_3$) spectrum showing the one-pot reaction of entry 5 Table 8 as registered using Jeol 400yh apparatus.*

By lowering the temperature from 110 °C to room temperature and performing the reaction without a base, I investigated the effect on the diastereoselectivity of the system. During the investigation, I discovered that the condensation process yielded both α-aminophosphonate **204c** and α-hydroxyphosphonate **205**, as evidenced by the ^{31}P NMR analysis by analysis of the crude reaction mixture. The signals at chemical shifts of δ_P = 18.49 ppm and δ_P = 17.08 ppm corresponded to the major and minor diastereoisomers of α-aminophosphonate **204c**, whereas the signals at δ_P =16.98 ppm and δ_P = 15.32 ppm represented the major and minor diastereoisomers of α-hydroxyphosphonate **205** (Figure 22, Table 8, entry 6). Additionally, the HR-MS analysis confirmed the presence of both products in the crude reaction mixture. This result was predictable and could be attributed to the challenge associated with Kabachnik-Fields reaction due to the simultaneous presence of two nucleophiles: the benzhydrylamine and the *H*-

phosphonate derived from TADDOL. These nucleophiles compete for the electrophilic carbon centre of the aldehyde, resulting in the formation of aminophosphonate as the desired product, along with the generation of hydroxyphosphonate as a side product[65,66].

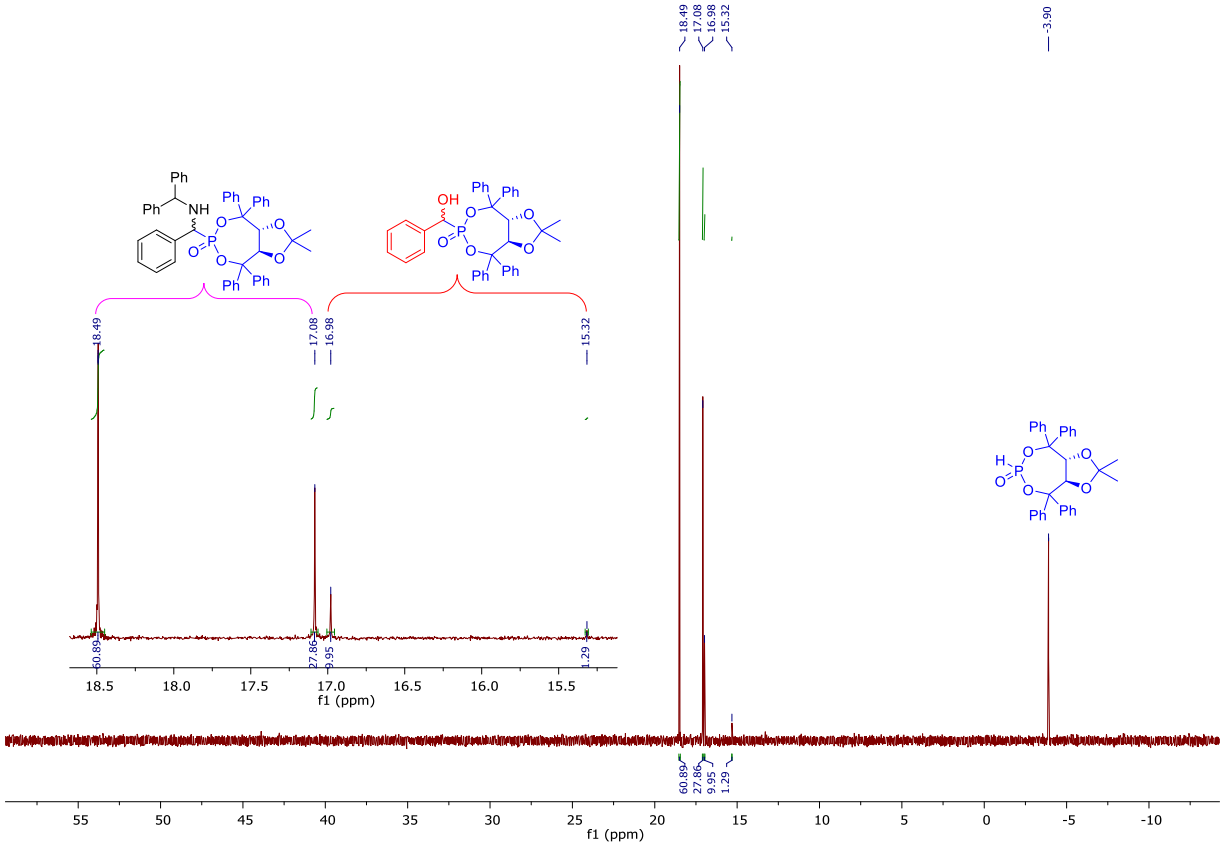


Figure 22. *^{31}P NMR (162MHz, $CDCl_3$ Jeol 400hy apparatus) spectrum of the crude reaction mixture of the one-pot reaction between benzhydrylamine, benzaldehyde and TADDOL-derived H-phoshonate (Table 8, entry 6).*

When this reaction was carried out at -30 ^{o}C, hydroxyphosphonate rather than aminophosphonate was formed (Table 8, entry 7, Figure 24). This result suggests that at a lower temperature, the amine assumes the role of a base, activating the nucleophilicity of the *H*-phosphonate, and subsequent addition to the aldehyde results in the formation of the hydroxyphosphonate (Table 8, entry 7 and Figure 23), rather than forming the imine *in situ* by reaction with the aldehyde.

Finally, at room temperature, in a one-pot condensation, the quinine facilitates the activation of the H-P species for nucleophilic addition, exclusively leading to the formation of the hydroxyphosphonate as seen from the NMR and HR-MS analysis of the crude reaction mixture. However, the benzhydrylamine remained unreactive in the system and was subsequently recovered by column chromatography (Table 8, entry 8). More detailed information on this reaction pathway will be the focus of chapter three, which is devoted to the study of the hydrophosphonylation of carbonyl compounds.

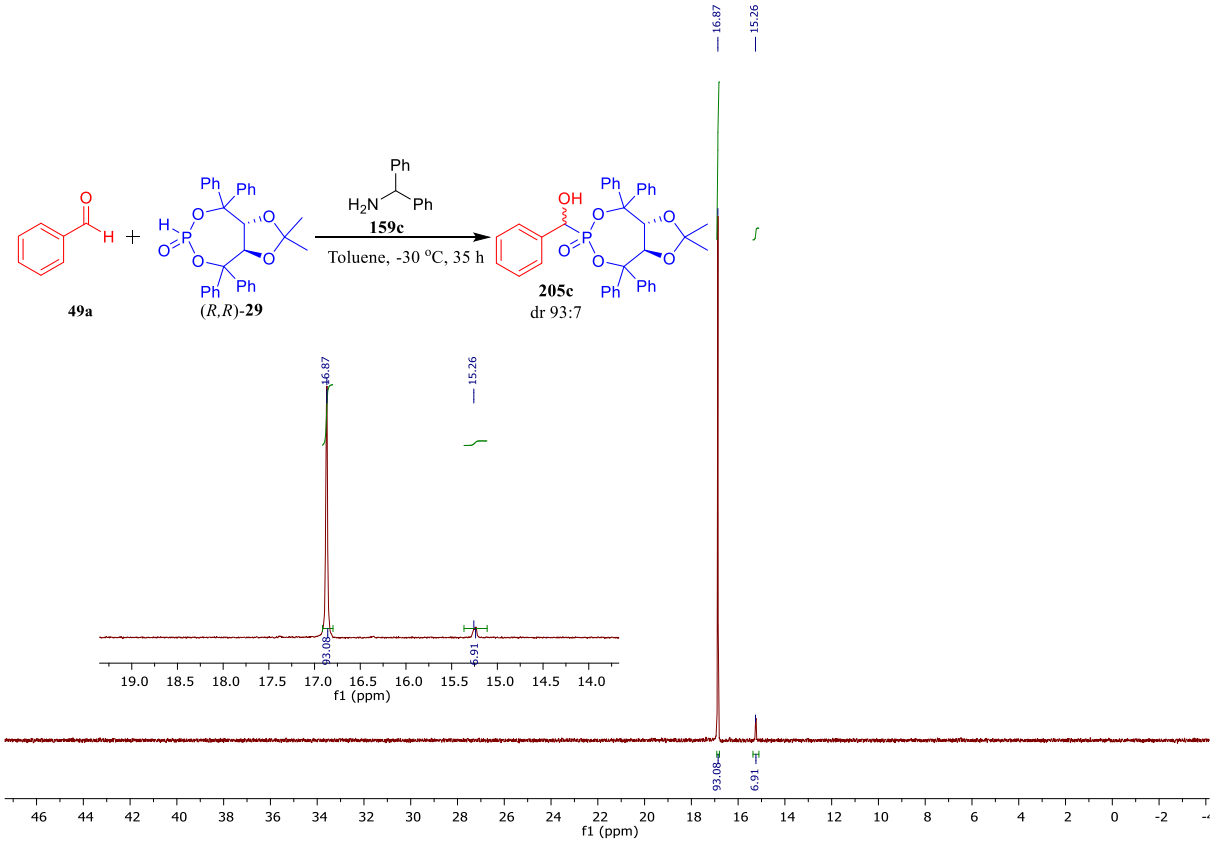
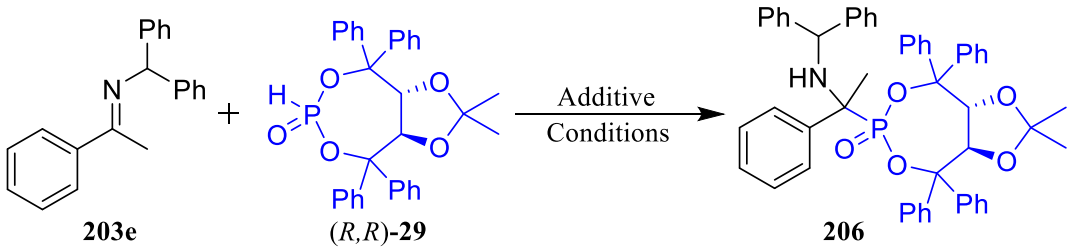


Figure 23. *^{31}P NMR (162MHz, $CDCl_3$) spectrum showing the one-pot reaction of entry 8 Table 8 as registered using Jeol 400yh apparatus.*

The hydrophosphonylation of ketimine **203e** with (*R*,*R*)-**29** at room temperature without a base showed no reactivity (Table 9, entry 1). Upon performing the aza-Pudovik reaction at 110°C under the influence of different bases, the outcome was the formation of the quaternary α-aminophosphonate, albeit with low reactivity (conversion ranging from 14% to 28%) and unsatisfactory diastereoselectivity (Table 9, entries 3-6). This low reactivity observed in the reaction could be attributed to two key factors. Firstly, ketimine **203e** may have a relatively low electrophilic nature due to the electronic effect of the substituents attached to the nitrogen atom. This low electrophilicity reduces the susceptibility of the ketimine to undergo the hydrophosphonylation reaction. Secondly, the steric hindrance resulting from the structural arrangement of the ketimine can be a formidable obstacle to a successful nucleophilic attack. The spatial congestion around the C=N bond hinders the approach of the bulky *H*-phosphonate **29**, slowing the reaction down and resulting in lower conversion rates observed. This steric hindrance may also play a key role in the low diastereoselectivity observed in the product, although I was hoping that the increased steric hindrance could also act in favour of higher diasteroselectivity of the reaction.

Table 9. Optimizations of hydrophosphonylation of ketimines with TADDOL derived H-phosphonate (*R,R)*-**29**.

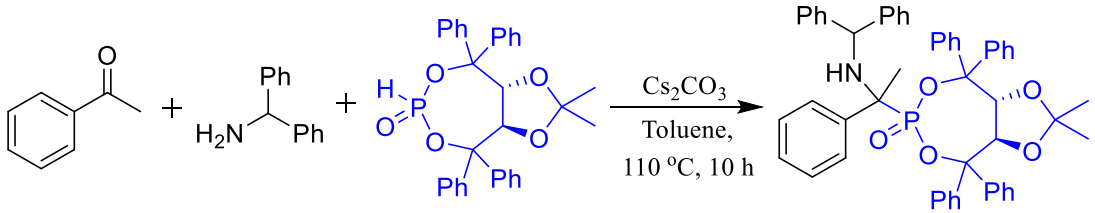


203e (*R,R*)-**29** **206**

Entry	Solvent[a]	Additive[b]	Temp (°C)	Time (h)	Conv[c]. (%)	dr[c]
1	Toluene	-	rt	24	-	-
2	Toluene	Cs_2CO_3	rt	24	trace	nd
3	Toluene	Cs_2CO_3	110	10	21	61:40
4	Toluene	Et_3N	110	10	19	62:38
5	Toluene	Quinine	110	10	14	63:37
6	Toluene	Quinine (20 mol%)/Cs_2CO_3	110	10	28	63:37

[a]Reaction conditions: reactions were performed in 0.60 mL of the solvent on 0.10 mmol of ***203e*** *and 0.10mmol of (R,R)-****29****.[b]The 1.0 equivalent of the base was used. [c]The dr and conversion were determined based on* ^{31}P *NMR analysis of the crude reaction mixture, nd stands for not determined.*

Finally, I also tested the one-pot condensation of simple ketone **207** with benzhydrylamine **159** and TADDOL-derived *H*-phosphonate **29** in the presence of Cs_2CO_3 at the boiling point of toluene. After 10h, the analysis of the crude reaction mixture revealed the formation quarternary α-aminophosphonate **207** albeit with poor yield and moderate diastereoselectivity (Scheme 79). I attempted multiple strategies to enrich one of the diastereoisomers in the product by employing techniques such as crystallization or chromatography. Unfortunately, my endeavors were fruitless due to the closeness of the two diastereoisomers, as evident from the TLC plate analysis.



207 **159c** (*R,R*)-**29** **206**
26% conversion
dr 64:36

Scheme 79*. The one-pot reaction of acetophenone* ***207*** *with benzhydrylamine* ***159c*** *and (R,R)-****29****.*

3.0. Conclusions

In conclusion, the research presented in this chapter demonstrated the attempts I made in utilizing TADDOL-derived *H*-phosphonate **29** as a chiral auxiliary in the development of simple diastereoselective method for the hydrophosphonylation of *N*-substituted imines. The main idea revolved around utilizing non-chiral imines with substituents of different sizes on the nitrogen atom. This approach aimed to study how the steric hindrance caused by these substituents could affect the diastereoselectivity of the reaction.

In general, the best results were observed when employing a benzhydryl group as the protective moiety for the nitrogen atom. The reactions led to the formation of α-aminophosphonates with significant conversions (up to 100%) but moderate diastereoselectivity (70:30 dr in the best case).

Various strategies were employed to enhance the diastereoselectivity, encompassing the screening of different solvents, organic and inorganic bases, variations in temperature, catalyst types, and various Lewis acids. Additionally, I made attempts to enrich the post-reaction mixture in one of the diastereoisomers by chromatography and/or crystallization, taking advantage of the presence of the chiral auxiliary on the phosphorus atom, which could potentially favour the separation of the diastereoisomers. Unfortunately, all these attempts resulted in rather unsatisfactory outcomes in terms of diastereoselectivity.

Finally, I investigated a one-pot protocol in which aldehydes, benzhydrylamine, and TADDOL *H*-phosphonate were directly condensed. While this approach showed promise in terms of reactivity, the diastereoselectivity was still poor (100% conversion, 62:38 dr). Although during this study, I observed the formation of undesired hydroxyphosphonate as a by-product due to the coexistence of two competing nucleophiles for one electrophilic center, the diastereoselectivity of the latter product (100% conversion, 97:3 dr) gave promising results for further investigations in the preparation of hydroxyphosphonates (discussed in more detail in chapter three of the dissertation).

Furthermore, I examined the hydrophosphonylation of ketimies, however this reaction suffered from low conversions and low diastereoselectivity. Also, in this case my attempts to enrich the reaction product in one of the diastereoisomers by both chromatography and crystallization techniques were unsuccessful.

Chapter Three

Asymmetric hydrophosphonylation of carbonyl compounds

1.0 Introduction

Asymmetric hydrophosphonylation of carbonyl compounds (aldehydes and ketones), also known as the Pudovik reaction, is a robust and straightforward approach for the synthesis of optically active α-hydroxyphosphonates and their corresponding α-hydroxyphosphonic acids[14,94,238,239]. These compounds exhibit exceptional biological and pharmaceutical properties, including potent inhibition of the aspartyl protease renin (e.g., tripeptidic α-hydroxyphosphonate **I**[240]), function as antibiotics (as demonstrated by fosfazinomycin A **II**[241] and valinophos **IV**[242]), act as growth inhibitors for Plasmodium falciparum, the malaria-causing parasite (as seen with acyclonucleoside phosphonate **III**[243]), and possess insecticidal properties as demonstrated by trichlorfon **V**[244] (Figure 24).

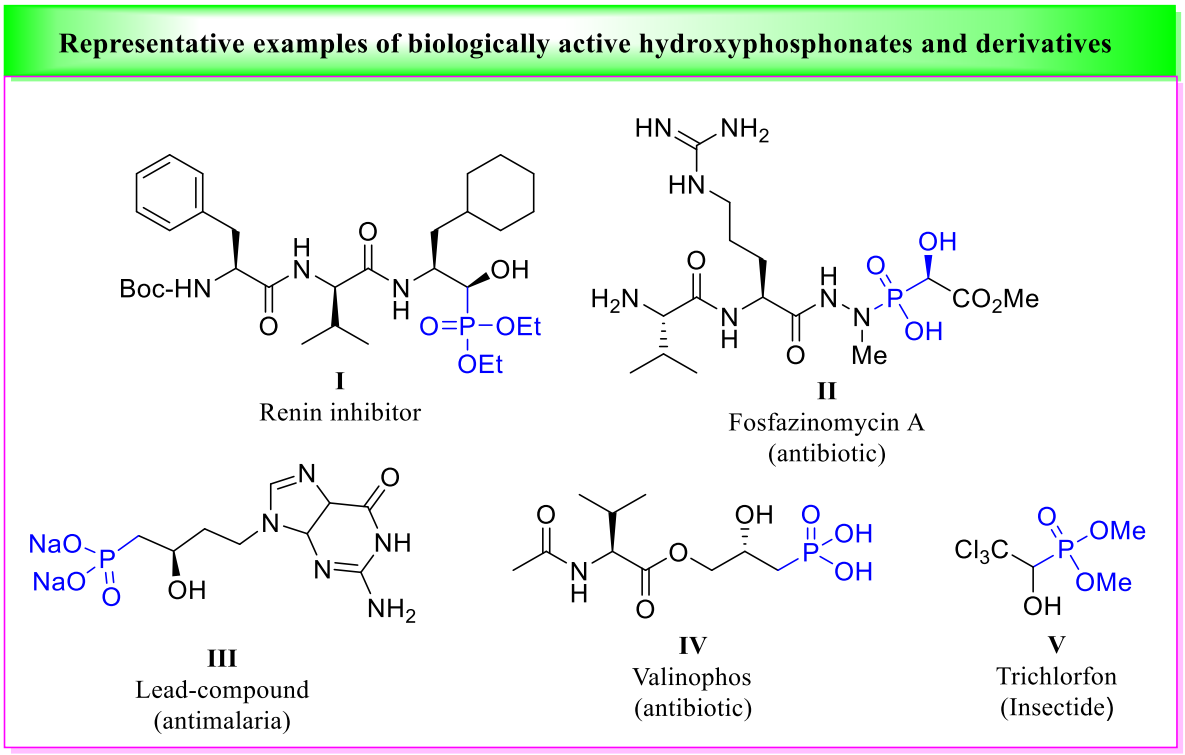


Figure 24. *Representative examples showing the biological activity of selected hydroxyphosphonates and their derivatives.*

Furthermore, hydroxyphosphonates and their derivatives find utility as valuable intermediates in the synthesis of intricate molecules through diverse post-transformation processes[245]. For example, *O*-allylation of these compounds results in intermediates amenable to facile isomerization/Claisen rearrangement, or subsequent ring-closing metathesis[246]. Another transformation involves amination, wherein they react with primary amines to produce α-aminophosphonates and their corresponding α-aminophosphonic acids[247]. Additionally, these

compounds can undergo phospha-Brook rearrangement[248], alkylation[249], acylation[250], as well as reduction[251], oxidation to ketophosphonates[252], and halogenation[253] reactions (Figure 25).

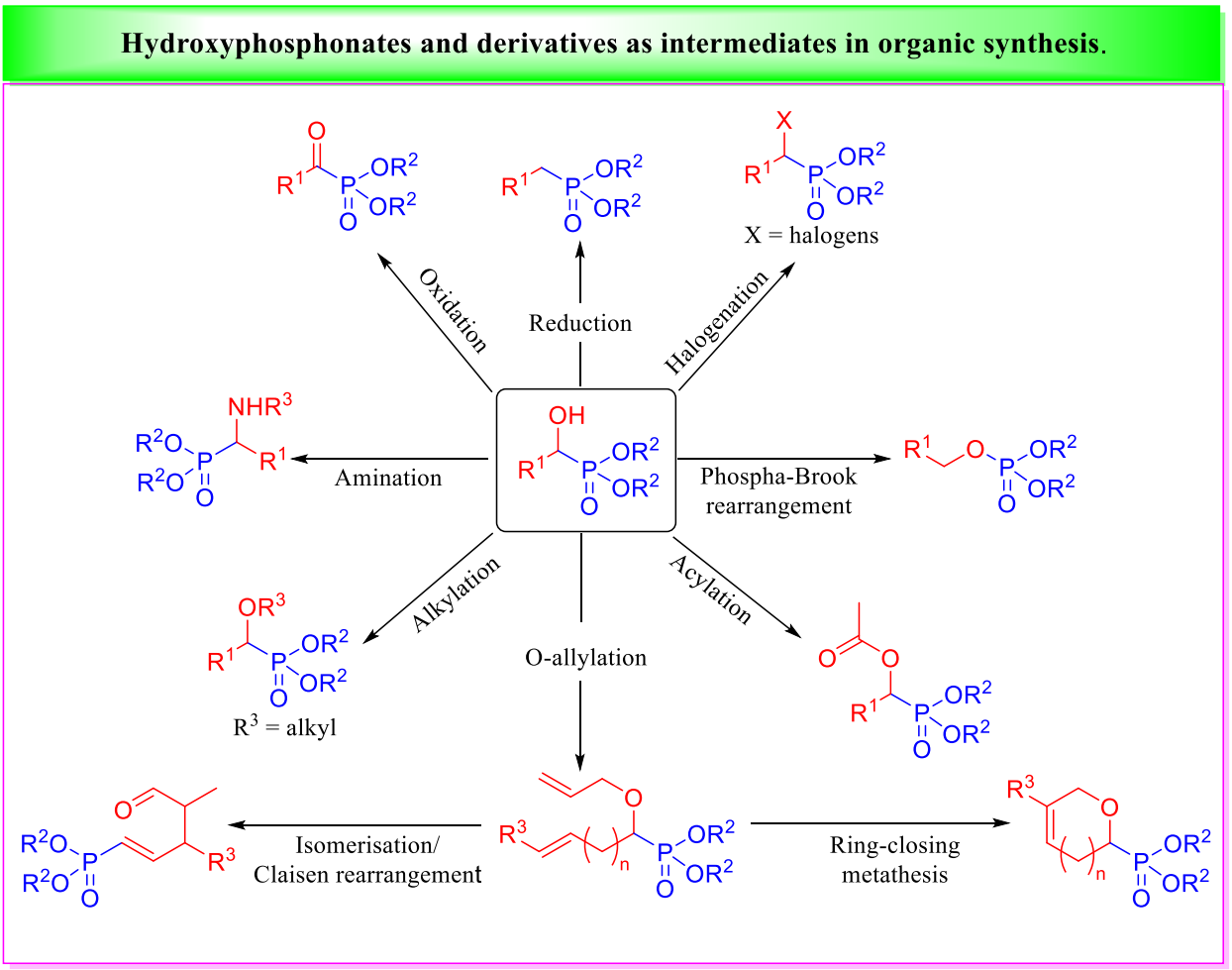
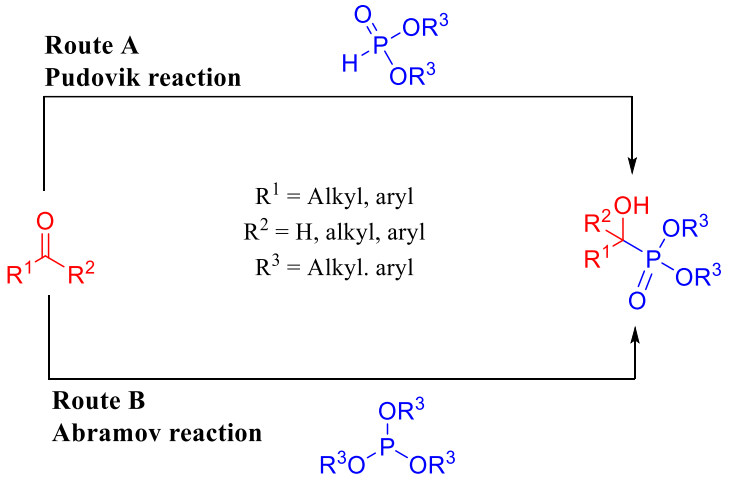


Figure 25. *Selected applications of hydroxyphosphonates and their derivatives as intermediates in the preparation of diverse molecular structures.*

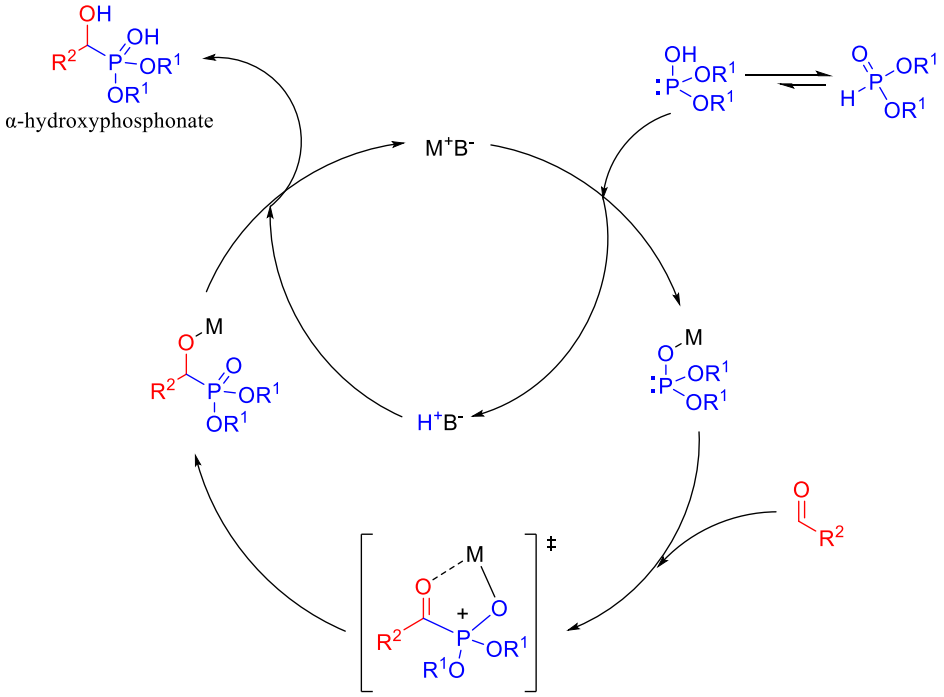
It is important to mention that the absolute configuration of the carbon attached to the hydroxy group in the hydroxyphosphonates plays a crucial role in their pharmaceutical and biological activity[254]. As a result, over the years, the synthesis of hydroxyphosphonates and their derivatives with precise stereochemistry has captured the attention of organic chemists worldwide, resulting in the development of several methodologies. However, the hydrophosphonylation of carbonyl compounds, especially aldehydes, and ketones, using nucleophilic agents such as *H*-phosphonates, predominantly catalyzed by bases although a few acid-catalyzed variations exist, has prevailed as a significant route for the preparation of α-hydroxyphosphonates and their derivatives (known as the Pudovik reaction) (Scheme 80, rounte A). The general mechanism of the Pudovik reaction is presented on Scheme 81, and it

involves the activation of the *H*-phosphonate and shifting the tautomeric equilibrium towards more nucleophilic phosphite form with free electron pair at the P atom.



Scheme 80. *Most common synthetic pathway for accessing α-hydroxyphosphonates*

Their synthesis can also be achieved through an alternative method, which involves the condensation of carbonyl compounds with trialkyl/aryl phosphite in the presence of acid catalysts, and this approach is commonly known as the Abramov reaction (Scheme 80, route B). These two methods represent the dominant ways of synthesizing this class of compounds. Although other methods such as the reaction of α-ketophosphonates with Grignard reagent[255] or organometallic compounds[255,256], as well as the oxidation of α-alkyphosphonates[257,258] have led to the formation α -hydroxyphosphonates.



Scheme 81. *The general concept of the catalytic cycle of Pudovik reaction.*

1.1. Pudovik reaction

In this chapter, I will explore recent progress regarding the preparation of α-hydroxyphosphonates in an asymmetric manner using the Pudovik reaction, wherein the introduction of metal complexes[25,259–265], organocatalysts[238,266–273], or chiral auxiliaries[94,95,126,141,142,144–146,254] leads to the induction of stereoselectivity. The general mechanism of the Pudovik reaction involves the use of metal complexes, catalysts, or reagents to either transform the phosphonate tautomer into active phosphite or to activate the electrophilicity of the carbonyl compounds or the simultaneous activation of both the carbonyl compound and the phosphorus-nucleophile leading to the catalytic cycle demonstrated in Scheme 81. However, the general problems encountered with the Pudovik reaction are the occurrence of side reactions because of retro-hydrophosphonylation and phospha-Brook rearrangement (Figure 26). These problems usually arise in the nucleophilic addition of *H*-phosphonates to ketones, presumably due to the steric hindrance effect between the $P(O)(OR)_2$ group of the nucleophile and the R^2 and R^3 moieties of the ketone in the formed alkoxide intermediate[270]. Also, since the P-C bond formation is reversible, the presence of an alkoxide ion adjacent to the phosphorus atom aids in the cleavage of the P-C bond leading to the observed retro-reaction (Figure 26).

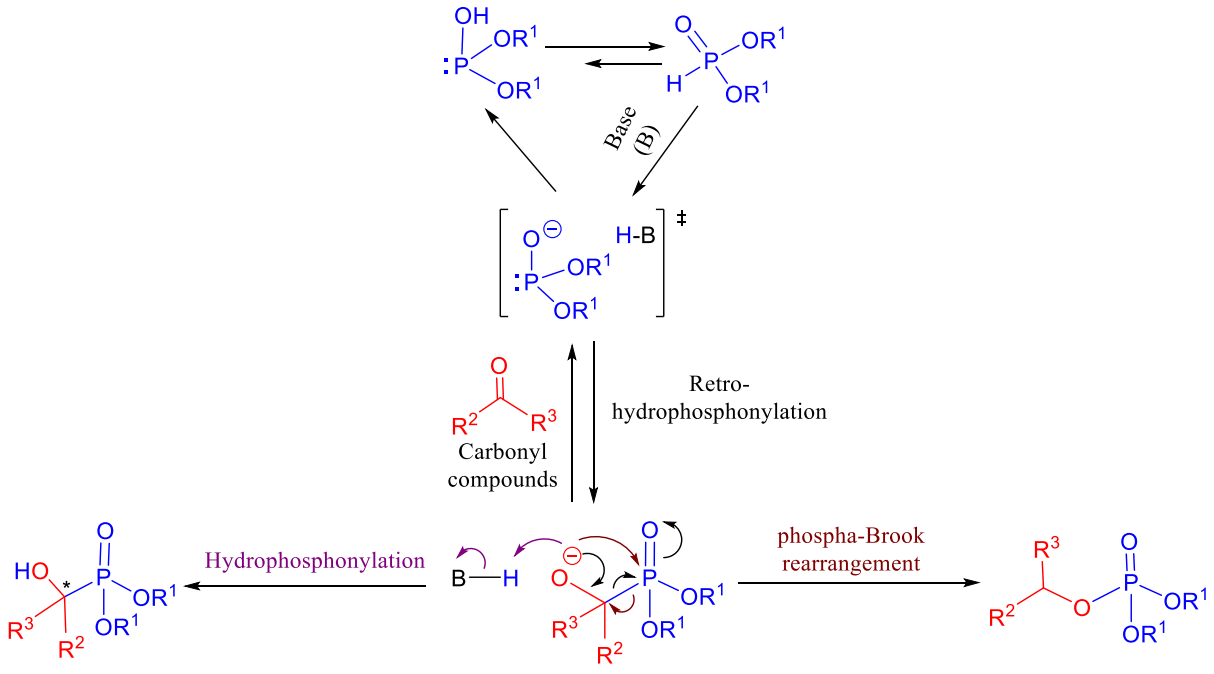


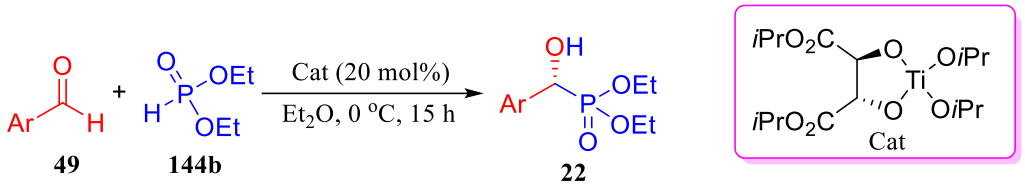
***Figure 26**. General problems encountered with hydrophosphonylation of carbonyl compounds.*

Therefore, rapid protonation of the alkoxide ion in the base-catalyzed hydrophosphonylation is essential to prevent the undesired retro-hydrophosphonylation. Protonation also helps to avoid

the intramolecular nucleophilic attack of the oxyanion on the phosphorus atom, which causes the phospha-Brook rearrangement. Therefore, the appropriate choice of base, catalyst, and reagent with high proton transfer capability is crucial in controlling the reaction pathway toward the formation of the hydrophosphonylation products.

1.1.1. Pudovik reaction catalyzed with metal complexes

In 1993, Shibuya and his research team reported the first transition metal catalyzed asymmetric Pudovik reaction using Sharpless titanium (IV) tartrate as a catalyst in the hydrophosphonylation of aromatic aldehydes with diethyl phosphonate[259]. The α-hydrophosphonates **22** were obtained with satisfactory yields (up to 76%) and moderate enantioselectivities (53% ee in the best case) with (*R*)-configuration at the carbon attached to the hydroxyl group (Scheme 82).

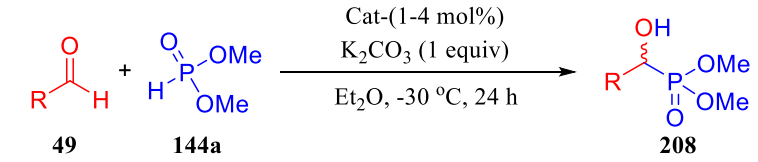


49 **144b** **22**

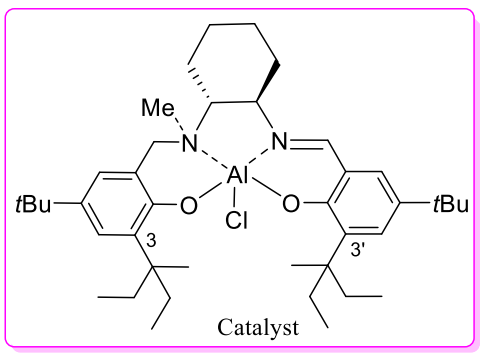
(*R*)-**22a,** Ar = C_6H_5, 75% yield, 53% ee
(*R*)-**22b,** Ar = 4-ClC_6H_4, 76% yield, 52% ee

Scheme 82*. Enantioselective hydrophosphonylation of aromatic aldehydes in the presence of titanium tartrate-selected examples.*

In 2010, Katsuki's group reported a catalyzed potassium carbonate (K_2CO_3) enhanced aluminum-salalen enantioselective Pudovik reaction of both conjugated and non-conjugated aldehydes **49** coupled with dimethyl *H*-phosphonate **144a** in diethyl ether (Scheme 83)[260].



49 **144a** **208**

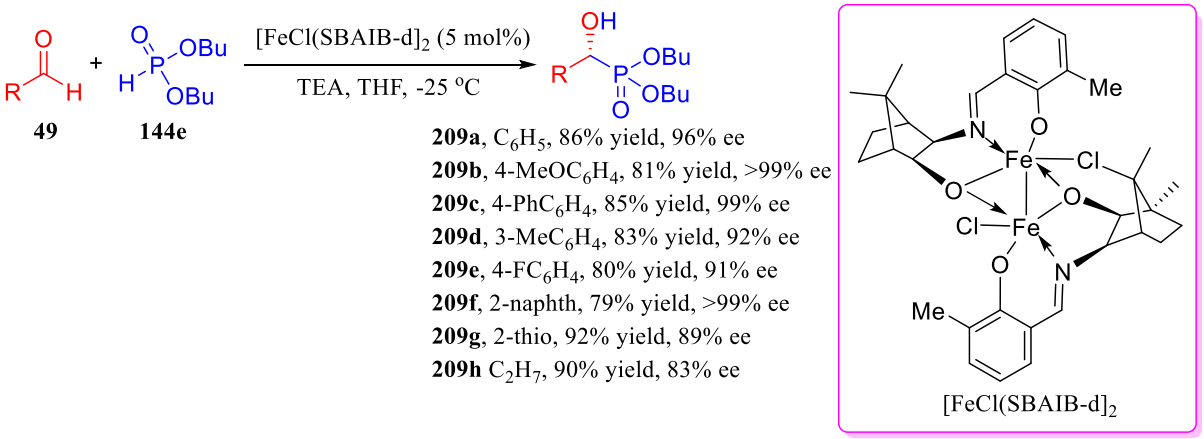


208a, R = 4-$MeOC_6H_4$, 98% yield, 93% ee
208b, R = 2-ClC_6H_4, 94% yield, 97% ee
208c, R = (*E*)-PhCH=CH, 97% yield, 95% ee
208d, R = $PhCH_2CH_2$, 93% yield, 97% ee
208e, R = nC_7H_{15}, 90% yield, 996% ee
208f, R = $CH(CH_3)_2$, 96% yield, 96% ee

Scheme 83. *Enantioselective hydrophosphonylation of conjugated and non-conjugated aldehydes catalyzed by aluminum-salalen complex- selected examples.*

The presence of the base helped to overcome the low reactivity encountered in their previous work[261] by enhancing the reactivity of the hydrophosphonylation reaction and reducing the catalyst loading (from 10 mol% to 1-4 mol%) towards the formation of the products **208** with satisfactory yields and excellent enantioselectivities (93-98% ee)[260]. No information was given regarding the absolute configuration of the obtained products.

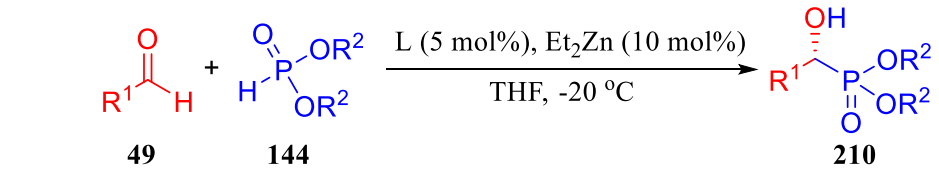
Describing a highly enantioselective Pudovik reaction, Chen et al. presented the use of newly synthesized camphor-based Fe-(III)-Schiff base complexes derived from aminoisoborneol. Employing this air- and moisture-stable catalyst, they achieved a smooth hydrophosphonylation reaction of various aldehydes (aliphatic, aromatic, heteroaromatic, and polycyclic aromatic) with dibutyl *H*-phosphonate in THF (Scheme 84)[262]. The reaction resulted in the formation of (*R*)-α-hydroxyphosphonates **209** with yields ranging between 70% and 99% and high enantioselectivities (79–99% ee). This approach brings about several advantages, including the utility of an easily synthesized catalyst that showed high asymmetric induction, minimal catalyst loading, cost-effective starting materials, and simple aerobic reaction conditions. However, it's worth noting that the protocol has a longer reaction time, particularly when dealing with aliphatic aldehydes (up to 96 hours)[262].

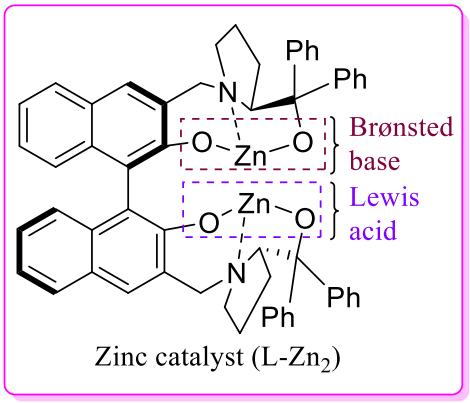


Scheme 84. *Enantioselective hydrophosphonylation of aldehydes catalyzed by iron complex-representative examples.*

Enantioselective hydrophosphonylation of aldehydes with dialkyl *H*-phosphonate catalyzed by a C2-symmetric chiral homobimetallic Zn complex in THF was reported by Da et al.[263]. The incorporation of two identical alkoxide groups (each serving a distinct purpose – one as a Brønsted base and the other as a Lewis acid) within its structure enables this Zn complex catalyst to exhibit dual functionality. The Brønsted base component plays a role in activating the nucleophilicity of the dialkyl *H*-phosphonate **144**, while the Lewis acid activates the electrophilicity of the aldehydes **49**. Consequently, the Pudovik reaction was catalyzed,

resulting in the formation of α-hydroxyphosphonates **210** with high yields (up to 99%) and moderate to excellent enantioselectivities ranging from 36% to 94% ee. The absolute configuration of the newly formed α-carbon was determined to be *R* (Scheme 85).



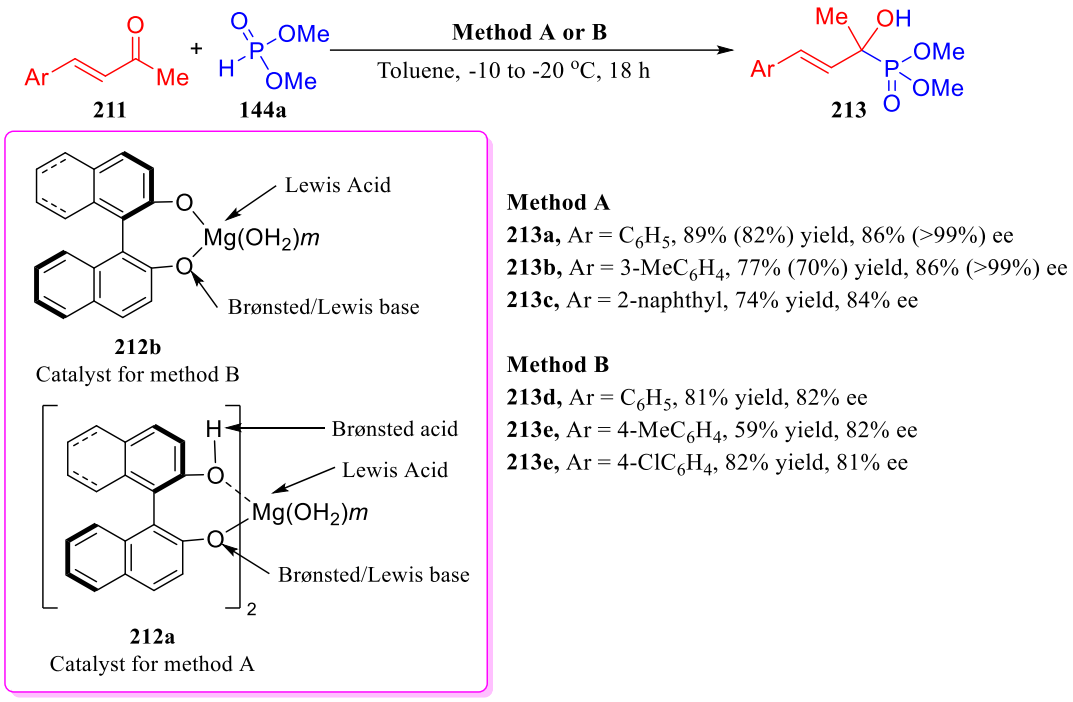


210a, $R^1 = C_6H_5$, R^2 = Me, 71% yield, 81% ee
210b, R^1 = 2-$MeOC_6H_4$, R^2 = Me, 89% yield, 81% ee
210c, R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = Me, 70% yield, 81% ee
210d, R^1 = 2,4-$Me_2C_6H_3$, R^2 = Me, 99% yield, 85% ee
210e, R^1 = 4-$NO_2C_6H_4$, R^2 = Me, 99% yield, 51% ee
210f, R^1 = 1-naphthyl, R^2 = Me, 99% yield, 84% ee
210g, R^1 = (*E*)-PhCH=CH, R^2 = Me, 83% yield, 53% ee
210h, $R^1 = CH_3(CH_2)_8$, R^2 = Me, 58% yield, 36% ee
210i, R^1 = 2,4,6-$Me_3C_6H_2$, R^2 = Et, 98% yield, 893% ee

Scheme 85. *Enantioselective hydrophosphonylation of aldehydes catalyzed by chiral homobimetallic zinc complex-representative examples.*

Ishihara's group also reported the use of the *in-situ* generated chiral magnesium(II) binaphtholate aqua complex **212a** (derived from the reaction of (*R*)-BINOL, Bu_2Mg, and H_2O in the ratio of 3:2: 2 in 10 mol% of Mg^{II}) in the 1,2-hydrophosphonylation of unreactive α,β-unsaturated ketones **211** with dialkyl *H*-phosphonates **144** to produce tetrasubstituted α-hydroxyphosphonates **213** in moderate to excellent yields (59-96%) and high enantioselectivities (81-99% ee) (Scheme 86, method A)[264]. The chiral magnesium (II) binaphtholate complex **212b**, formed *in-situ* by reacting (*R*)-BINOL and Bu_2Mg in a 2:1 ratio in the absence of water, proved instrumental in enhancing enantioselectivity. This modification that led to the *in-situ* generation of catalyst **212b** addressed the decreased selectivity observed in some cases when utilizing catalyst **212a** (Scheme 86, method B). The efficacy of the devised method owes itself to the distinctive structure of the magnesium complex, wherein the naphthoxide fragments, possessing strong Brønsted/Lewis basicity, assume a pivotal role in activating the inert P-nucleophile into its reactive tautomer. Leveraging its strong Lewis acidity properties, the Mg (II) ion center facilitates the activation of the less reactive α,β-unsaturated ketones. This dual functionality within the magnesium complex serves to catalyze the reaction, resulting in the formation of the desired products. The authors also noted that the

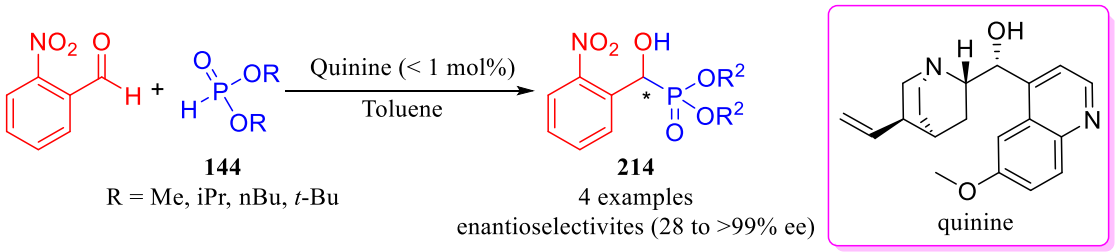
regioselectivity exhibited by this protocol is highly dependent on the choice of the solvent and substrate and the configuration at the newly formed chiral carbon center wasn't stated[264].



Scheme 86. *Enantioselective hydrophosphonylation of α,β-unsaturated ketones catalyzed by chiral magnesium complex-representative examples;* ***Method A****: 15 mol% of (R)-BINOL, 10 mol% of Bu_2Mg, 10 mol% of H_2O;* ***Method B****: 20 mol% of (R)-BINOL 10 mol% of Bu_2Mg (10 mol%): in parenthesis yield and ee value after recrystallization.*

1.1.2. Pudovik reaction catalyzed by chiral organocatalyst

In 1983, Wynberg was the pioneering researcher to employ a basic organic catalyst, quinine in the asymmetric hydrophosphonylation of *o*-nitrobenzaldehyde with different alkyl *H*-phosphonates to furnish the α-hydroxyphosphonates **214** (Scheme 87)[266].

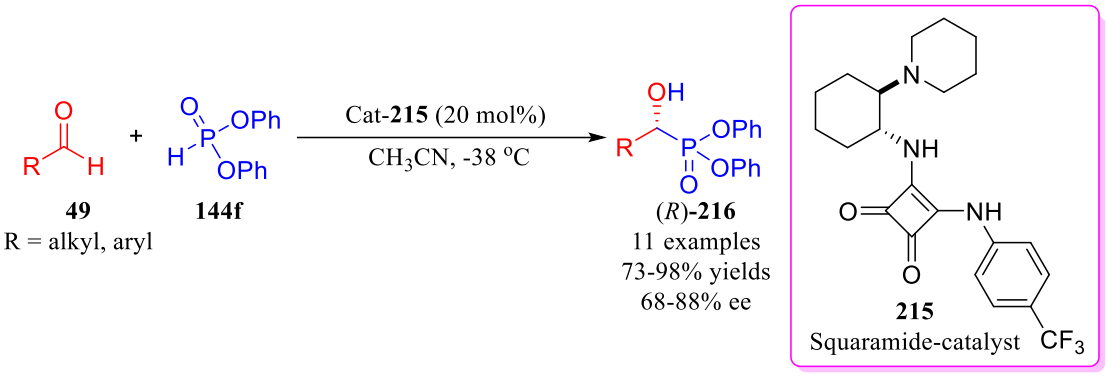


Scheme 87*. The first asymmetric hydrophosphonylation of aldehyde in the presence of organocatalyst.*

However, the early studies had limited examples because the protocol is only applicable to very reactive aromatic aldehyde, and the process required extensive recrystallization to obtain enantioenriched products with enantiomeric excess ranging from 28% to nearly 100%. The authors found that the enantioselectivity of the reaction product increases as the size of the

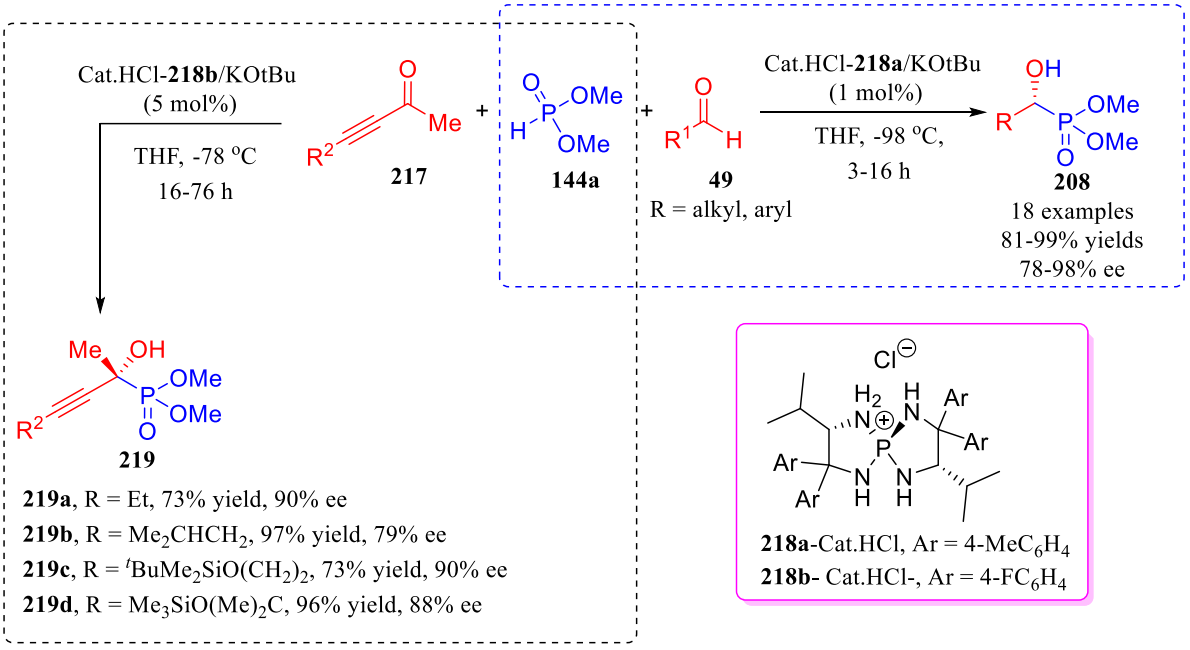
phosphonate ester increases but at the cost of a decrease in reactivity. The absolute configuration at the newly formed α-carbon of the products was not determined.

The Herrera group demonstrated an enantioselective hydrophosphonylation reaction of aldehydes with diphenyl *H*-phosphonate **144f** using squaramide **215**, a catalyst based on hydrogen bonding, to give the desired (*R*)-α-hydroxyphosphonates **216** with yields ranging from 73% to 98% and satisfactory enantioselectivity (68-88%)[238]. However, this protocol required high catalyst loading, longer reaction times, and low temperatures to achieve high enantioselectivity (Scheme 88).



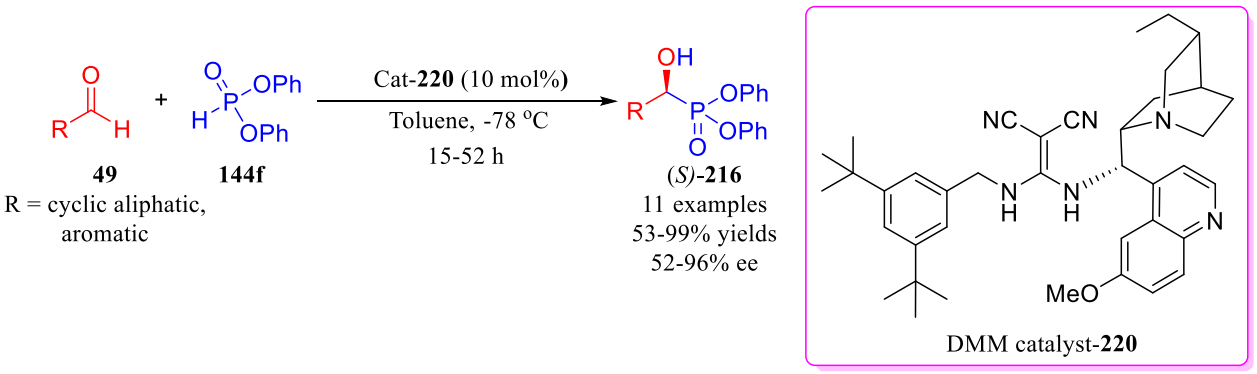
***Scheme 88**. Squaramide catalyzed enantioselective hydrophosphonylation of aldehydes with diphenyl phosphite.*

Ooi et al. reported a [5.5]-P-spirocyclic chiral triaminoiminophosphorane **218a** catalyzed nucleophilic addition of dimethyl *H*-phosphonate **144a** to aldehyde **49** to afford the α-hydroxyphosphonates **208** in high yields and enantioselectivities (Scheme 89)[270]. The absolute configuration at the carbon atom attached to the hydroxy group of products **208** was determined to be (*R)* based on the comparison of their optical rotation values with those reported in the literature. Addition to ynones **217** in the presence of catalyst **218b** gives tetrasubstituted α-hydroxyphosphonates **219** in acceptable yields (73-96%) and high enantioselectivities (79-91% ee) with (*R*) configuration at the newly formed stereogenic carbon (Scheme 89)[269,270]. The success of this protocol is attributed to the specific features of the chiral organic base catalysts **218**, such as their strong basicity, which allows the activation of the P-nucleophile, and the donating ability of their conjugated acid due to the presence of hydrogen bonding, which strictly control the stereochemical outcome of the reaction leading to desired products and suppress the undesired side reactions (that can be obtained from either retro-hydrophosphonylation or phospha-Brook rearrangement).



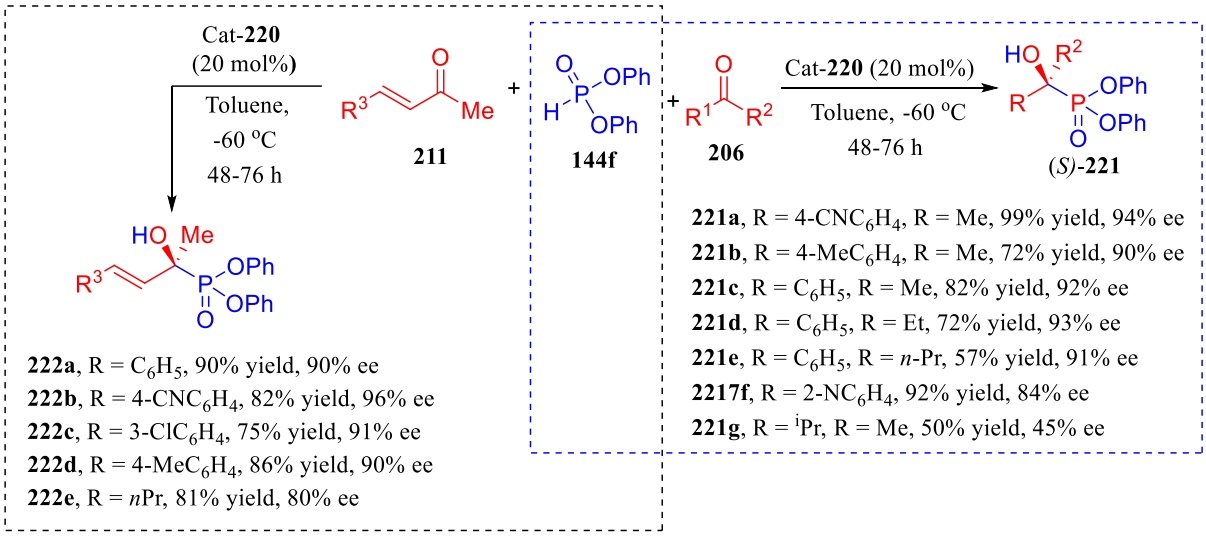
***Scheme 89**. Enantioselective hydrophosphonylation of aldehydes and ynones catalyzed by chiral triaminoiminophosphorane*

Diaminomethylenemalononitrile (DMM) **220** with hydrogen-bonding donor capability was employed by Miura et al. in the asymmetric Pudovik reaction of aldehydes with diphenyl phosphite in toluene to give the desired α-hydroxyphosphonates **216** with moderate to quantitative yields (53-99%) and enantiomeric ratio up to 98% (Scheme 90)[271]. The authors postulated that apart from activating the diaryl phosphonate, the two hydrogen bonding donor protons at the two amino groups of the DMM motif interact with the oxygen atom of the aldehydes to direct the nucleophilic attack of the active phosphite on the *Si*-face of the aldehydes, as opposed to the *Re*-face. This preference arises due to steric hindrance caused by the 3,5-di-*tert*-butyl group. As a result of this favored transition state, the corresponding products were obtained with an *S*-configuration.



***Scheme 90**. Cinchona–diaminomethylenemalononitrile catalyzed enantioselective hydrophosphonylation of aldehydes.*

Continuing their work on the utility of the cinchona diaminomethylenemalononitrile (DMM) organocatalyst, Miura et al. reported a highly enantioselective hydrophosphonylation protocol involving the use of simple ketones with diphenyl phosphonate in the presence of DMM catalyst **220** in toluene[272]. The reaction afforded the corresponding quaternary (*S*)-α-hydroxyphosphonates **221** in yields ranging from 50% to 99% and with moderate to excellent enantioselectivities (45-91% ee) (Scheme 91). DMM catalyzed 1,2-hydrophosphonylation of α,β-unsaturated ketones **211** with diphenyl phosphonate afforded the adducts **222** with yields up to 96% and with high enantioselectivities up to 96% ee (Scheme 91)[272].



Scheme 91. *Cinchona–diaminomethylenemalononitrile catalyzed enantioselective hydrophosphonylation of ketones and enones*.

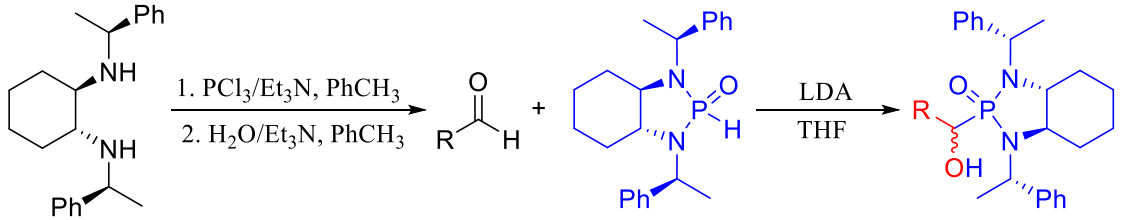
1.1.3. Pudovik reaction with chiral auxiliaries containing phosphorus atom

The primary objective of this project was to explore the utilization of chiral phosphorus nucleophiles in inducing high diastereoselectivity under mild reaction conditions. Before this study, only a limited number of reports existed in the literature concerning the synthesis of α-hydroxyphosphonates through diastereoselective Pudovik reaction using chiral *H*-phosphonates[20]. These methods involved the application of *H*-phosphonates derived from compounds such as ephedrine[274], 1,2-diaminocyclohexane[275–277], borneol, menthol, or 1,2:5,6-di-O-isopropylidene-D-glucofuranose[254], resulting in the formation of the products α-hydroxyphosphonates with decent yields but moderate diastereoselectivities.

As reported by de Parrodi et al., in the presence of Et_3N, the diamines (*1S,2S,1'S,1''S*)-**223a** and (*1R,2R,1'S,1''S*)-**223b** underwent condensation with PCl_3, resulting in the formation of chlorodiazaphospholes. Subsequent hydrolysis of these compounds yielded the corresponding chiral auxiliaries, diazaphosphole oxides, also known as *N, N'*-bis-[(*S*)-α-phenylethyl]-bicyclic

phosphorous acid diamides **224** (Table 10)[277]. The nucleophilic addition of these synthesized diazaphosphole oxides **224** to various aldehydes was carried out, leading to products **225** with good to excellent conversions (65–100%) and moderate diastereoselectivities (Table 10)[278]. The stereochemical configuration observed at the α-carbon of the products **225** is significantly influenced by the nature of the aldehydes **49** and the chiral diazaphosphole oxides **225** used.

Table 10. Diastereoselective addition of (1S,2S,1'S,1''S)- and (1R,2R,1'S,1''S)-N,N'-(α-phenylethyl)-substituted phosphorous acid diamide with aldehydes.



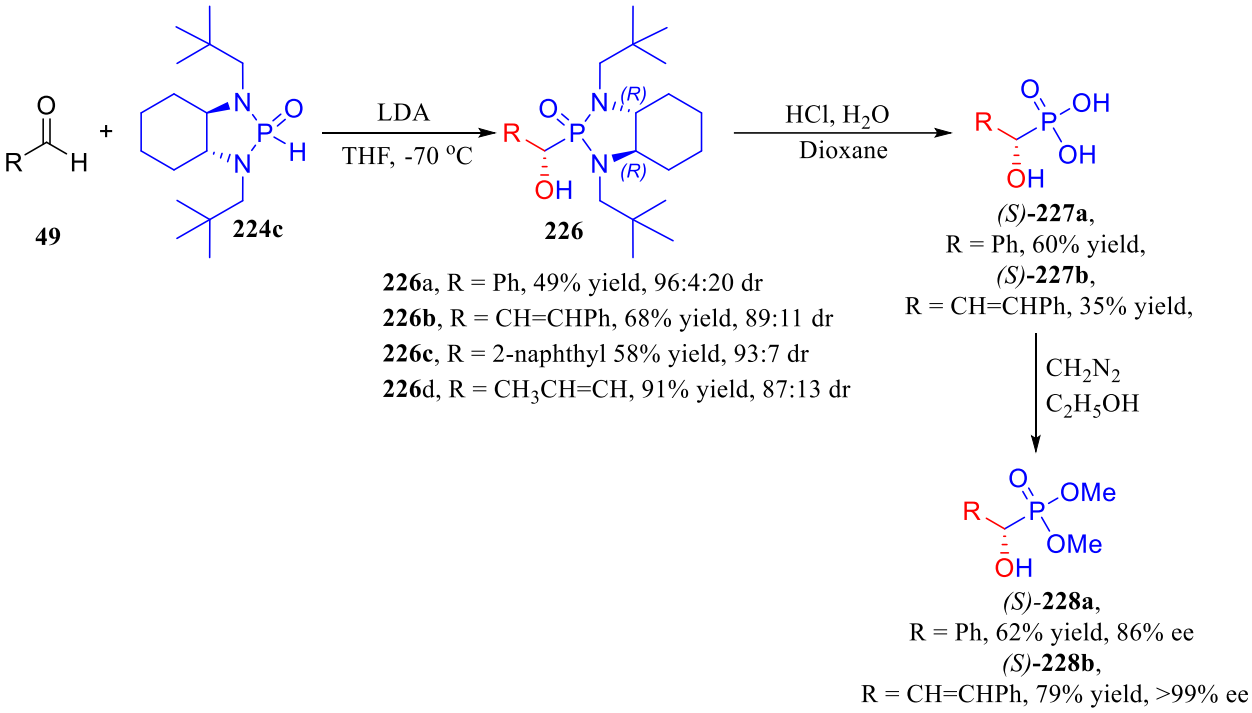
(1*S*,2*S*,1′*S*,1″*S*)-**223a**
(1*R*,2*R*,1′*S*,1″*S*)-**223b**

(1*S*,3*S*,1′*S*,1″*S*)-**224a**
(1*R*,3*R*,1′*S*,1″*S*)-**224b**

(1*S*,3*S*,1′*S*,1″*S*)-**225a**
(1*R*,3*R*,1′*S*,1″*S*)-**225b**

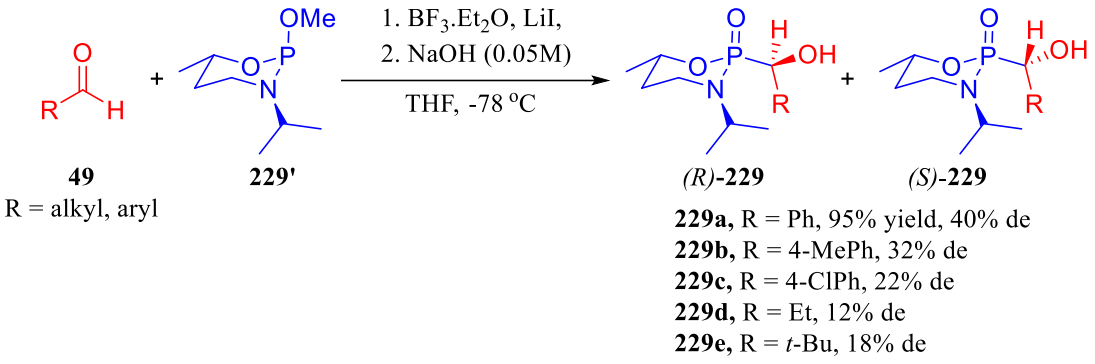
Entry	**Chiral auxiliary**	**R**	**Product**	**Conv. (%)**	**dr**	**Conf.**
1	**224a**	C_6H_5	**225a**	92	64:36	*R*
2	**224a**	4-$MeOC_6H_4$	**225b**	87	62:38	*R*
3	**224a**	*i*Pr	**225c**	99	62:38	*S*
4	**224b**	C_6H_5	**225d**	98	57:43	*S*
5	**224b**	4-$MeOC_6H_4$	**225e**	100	64:36	*S*
6	**224b**	*i*Pr	**225f**	97	63:37	*R*

In 1994, Spilling and co-workers presented the diastereoselective addition of phosphonylating agents, namely bicyclic diazaphosphole oxide **224c** to aldehydes in THF at -70°C. Following recrystallization from ethyl acetate and hexane, the resulting reaction mixture yielded the major diastereoisomers of the (*S*)-configured products **226**, with yields ranging from moderate to high (49-91%) and diastereoselectivities ranging from 5% to 93% de (Scheme 92)[276]. Subsequently, the α-hydroxyphosphonamides **226a,b** underwent hydrolysis in the presence of aqueous HCl in dioxane, leading to the synthesis of α-hydroxyphosphonic acids **227a,b** with isolated yields of 60% and 35%, respectively. When subjected to the methylating agent diazomethane in ethanol, the obtained compounds **227a,b** were transformed into their corresponding phosphonates **228a,b** with isolated yields of 62% and 79% and enantioselectivities of 86% and >99% ee, respectively (Scheme 92)[276,279]. Notably, the stereochemistry of the resulting products **227a,b** and **228a,b** remained unchanged.



Scheme 92. *Stereoselective synthesis of α-hydroxy-phosphonamides, phosphonates and phosphonic acids using diazaphosphole oxides* ***224c***

Evans et al. reported the diastereoselective condensation of 2-methoxy-1,3,2-oxazaphosphite with different aldehydes utilizing boron trifluoride etherate ($BF_3.Et_2O$) in THF (Scheme 93). This reaction resulted in the synthesis of α-hydroxy-2-oxo-l,3,2-oxazaphosphorinanes, with diastereoselectivities ranging from poor to moderate (4-40% de)[274]. The presence of $BF_3.Et_2O$ in the reaction setup assumes a pivotal role by enhancing the electrophilic strength of the aldehydes, thereby accelerating the reaction rate. Through recrystallization, the major diastereoisomer of **229a** was separated and subsequently subjected to X-ray analysis. This analysis revealed that the absolute configuration at the α-carbon of the product to be *R*.



Scheme 93*. Diastereoselective hydrophosphonylation of aldehydes with oxaphosphite* ***229'***

More examples of the use of chiral P-nucleophiles in the asymmetric hydrophosphonylation of carbonyl compounds were described in the introductory section of this dissertation (Schemes 12, 13, 26a, 35, 36, 37, 38 and 39).

Our research group previously reported on the hydrophosphonylation of aldehydes, employing TADDOL-derived *H*-phosphonate **29** as a chiral reagent, leading to the formation of α-hydroxyphosphonates with notable diastereoselectivity (see the introductory part, Scheme 12 of this dissertation)[94]. To achieve these high diastereoselectivities, the reactions were performed at very low temperatures in the presence of an organometallic compound and tetramethylethylenediamine (TMEDA). The inclusion of TMEDA enhanced the solubility of the formed organozinc-phosphorus adducts and was essential to the success of the developed strategy. However, due to the limitations associated with this protocol such as low temperature (-78 ^{o}C), presence of pyrophoric (Et_2Zn) and fragile (LDA) reagents, anhydrous conditions, and atmosphere of inert gas, I conducted further investigations and presented herein a straightforward and efficient method for the hydrophosphonylation of aldehydes.

The developed protocols enable the asymmetric synthesis of α-hydroxyphosphonates with high diastereoselectivity under mild reaction conditions. The chirality of the TADDOL-derived *H*-phosphonate enabled control over the stereochemistry at the newly formed carbon atom. The absolute configuration was unambiguously confirmed by X-ray crystallography. Furthermore, I successfully cleaved the chiral auxiliary, leading to the formation of enantiomerically pure α-hydroxyphosphonic acids.

2.0. Results and discussion

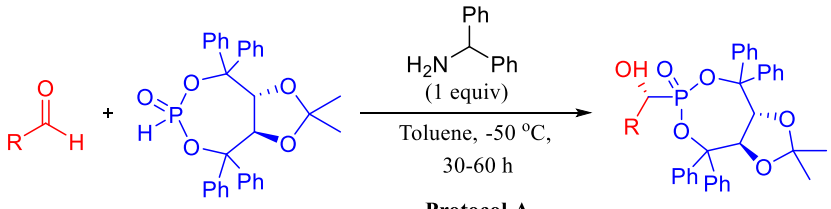
In my continuous pursuit to demonstrate the application of TADDOL-derived *H*-phosphonate in the hydrophosphonylation of different and easily available starting materials containing carbon-heteroatom bonds, I decided to use the carbonyl compounds (aldehydes and ketones).

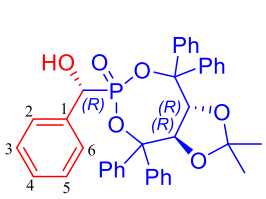
In the second chapter of this dissertation, while working on the hydrophosphonylation of imines (Table 8, page 113), I observed that during the one-pot three-component Kabachnik-Fields reaction next to the desired α-aminophosphonate also secondary product, namely the α-hydroxyphosphonate was formed. Remarkably, the generation of the latter displayed high diastereoselectivity depending on the conditions under which the reaction was performed (Table 8, entries 6-8). Motivated by this result, I decided to carry out the reaction in the presence equimolar amount of benzhydryl amine acting as the base at a lower temperature of -50 ^{o}C

under the same conditions (toluene, room temperature, 35h, Protocol A) where I observed the formation of only α-hydroxyphosphonate **205a** with 90% yield and high diastereoselectivity (up to 98:2 dr) and subsequently, after simple crystallization from diethylether I was able to obtain the product as a single diastereoisomer. This result suggests that amine in the reaction system functioned as a base, activating the nucleophilicity of the H-P species, which led to a nucleophilic attack on the electrophilic carbon of the aldehyde.

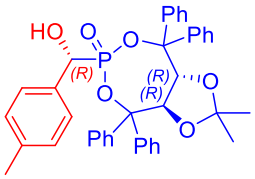
Delighted with the optimized reaction conditions, I proceeded to expand the scope of this method by investigating its applicability to various aldehydes. The reaction proceeded smoothly, resulting in the desired products with excellent diastereoselectivity when tested with simple benzaldehyde **49a**, or its derivatives containing electron donating group **49b** or electron withdrawing-group at the para and/or meta position(s) **49c-j**, polycyclic aromatic **49k**, and heteroaromatic aldehydes **49l-n** to give the products **205a-n** with diastereoselectivities ranging from 86:14 dr to 98:2 dr in the crude products which were significantly improved after crystallization to obtained a single diastereomer in majority of cases (Scheme 94). However, a decrease in the diastereomeric ratio was observed when a nitro-group was introduced at position 2 of the ring **205j** with 68% yield and 89:11 dr after crystallization although slightly lower diastereoselectivity was observed in the crude reaction mixture (73:27 dr). Additionally, low diastereoselectivities were initially obtained with aliphatic aldehydes (74:26 dr for **205o** and 69:31 dr for **205p**) but were significantly improved through column chromatography to >99:1 and 92:8 dr, respectively.

Based on the protocol discussed above, the diastereoselective hydrophosphonylation of the aldehydes occurred through single asymmetric induction where the TADDOL-derived *H*-phosphonate played a pivotal role as the primary inducer of chirality at the newly formed chiral center. Achieving greater diastereoselectivity with this protocol necessitates longer reaction times, an equimolar amount of the base, and low temperatures, which are among its limitations. Hence, I envisioned an alternative strategy to overcome these challenges by performing the diastereoselective hydrophosphonylation of the aldehydes under milder reaction conditions without affecting the diastereoselectivity.

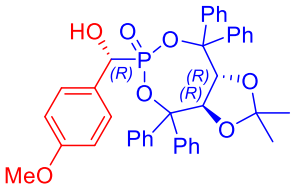




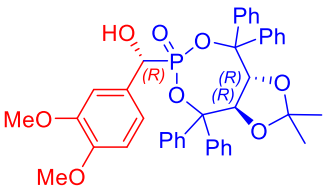
205a, 90% yield,
dr: 98:2 (>99:1), 48 h



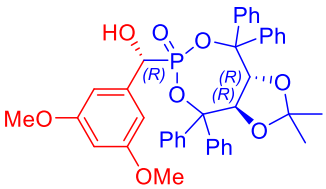
205b, 89% yield,
dr: 95:5 (>99:1), 52 h



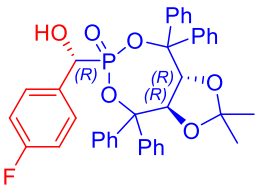
205c, 88% yield,
dr: 90:10 (94:6), 55 h



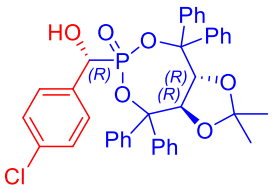
205d, 87% yield,
dr: 90:10 (96:4), 60 h



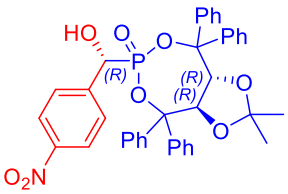
205e, 85% yield,
dr: 94:6 (>99:1), 60 h



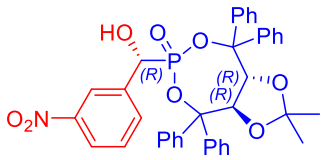
205f, 90% yield,
dr: 95:5 (>99:1), 30 h



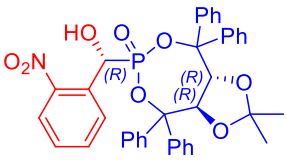
205g, 89% yield,
dr: 94:6 (>99:1), 30 h



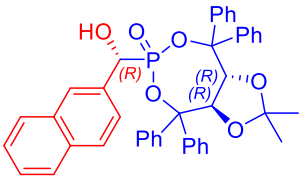
205h, 89% yield,
dr: 89:11 (>99:1), 35 h



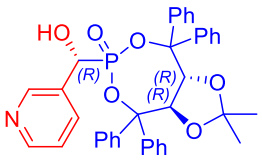
205i, 87% yield,
dr: 86:14 (92:8), 35 h



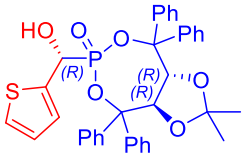
205j, 68% yield,
dr: 73:27 (89:11), 35 h



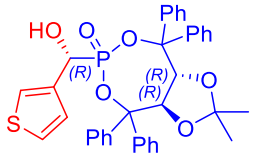
205k, 91% yield,
dr: 97:3 (>99:1), 60 h



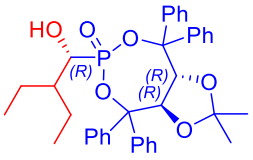
205l, 81% yield,
dr: 89:11 (91:9), 60 h



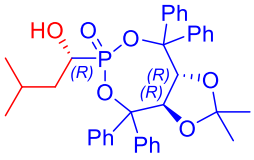
205m, 88% yield,
dr: 92:8 (97:3), 60 h



205n, 90% yield,
dr: 95:5 (>99:1), 60 h



205o[c], 76% yield,
dr: 74:26 (>99:1), 48 h

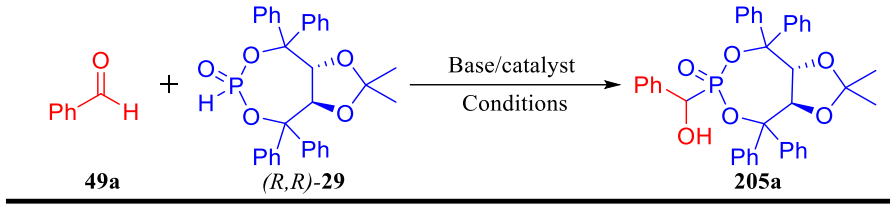


205p[c], 70% yield,
dr: 69:31 (92:8), 48 h

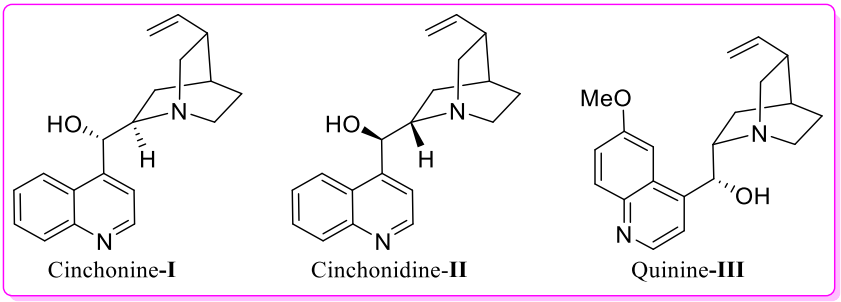
Scheme 94. *Substrate scope for diastereoselective hydrophosphonylation of aldehydes at -50 °C based on* ***protocol A.*** *yields are given for isolated products; dr reported in the brackets is for isolated pure product* [a]*Isolated yield after crystallization,* [b]*The diastereomeric ratio (dr) was determined by analyzing* ^{31}P *NMR spectra of the crude reaction mixture.* [c]*Column chromatography was employed as the method of purification.*

I initiated this study by testing the nucleophilic addition of (*R,R*)-**29** to model aldehyde **49a** in the absence of a base in toluene, no reactivity was observed (Table 11, entry 1). However, in the presence of inorganic bases (K_2CO_3 or Cs_2CO_3) as well as a non-chiral organic base (Et_3N), 100% conversion was achieved, although with poor to moderate diastereoselectivity, even at a lower temperature of -30 °C (dr 79:21 in the best case) (Table 11, entries 2-6).

Table 11. Optimization of the reaction conditions for the hydrophosphonylation of aldehydes**.**



49a *(R,R)*-**29** **205a**



Cinchonine-**I** Cinchonidine-**II** Quinine-**III**

Entry	Solvent[a]	Base[b]/Cat.	Temp (°C)	Time (h)	Conv. (%)	dr[c]
1	Toluene	-	rt	24	0	-
2	Toluene	K_2CO_3	rt	24	100	58:42
3	Toluene	Cs_2CO_3	rt	24	100	61:39
4	Toluene	Et_3N	rt	24	100	71:29
5	Toluene	Et_3N	100	10	100	69:31
6	Toluene	Et_3N	-30	30	96	79:21
7	Toluene	**I** (20mol%)	rt	24	87	83:17
8	Toluene	**II** (20mol%)	rt	24	95	89:11
9	Toluene	**III** (20mol%)	rt	24	100	90:10
10	THF	**III** (20mol%)	rt	24	100	89:11
11	CH_2Cl_2	**III** (20mol%)	rt	24	90	83:17
12	DME	**III** (20mol%)	rt	24	100	89:11
13	DMF	**III** (20mol%)	rt	24	100	75:25
14	Dioxane	**III** (20mol%)	rt	24	100	89:11
15	Toluene	**III** (20mol%)	-30	70	100	93:7
16	Toluene	**III** (10mol%)	rt	24	100	9:10
17	Toluene	**III** (5mol%)	rt	24	100	91:9
18	Toluene	**III** (2mol%)	rt	24	100	91:9
19	Toluene	**III** (1mol%)	rt	24	100	89:10
20	Toluene[d]	**III** (2mol%)	rt	24	100	89:10
21	Toluene[e]	**III** (2mol%)	rt	24	100	88:12
22	Toluene[f]	**III** (2mol%)	rt	24	100	88:12

[a]The reaction conditions: reactions were performed in 0.60 mL of the solvent on 0.10 mmol scale of ***49a*** *and (R,R)-****29****. [b]1.0 equivalent of the base used (unless otherwise stated). [c]dr and conversion were determined based on [31]P NMR analysis of the crude reaction, [d]The reaction performed in 1.0 mL of the solvent on 0.10 mmol scale. [e]The reaction is performed in 1.5 mL of the solvent on 0.10 mmol scale. [f]The reaction performed in 2 mL of the solvent on 0.10 mmol scale.*

These results suggested that the presence of the base is crucial in activating the less reactive *H*-phosphonate **29** into its active tautomer for subsequent nucleophilic addition to the aldehyde to give the desired hydroxyphosphonate **205**. I was pleased to observe improved results when screening the reaction with different cinchona alkaloids such as cinchonine, cinchonidine, and quinine (Table 11 entries 7-9). Notably, the utilization of 20 mol% of quinine gave the best results in terms of reactivity and diastereoselectivity, as seen in Table 11 entry 9. Subsequently, I performed additional reactions to investigate the influence of solvents on the system. The reaction proceeded in all tested solvents, albeit with slight variations in diastereoselectivity (Table 11 entries 9-14). Notably, when toluene was employed as the solvent, better reactivity (100% conversion) and diastereoselectivity (90:10 dr) were achieved based on the analysis of the ^{31}P NMR spectrum. This analysis revealed two distinct signals corresponding to the two diastereoisomers of the desired α-hydroxyphosphonate, with chemical shifts at δ_{major} = 16.96 ppm and δ_{minor} = 15.31 ppm (Table 11, entry 9 and Figure 27). To further demonstrate the reactivity of the system, the reaction was conducted at -30 °C, resulting in improved diastereoselectivity (93:7 dr) at the expense of a longer reaction time of 70 h (Table 11 entry 15).

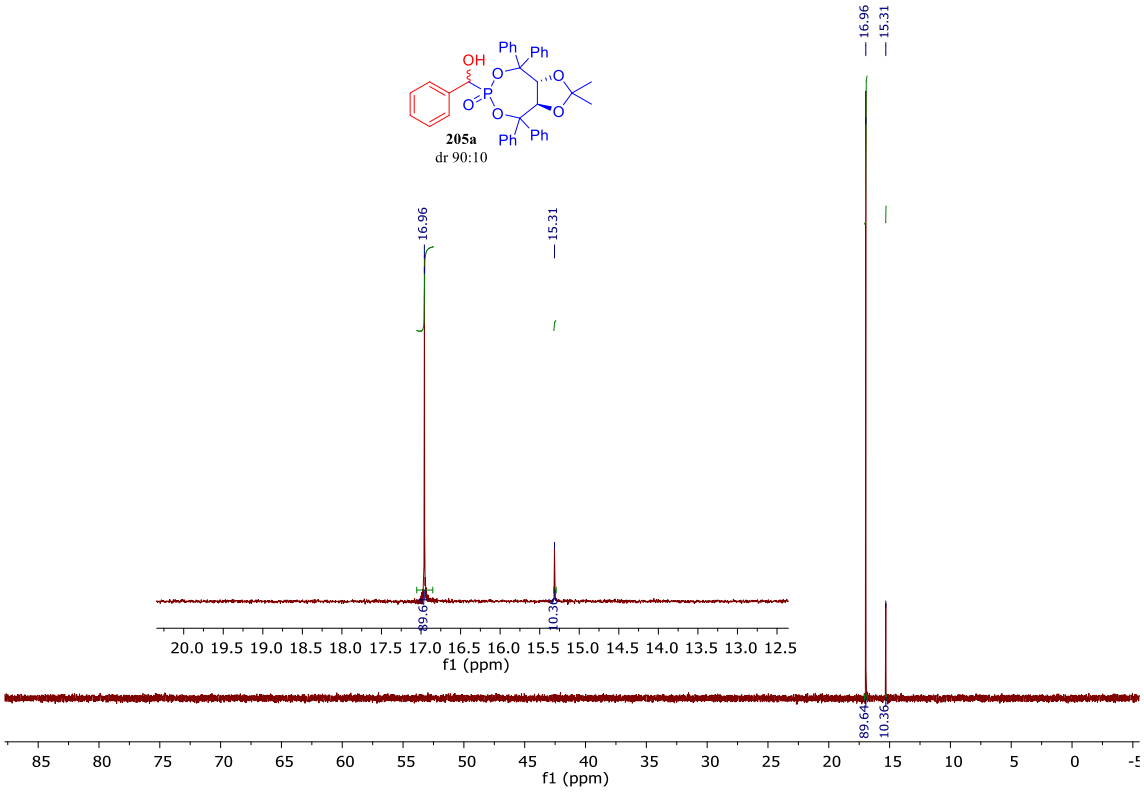
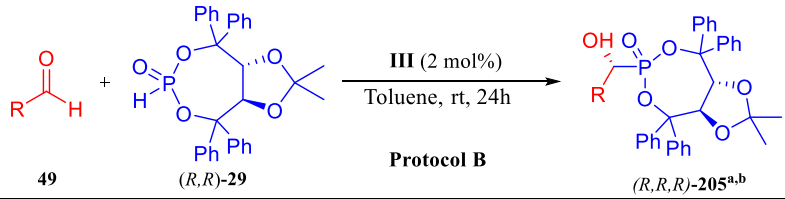


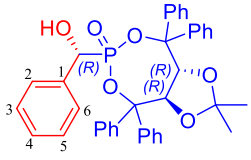
Figure 27. *The ^{31}P NMR spectrum (162MHz, $CDCl_3$ using Jeol 400yh apparatus) of the crude reaction mixture showing the result of hydrophosphonylation of benzaldehyde **49a** with (R,R)-**29** in presence of quinine (Table 11, entry 9).*

The impact of varying the amount of quinine on the reactivity and diastereoselectivity of the reaction was assessed by investigating different amounts of quinine (Table 11, entries 16-19). I was pleased to discover that the reaction proceeded smoothly even with as low as 1 mol% of quinine (Table, entry 19), and the optimal result was obtained when 2 mol% was utilized (Table 11, entry 18). Lastly, I examined the effect of dilution on the reaction and found that it had negligible effects on the reactivity. However, it did have a slight negative influence on the diastereoselectivity (Table 11, entries 20-22).

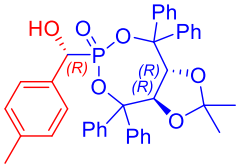
To expand the applicability of this protocol, I employed the optimized reaction conditions (quinine (2mol%), room temperature, 24 h, toluene) to explore the scope and limitations of the asymmetric hydrophosphonylation of various aldehydes **49a-r** (Scheme 95). The reaction proceeded smoothly, leading to the formation of different optically active substituted α-hydroxyphosphonates with good to excellent yields (64-92%) and diastereoselectivity (dr up to >99:1) after crystallization (Scheme 95). The diastereoselectivity and yields varied depending on the specific aldehyde used and the position of the substituents on the aromatic ring in the case of aromatic aldehydes. With simple benzaldehyde, the desired product **205a'** was obtained with 91% isolated yield and the diastereoselectivity of 91:9 diastereomeric ratio which was improved to >99:1dr after crystallization. Upon introducing an electron-donating group (EDG), such as a methyl group, to the para position of the aromatic ring, the yield and diastereoselectivity of the isolated product **205b'** remained constant (90% yield, dr >99:1 after crystallization) although slightly lower diastereoselectivity was observed in the crude reaction mixture (dr 88:12). When electron-withdrawing groups (EWG) were present on the aromatic ring, the influence on the reaction diastereoselectivity and yield was more visible. Placing EWG groups in the para position resulted in slightly decreased yield and diastereoselectivity in the case of methoxy group (compound **205c'**, yield 88%, dr 87:13 and after purification dr 90:10, Scheme 95), fluorine (compound **205g'**, yield 89%, dr 89:11 and after purification >99:1), chlorine (compound **205h'**, yield 91%, dr 90:10 and after purification dr >99:1, Scheme 95) and nitro group (compound **205i'**, yield 82%, dr 84:16 and after purification dr 94:6, Scheme 94). The influence of an electron-withdrawing group (EWG) positioned at the ortho or meta position had a more pronounced impact on the reaction's outcome. This effect was particularly evident in the case of product **205k'**, where a nitro group was placed in the ortho position,



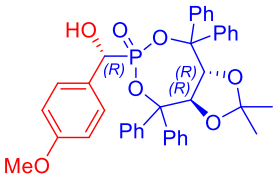
49 (*R,R*)-**29** (*R,R,R*)-**205**[a,b]



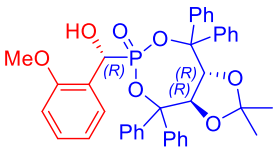
205a'
91% yield, dr: 91:9 (>99:1)



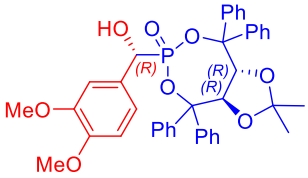
205b'
90% yield, dr: 88:12 (>99:1)



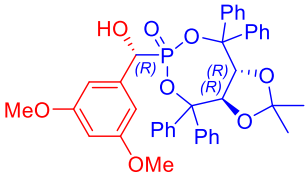
205c'
88% yield, dr: 87:13 (90:10)



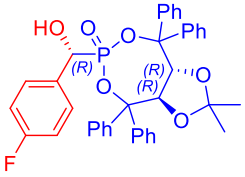
205d'
77% yield, dr: 62:38 (71:29)



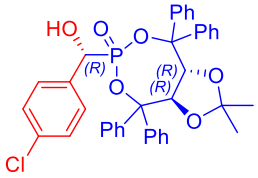
205e'
90% yield, dr: 87:13 (92:8)



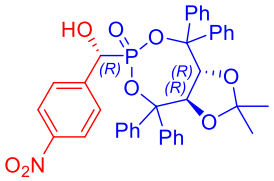
205f'
88% yield, dr: 86:14 (91:9)



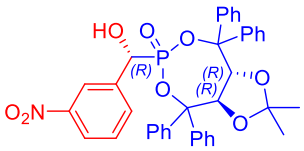
205g'[c]
89% yield, dr: 89:11 (>99:1)



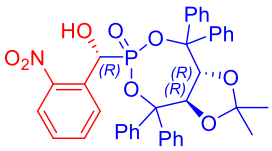
205h'[d]
91% yield, dr: 90:10 (>99:1)



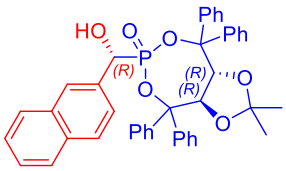
205i'[d]
82% yield, dr: 84:16 (94:6)



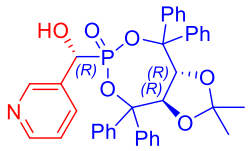
205j'[d]
81% yield, dr: 82:18 (88:12)



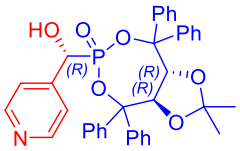
205k'[d]
74% yield, dr: 60:40 (72:28)



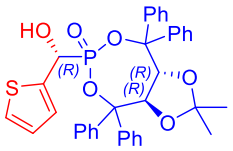
205l'
92% yield, dr: 91:9 (>99:1)



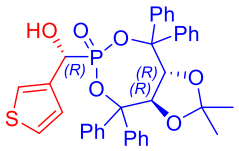
205m'
80% yield, dr: 84:16 (90:10)



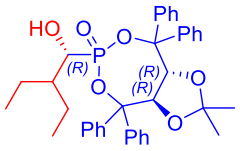
205n'
89% yield, dr: 91:9 (96:4)



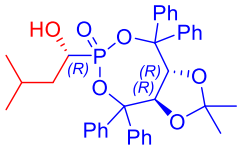
205o'
85% yield, dr: 88:12 (95:5)



205p'
88% yield, dr: 91:9 (>99:1)



205q'[e]
73% yield, dr: 70:30: (>99:1)



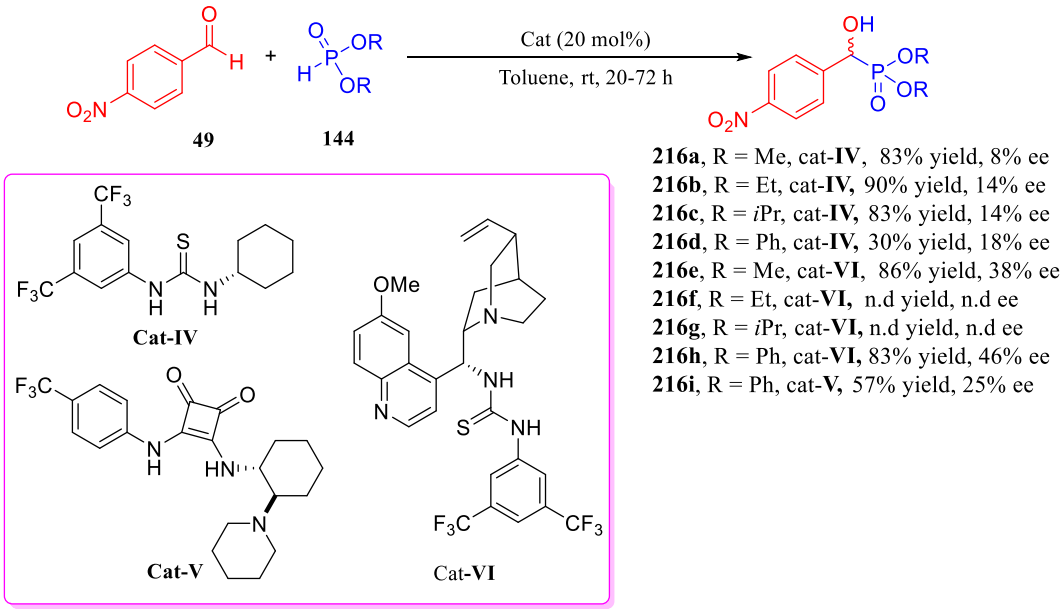
205r'[e]
64 % yield, dr: 65:35(92:8)

***Scheme 95**: The scope of the hydrophosphonylation of aldehydes based on **protocol B**: [a]reaction was performed in 2.0 mL of the solvent on 0. 290 mmol scale of **49** and (R,R)-**29**, and isolated yield after crystallization, [b]The diastereomeric ratio (dr) was determined by analyzing ^{31}P NMR of the crude product with the dr of isolated product in parentheses, [c]10h reaction time, [d]15h reaction time [e]Column chromatography was employed as the method of purification.*

resulting in a final yield of 76% and a diastereoselectivity ratio of 72:28. Notably, the crude product initially exhibited a diastereoselectivity ratio of 60:40. This outcome can be attributed to steric hindrance around the reaction center, induced by the presence of the substituent in the

ortho position of the carbonyl compound, coupled with the bulkiness of the TADDOL-derived *H*-phosphonate. In turn, the presence of the larger group (the naphthyl) in the carbonyl did not affect the diastereoselectivity and yield of the hydrophosphonylation reaction (product **205l'**, yield 92%, initial dr 91:9 improved by purification to >99:1). Likewise, the heteroaromatic substituents in the carbonyl substrate were well tolerated under the reaction conditions resulting in the formation of the desired heteroaromatic α-hydroxyphosphonates **205m'-p'**. Finally, when aliphatic aldehydes were utilized, moderate diastereoselectivity was initially obtained in the crude product (**205q'-r'**). However, this diastereoselectivity was significantly enriched through column chromatography (Scheme 95).

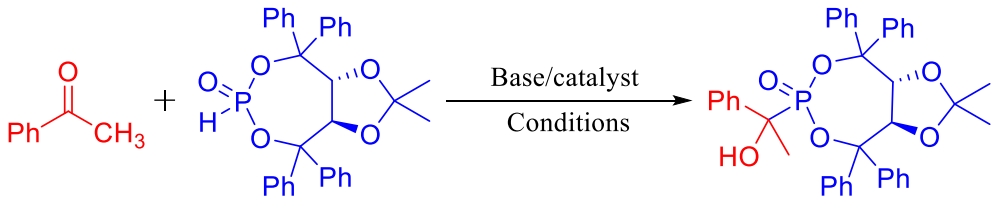
Based on the developed protocol B discussed above, the selectivity observed at the α-carbon atom attached to the phosphorus atom was established through double asymmetric induction by both the TADDOL-derived *H*-phosphonate **29** and the chiral base/catalyst **III**. The experiments reported by the group of Herrera supported these findings[238]. The authors conducted the hydrophosphonylation using 4-nitrobenzaldehyde as the model aldehyde with different non-chiral *H*-phosphonates **144** while exploring various organocatalysts **IV-VI** (acting through hydrogen bonding) under the same reaction conditions as my study (Scheme 96). In most instances, the product was obtained with unsatisfactory enantioselectivity. These results strongly suggested and gave me the idea that the combination of the chiral TADDOL-derived *H*-phosphonate **29** with the chiral catalyst **III** played a pivotal role in achieving the high diastereoselectivity observed in my developed protocol B.



216a, R = Me, cat-**IV**, 83% yield, 8% ee
216b, R = Et, cat-**IV**, 90% yield, 14% ee
216c, R = *i*Pr, cat-**IV**, 83% yield, 14% ee
216d, R = Ph, cat-**IV**, 30% yield, 18% ee
216e, R = Me, cat-**VI**, 86% yield, 38% ee
216f, R = Et, cat-**VI**, n.d yield, n.d ee
216g, R = *i*Pr, cat-**VI**, n.d yield, n.d ee
216h, R = Ph, cat-**VI**, 83% yield, 46% ee
216i, R = Ph, cat-**V**, 57% yield, 25% ee

***Scheme 96**. Hydrophosphonylation of benzyaldehyde with different non-chiral H-phosphonates in the presence of different organocatalysts based on Herrera's work. The n.d stands for not determined.*

Table 12. Optimization of the reaction conditions for the hydrophosphonylation of ketones.



207a *(R,R)*-**29** **230a**

Entry	Solvent[a]	Base[b]/Cat	Temp. (°C)	Time (h)	Conv. (%)[c]	dr[c]
1	Toluene	-	rt	48	-	-
2	Toluene	KOH	rt	48	-	-
3	Toluene	Cs_2CO_3	rt	48	-	-
4	Toluene	K_2CO_3	rt	48	38	68:32
5	Toluene	TEA	rt	48	43	72:28
6	Toluene	NH_2CHPh_2	rt	48	53	73:27
7	Toluene	NaH	rt	48	-	-
8	Toluene	n-BuLi	rt	48	-	-
9	Toluene	**III (**20 mol%)	rt	48	58	76:24
10	THF	**III** (20 mol%)	rt	70	51	68:32
11	DME	**III (**20 mol%)	rt	70	43	70:30
12	DMF	**III** (20 mol%)	rt	70	58	72:28
13	Dioxan	**III (**20 mol%)	rt	70	63	74:26
14	CH_3CN	**III** (20 mol%)	rt	70	36	61:39
15	Dioxan	**III** (2 mol%)	rt	70	43	71:29
16	Dioxan	**III** (5 mol%)	rt	70	52	75:25
17	Dioxan	**III** (10 mol%)	rt	70	59	74:26
18	Dioxan	**III** (50 mol%)	rt	70	46	79:21
19	Dioxan	**III** (20 mol%)	80	24	21	64:36
20	Dioxan	**III** (20 mol%)	-10	96	26	80:20

[a]The reaction conditions: reactions were performed in 1.0 mL of the solvent on 0.10 mmol scale of ***207a*** *and 0.10 mmol scale of (R,R)-****29****. [b]1.0 equivalent of the base used (unless otherwise stated). [c]dr and conversion were determined based on ^{31}P NMR analysis of the crude reaction mixture.*

Continuing the exploration of the utility of TADDOL-derived *H*-phosphonate **29**, I further investigated the asymmetric hydrophosphonylation of acetophenone **207a**, as a model ketone, with (*R,R*)-**29** under various reaction conditions (using both protocol A and B), and the results are presented in Table 12.

The successful use of ketones as substrates would allow the formation of quaternary aminophosphonates in an asymmetric fashion. No reactivity was observed when the reaction was performed in the absence of a base (Table 12 entry 1). Similar results were obtained when the reaction was carried out in the presence of bases such as KOH, Cs_2CO_3, NaH, and n-BuLi (Table 12, entries 2-3, 7-8). In the presence of inorganic base like K_2CO_3, organic bases such as triethyl amine, benzhydryl amine, and chiral base/catalyst **III** gave the product with moderate diastereoselectivity and conversion (Table 12, entries 4-6, 9). The best result was obtained when quinine was used in the reaction system. This could be seen from the NMR spectra of the crude reaction mixture where the chemical shift of the signal corresponding to the unreacted *H*-phosphonate **29** at δ_P = -3.56 ppm and the signals corresponding to the two diastereoisomers of the product **230a** at δ_{major} = 19.47 ppm and δ_{minor} = 18.84 ppm, in $CDCl_3$ where clearly observed (Table 12, entry 9 and Figure 28).

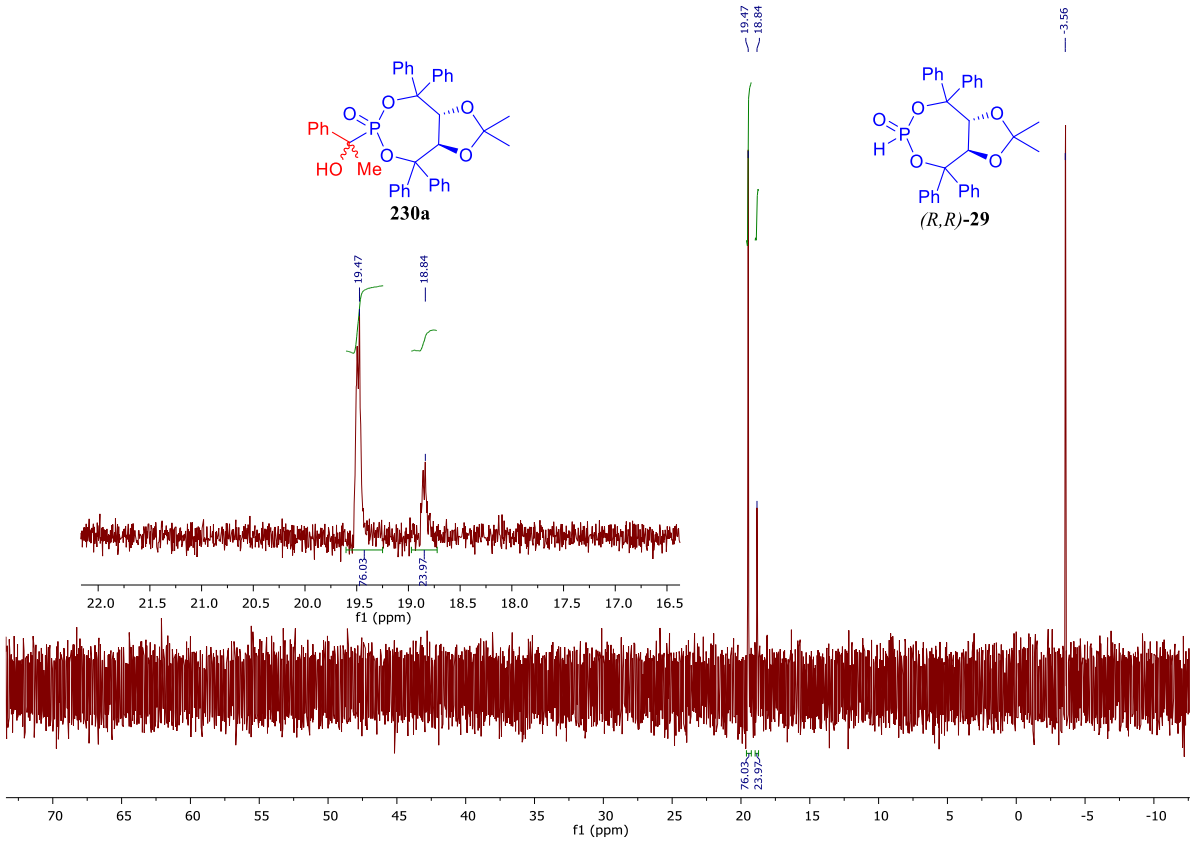
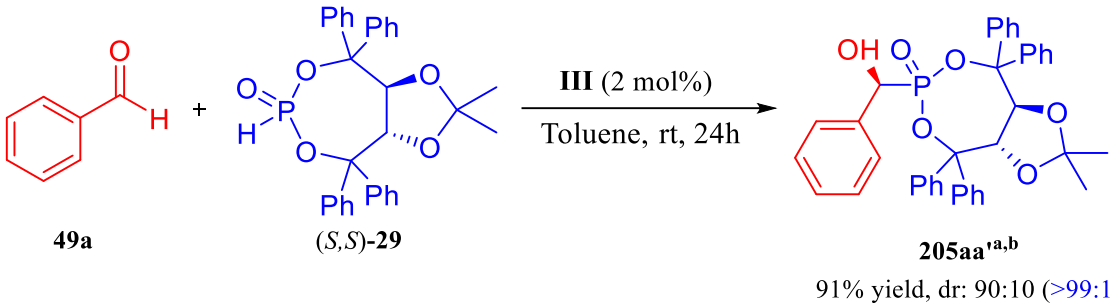


Figure 28. *^{31}P NMR (162MHz, $CDCl_3$ using Jeol 400yh apparatus) spectrum showing hydrophosphonylation of acetophenone with (R,R)-**29** in presence of quinine (Table 12, entry 9).*

Among the array of representative reaction solvents tested (Table 12, entries 9-15), dioxane gave the most optimal result in terms of both conversion rate and diastereoselectivity (Table 12, entry 13). Next, I investigated the influence of the amount of quinine loading on the

reactivity and selectivity of the system, and the best result arose when 20 mol% of quinine was utilized to give the product with 63% conversion and the diastereomeric ratio of 76:24 (Table 12 entry 13). Raising the reaction temperature to 80°C resulted in a reduction in both conversion rate and diastereoselectivity (Table 12, entry 19). Conversely, lowering the temperature to -10 °C led to decreased conversion, although the diastereoselectivity achieved was comparable to that observed in Entry 13 (Table 12, entry 20). In an effort to enrich one of the diastereoisomers in product **230a** obtained from the optimized reaction conditions of entry 13, Table 12 was unsuccessful. The low reactivity observed with this reaction could be attributed to the low reactivity associated with ketones. As a result, I chose not to pursue the investigation into the substrates scope of the hydrophosphonylation of ketones, primarily because of the difficulties encountered in enhancing the conversion and diastereoselectivity.

Drawing upon my prior experience with hydrophosphonylation of amido sulphones, I decided to investigate the reaction between aldehydes **49a** and the enantiomer of the (*R,R*)-**29** namely the TADDOL-derived *H*-phosphonate (*S,S*)-**29**. Under the optimized reaction conditions (Protocol B), product **205aa'** was obtained with a high yield of 91% and excellent diastereoselectivity of >99:1 dr after crystallization from the crude product with an initial diastereomeric ratio (dr) of 90:10 (Scheme 97).



***Scheme 97**: The hydrophosphonylation of benzaldehyde based on **protocol B**: [a]Reaction was performed in 2.0 mL of the solvent on 0.290 mmol scale of **49a** and H-phosphonate (S,S)-**29,** and isolated yield after crystallization, [b]The diastereomeric ratio (dr) was determined by analyzing ^{31}P NMR of the crude product with the isolated dr in parentheses.*

The *R* and *S* absolute configurations were conclusively assigned to the newly formed α-carbons of product **205a'** and **205aa'**, respectively, through X-ray analysis of their pure crystals (Figure 29). The observed stereochemistry suggests that the precise configuration of the chiral phosphorus auxiliary, either (*R,R*)-**29** or (*S,S*)-**29**, plays a vital role in determining the absolute configuration at the newly formed α-carbon of the products (**205a'** and **205aa'**). This highlights one of the advantages of utilizing the TADDOL-derived *H*-phosphonate as a chiral auxiliary in developed protocols. Therefore, all pure single diastereoisomers obtained from the

hydrophosphonylation reaction with (*R*,*R*)-**29** could be assumed to have the (*R*,*R*,*R*) configuration.

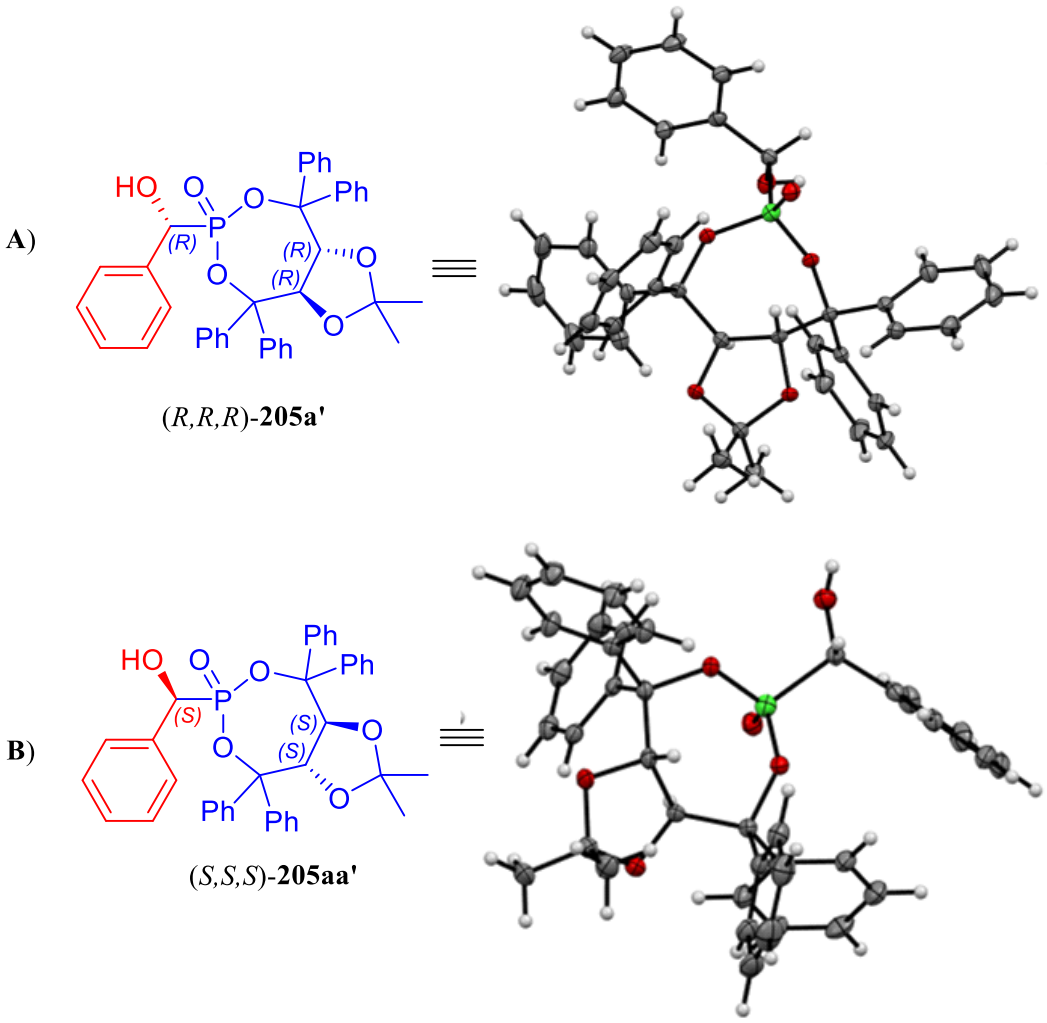
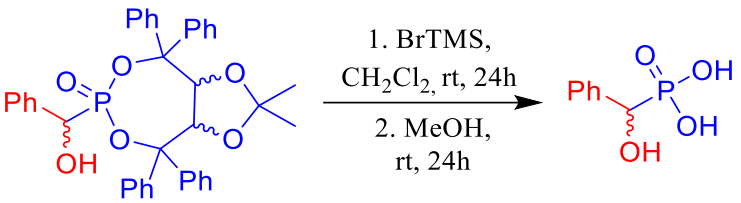


Figure 29. *The absolute configuration of the crystals* ***205a' (A)*** *and* ***205aa' (B)*** *as determined from X-ray analysis.*

To obtain the enantiomerically pure α-hydroxyphosphonic acid, the chiral auxiliary was removed. The pure major diastereoisomer (*R*,*R*,*R*)-**205a'** was treated with bromotrimethylsilane (BrTMS) in CH_2Cl_2 for 24 h at room temperature. Subsequently, MeOH was added to remove the resulting silylated ester, leading to the formation of the enantiomerically pure α-hydroxyphosphonic acid (*R*)-**51a** with 93% yield after crystallization from chloroform (Scheme 98). The reaction was also performed using pure diastereoisomers from (*S*,*S*,*S*)-**205aa** to afford (*S*)-**51aa** with 91% yield. It is worth mentioning that the configuration at the α-carbon for both **230a** and **230aa** was retained, as confirmed by comparing the specific optical rotation values with those reported in the literature[94,279].



(*R,R,R*)-**205a'**
(*S,S,S*)-**205aa'**

(*R*)-**51a**
(*S*)-**51aa**

***Scheme 98**: Cleavage of the chiral auxiliary*

From the experimental results, I put forth the following hypothesis regarding the mechanism of the reaction[238,280]. The quinine functions as a dual activating organocatalyst/base. The activation process involves the interaction between the hydroxyl group of quinine (acting as a hydrogen donor) and the carbonyl group of the aldehyde (acting as a hydrogen acceptor) through hydrogen bonding.

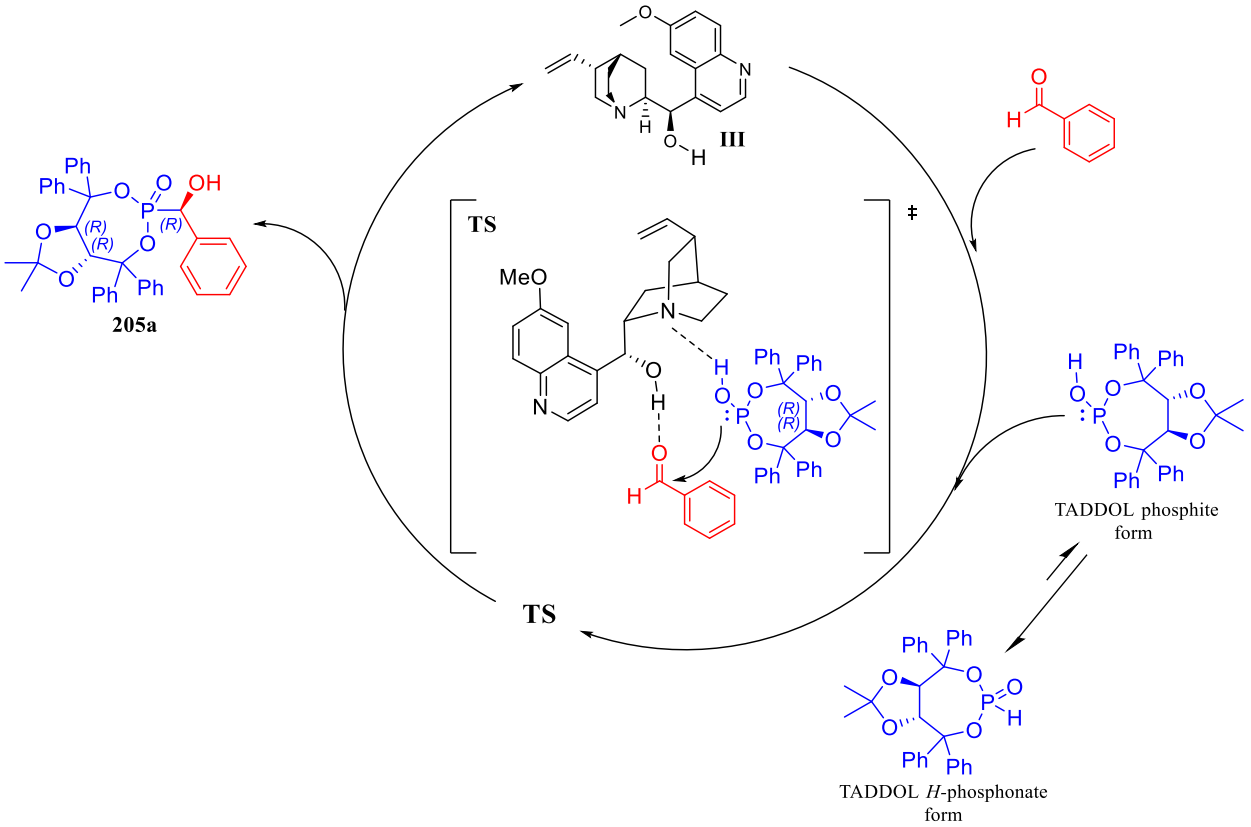


***Figure 30**: Proposed mechanism for the hydrophosphonylation of aldehyde using quinine.*

Simultaneously, the nitrogen in the quinuclidine ring of cinchona alkaloids has a Brønsted base property and hence, could enhance the nucleophilic strength of the TADDOL-derived *H*-phosphonate (*R,R*)-**29** by transforming it to its active tautomer. This, in turn, facilitates the nucleophilic attack of the active TADDOL phosphite on the *Re*-face of the aldehyde (Figure

30). This could give the *R*-configuration which agrees with the observed configuration on the analyzed crystal structure when (*R*,*R*)-**29** was used in the hydrophosphonylation reaction. It is important to note that the reaction demonstrates stereospecificity, as the newly formed absolute configuration at the α-carbon is determined by the configuration of the phosphorus-containing chiral auxiliary (*R*,*R*)-**29**.

3.0. Conclusions

In conclusion, I have developed two robust and straightforward methods for the synthesis of optically active α-hydroxyphosphonates. This is achieved through the diastereoselective hydrophosphonylation of aldehydes using a phosphorus-containing chiral auxiliary TADDOL derived *H*-phosphonate in the presence of benzylhydrylamine at -50 ^{o}C (protocol A) or catalyzed by quinine at room temperature (protocol B), resulting in yields up to 92% and diastereomeric ratio exceeding 99:1.

These developed protocols offer several advantages, including their simplicity, the utilization of readily available and affordable chiral auxiliary, mild reaction conditions, and a wide range of substrate compatibility. The first method provides better diastereoselectivity despite requiring a longer reaction time, whereas the second protocol offers the advantage of mild reaction conditions. It is important to note that the use of either TADDOL-derived *H*-phosphonate (*R*,*R*)-**29** or (S,*S*)-**29** enables easy control of the chirality at the stereogenic α-carbon atom. The utilization of (*R*,*R*)-**29** leads to the formation of (*R*,*R*,*R*)-α-hydroxyphosphonate, while the application of (*S*,*S*)-**29** results in the formation of (*S*,*S*,*S*)-α-hydroxyphosphonate. Finally, a plausible reaction mechanism involving double asymmetric induction was proposed.

Furthermore, the deprotection of the α-hydroxyphosphonates under mild reaction conditions leads to the formation of enantiomerically pure α-hydroxyphosphonic acids with excellent yield and retention of configuration.

I also made several optimization attempts when benzophenone (as representative ketone) was employed as the starting substrate along with (*R*,*R*)-**29** in the hydrophosphonylation reaction. The reaction led to the formation of quaternary α-hydroxyphosphonate with moderate conversions (up to 63%) and diastereoselectivity (78:22 dr in the best-optimized conditions). This low conversion can be attributed to the low reactivity commonly encountered with ketones. Furthermore, my effort to enrich one of the diastereoisomers of the product by both crystallization and chromatography was unsuccessful.

Chapter Four

Asymmetric hydrophosphonylation of hydrazones

1.0. Introduction

Hydrazones are a class of organic compounds that have gained considerable attention in organic chemistry as useful intermediates in the synthesis of various molecular structures[281–283]. These compounds are obtained from the direct condensation of hydrazine derivatives with carbonyl compounds such as aldehydes and ketones, resulting in the formation of a carbon-nitrogen double bond ($R^1R^2C{=}NNHR^3$, where R^1, R^3 = alkyl, aryl, R^2 = H, alkyl, aryl) between the carbonyl group and the hydrazine group. This versatile synthetic pathway allows for the preparation of a diverse array of hydrazone derivatives with different substituents and functional groups.

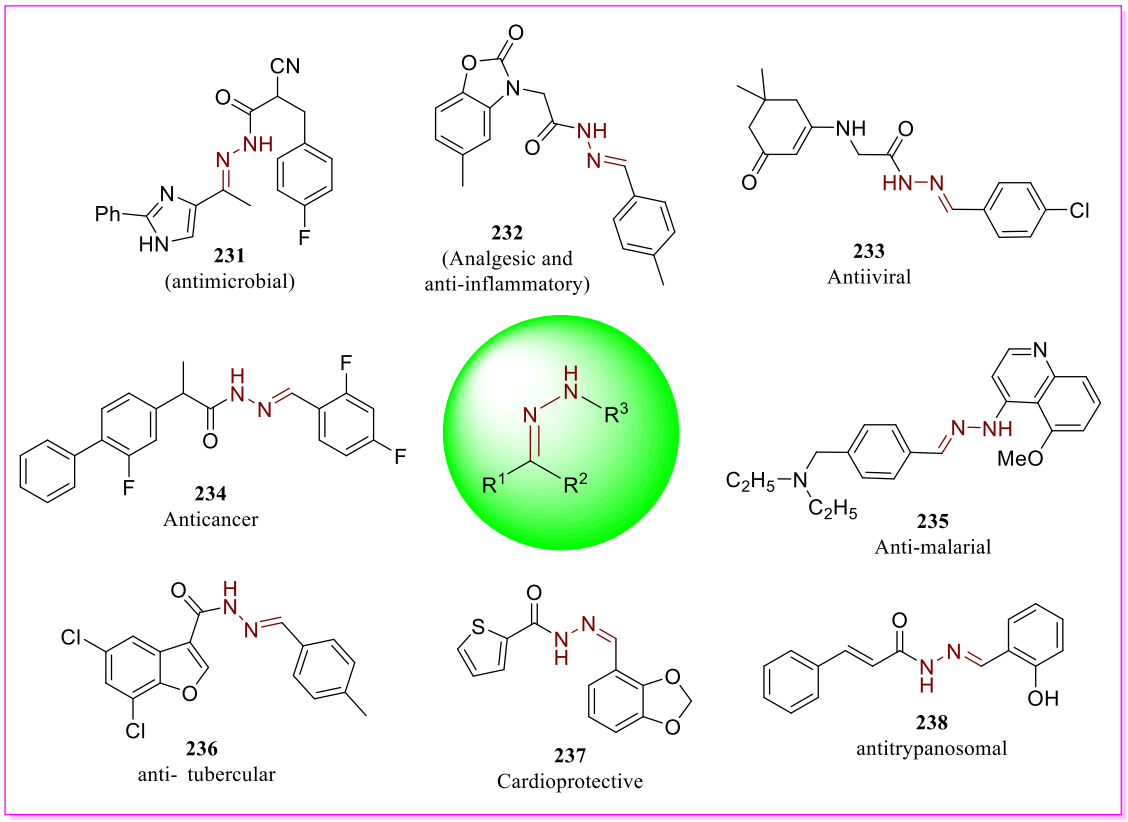


Figure 31. *Some selected examples of biologically active compounds bearing the hydrazone scaffold.*

Hydrazones have found a wide range of applications in the pharmaceutical industry, where they act as precursors for the synthesis of various compounds with remarkable biological activities such as antimicrobial (e.g. hydrazones containing imidazoles **231**)[284,285], anti-inflammatory and analgesic, antifungal (e.g. hydrazones bearing 5-methyl-2-benzoxazolinones **232**)[286], antiviral **233**[287], anticancer (flurbiprofen hydrazide derivatives **234**)[288] antimalarial **235**[289], antitubercular (benzofuran-3-carbohydrazide derivatives **236**)[290], cardioprotective (acylhydrazone derivative **237**)[291] or antitrypanosomal (cinamic *N*-acyl hydrazones **238**)[292]. (Figure 31). In addition to

their usefulness in the pharmaceutical industry, hydrazones are known for their ability to undergo other transformations in organic reactions such as oxidation[293,294], reduction[295–297], hydrophosphonylation[298–301], cycloaddition[302], allylation[303,304], alkylation[300,301] and Mannich reaction[305,306]. This diverse reactivity makes them important intermediates in the preparation of more complex molecules. (Figure 32).

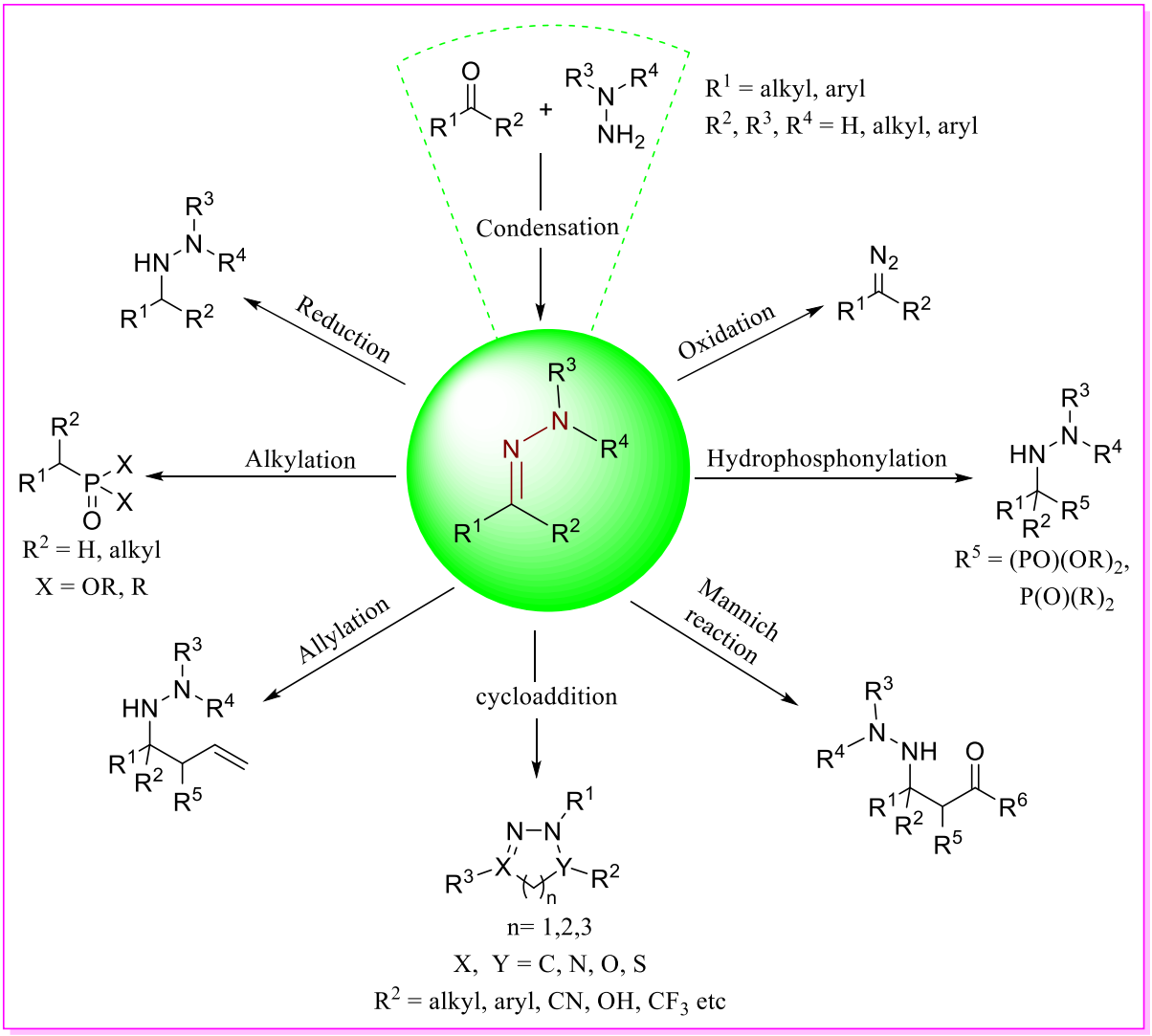
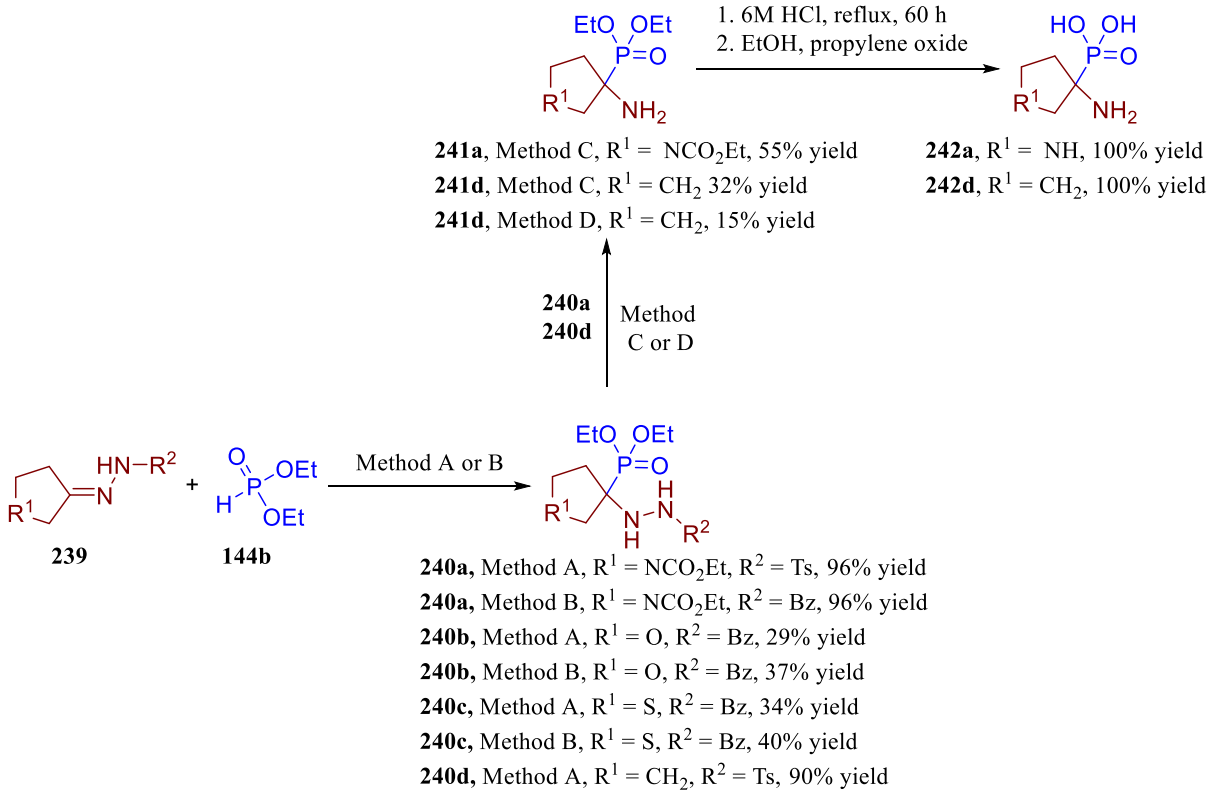


***Figure 32**. The preparation and utility of hydrazones as intermediates in the synthesis of structural diverse molecules*

The hydrophosphonylation of imines is a widely used and direct approach for the synthesis of α-aminophosphonic acids and their esters, which serve as structural analogues of amino acids. However, the use of imines as starting materials has suffered from some limitations, including the hygroscopic nature of many imines, and their isolation is problematic due to their instability, especially those derived from aliphatic aldehydes. In response to the challenges associated with the use of imines, hydrazones have been widely used as imine surrogates due to their improved stability and adaptable electrophilic strength, which allows

them to react with various nucleophiles in the synthesis of a wide range of nitrogen-containing compounds[282,298]. Although hydrazones find versatile applications in synthesizing a diverse array of molecular structures, it is unexpected that the existing literature pays relatively little attention to their potential as alternative precursors to imines in hydrophosphonylation reactions with phosphorus-containing nucleophiles. This provided an alternate route for producing aminophosphonic acids, a category of compounds known for their notable biological properties (for more information on their biological activities, please refer to the introductory section of this dissertation).

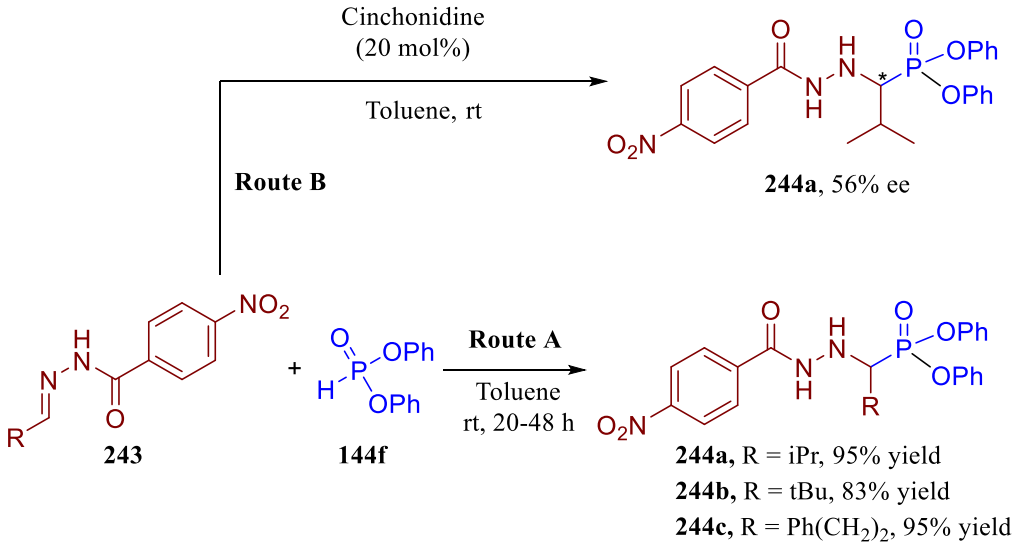
Among the scarcely known literature reports describing the use of hydrazones in the synthesis of aminophosphonates and aminophosphonic acids, the publication authored by Fadel et al[297] showed the nucleophilic addition of diethyl *H*-phosphonate **144b** to cyclic hydrazones **239** in the presence of trifluoromethanesulfonic acid (TfOH) to afford the cyclic hyrazinophosphonates **240** with yields ranging from 29% to 96% (Scheme 99).



***Scheme 99**. Selected examples of the synthesis of hydrazinophosphonates from hydrazones. **Method A**: $HP(O)(OEt)_2$ in excess, TfOH (0.3 equiv), 0 °C to rt, 4 h. **Method B**: $HP(O)(OEt)_2$ (1.1 equiv), TfOH (0.5 equiv), CH_2Cl_2, 0 °C, 1 h, then rt, 18-24 h. Removal of the N-N bonds of hydrazines. **Method C**: SmI_2 (2.2 equiv), THF, MeOH, 0 °C to rt, 1 h. **Method D**: Na (35 equiv), liquid NH_3, THF, EtOH, -50 °C to rt, 1 h.*

The subsequent removal of the hydrazine nitrogen-nitrogen bonds with either samarium (II) iodide or sodium liquid ammonia resulted in free cyclic aminophosphonates **241** with moderate yields (up to 55%). Finally, cyclic aminophosphonic acids **242** were obtained in quantitative yields by acid hydrolysis of the phosphonic ester moiety of compounds **241** and subsequently subjecting the resultant salts to treatment with propylene oxide (Scheme 99). In this established approach, the obtained yields tend to be modest, likely due to the low reactivity of the hydrazones employed. These hydrazones are derived from the condensation reaction involving cyclic ketones with either benzoyl- or tosylhydrazine.

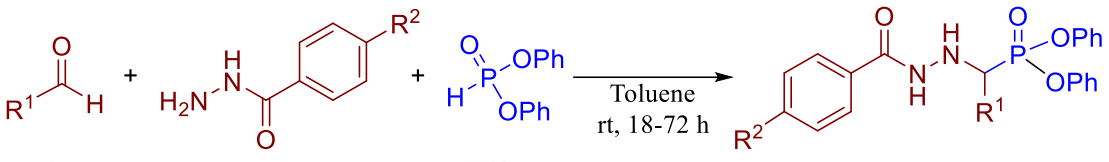
Herrera's research team conducted an uncatalyzed hydrophosphonylation process involving highly reactive *N*-acylhydrazones **243** and diphenyl *H*-phosphonate **144f** in toluene at ambient temperature. As a result of this reaction, α-hydrazinophosphonates **244** were generated, with impressive yields ranging from 83% to 95% (Scheme 100, route A). Performing the reaction in the presence of an organocatalyst (20 mol% of cinchonidine) resulted in the synthesis of the product with moderate enantioselectivity, achieving an enantiomeric excess of 56% (Scheme 100, route B)[298].



Scheme 100. *Uncatalyzed and catalyzed hydrophosphonylation of hydrazones* ***243***

The three-component reaction holds significant importance due to its ability to generate a diverse array of compound libraries. This method proves economically efficient in terms of solvent usage, and the products can be obtained through a single work-up and purification step. Owing to these advantages, the authors directed their focus towards employing the one-pot, three-component reaction involving aldehydes **49**, *N*-benzoylhydrazides **245**, and diphenyl *H*-phosphonate **144f** for the synthesis of α-hydrazinophosphonates **244**. This straightforward

condensation process led to the *in-situ* formation of the hydrazones, which subsequently underwent an addition reaction with the *H*-phosphonate to give the desired products **244** in yields ranging from moderate to excellent (50–95%) (Scheme 101)[298]. This developed protocol offers the advantages of being performed under mild reaction conditions and its atom economy, as it doesn't necessitate the use of a catalyst or an excess of the nucleophilic agent.

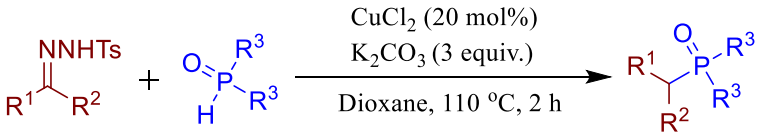


49 **245** **144f**

244a, R^1 = *i*Pr, R^2 = NO_2, 95% yield
244b, R^1 = *t*Bu, R^2 = NO_2, 62% yield
244c, R^1 = $Ph(CH_2)_2$, R^2 = NO_2, 50% yield
244d, R^1 = *i*Pr, R^2 = H, 70% yield
244e, R^1 = *i*Pr, R^2 = OMe, 60% yield
244f, R^1 = *c*-pentyl, R^2 = NO_2, 71% yield

Scheme 101. *Selected examples of uncatalyzed one-pot three-component reaction of aldehydes, N-acylhydrazides, and diphenyl H-phosphonate.*

A copper-mediated cross-coupling reaction, resulting in the construction of products with P-C(sp^3) bonds was reported by Wu et al (Scheme 102)[299]. This protocol involved the reductive coupling of *N*-tosylhydrazones **246** with either diphenyl phosphine oxide or *H*-phosphonates in the presence of copper (II) chloride and K_2CO_3 in dioxane to give the corresponding alkylphosphonates **247** in modest to good yields (50–82%) (Scheme 102).



246 **144**

247a, R^1 = Ph, R^2 = Me, R^3 = Ph, 66% yield
247b, R^1 = Ph, R^2 = Et, R^3 = Ph, 60% yield
247c R^1 = 4-MePh, R^2 = Me, R^3 = Ph, 70% yield
247d, R^1 = 4-MeOPh, R^2 = Me, R^3 = Ph, 80% yield
247e, R^1 = 4-CF_3Ph, R^2 = Me, R^3 = Ph, 63% yield
247f, R^1 = Naphthyl, R^2 = Me, R^3 = Ph, 65% yield
247g, R^1 = *n*-C_3H_7, R^2 = Me, R^3 = Ph, 67% yield
247h, R^1 = Ph, R^2 = H, R^3 = Ph, 80% yield
247i, R^1 = 4-MeOPh, R^2 = Me, R^3 = 2,4-diMePh, 76% yield
247j, R^1 = 4-MeOPh, R^2 = Me, R^3 = OEt, 75% yield
247k, R^1 =4-MeOPh, R^2 = Me, R^3 = OPh, 70% yield
247l, R^1 = 4-MeOPh, R^2 = Me, R^3 = BINOL, 66% yield

Scheme 102. *Copper-catalyzed cross-coupling of N-tosylhydrazones with either diphenyl phosphine oxides or H-phosphonates.*

This method demonstrates high efficiency with various hydrazones (including aliphatic, aromatic, and polycyclic aromatic types) and diverse cyclic or acyclic phosphorus-containing nucleophiles within a short reaction time. The authors proposed a mechanism for this reductive coupling, which commences with the *in-situ* reduction of the Cu (II) catalyst to Cu (I) species by the diazo compound derived from the oxidation of *N*-tosylhydrazones under basic and thermally induced conditions. The Cu (I) species, now in its reduced state, facilitates the formation of copper(I)-carbene complex **TS1** through the decomposition of the diazo compound. The presence of K_2CO_3 activates the diphenyl phosphine oxide, prompting a nucleophilic attack on the carbene center **TS1**. This results in the formation of a copper intermediate **TS2**, which is then subjected to protonation to yield the desired product **247** (Figure 33).

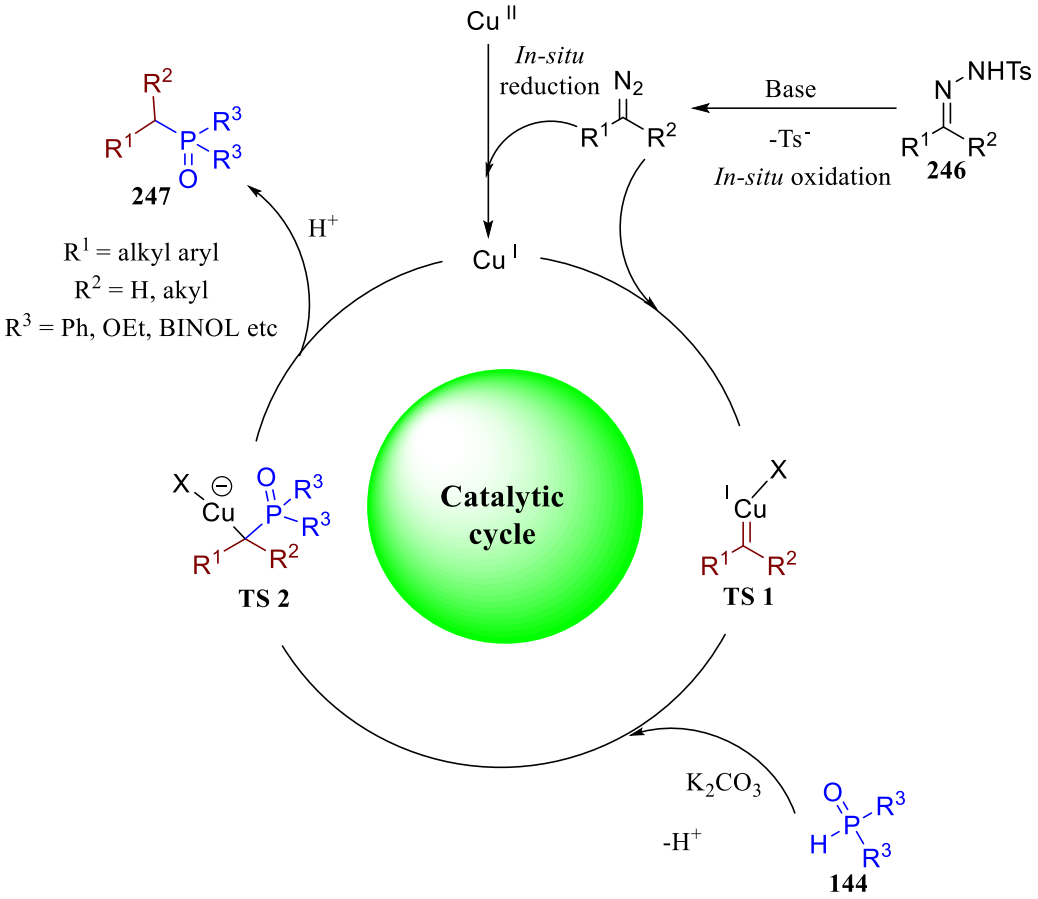
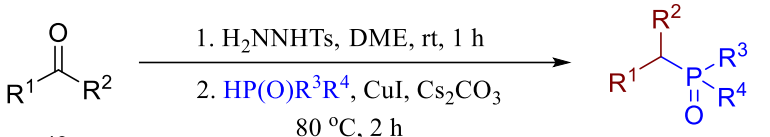


***Figure 33**. Proposed catalytic mechanism for copper-catalyzed cross-coupling of N-tosylhydrazones with P-nucleophiles.*

In the same year, another research group published an article related to the alkylation of either diphenyl phosphine oxide or *H*-phosphonates with *N*-tosylhydrazones **246** in the presence of copper (I) iodide and Cs_2CO_3 in dimethoxyethane (DME) instead to produce alkylphosphonates

247 in good to excellent yields (up to 92%) (similar to Scheme 102 but the conditions varries)[300]. In this protocol, the reactions were carried out at a lower temperature and with a lower catalyst loading (10 mol%) compared to Wu's protocol above (Scheme 102). Additionally, the yields obtained in this method were higher. The authors also demonstrated a one-pot protocol in which the carbonyl compounds (aldehydes and ketones) reacted directly with sulfonyl hydrazides in DME for an hour. The *in-situ* generated *N*-tosylhydrazones **246** were then subjected to reductive coupling with the P-nucleophile in the presence of CuI and Cs_2CO_3 to afford the P-C(sp^3) alkylphosphonates **247** with yields ranging from 60% to 80% (Scheme 103). The one-pot approach afforded products **247** with lower yields than those obtained by direct hydrophosphonylation of the isolated *N*-tosylhydrazones **246**[300].



49

247f, R^1 =Ph, R^2 = H, R^3, R^4 = Ph, 60% yield
247k, R^1 =Ph, R^2 = H, R^3, R^4 = OEt, 75% yield
247l, R^1 =4-NCPh, R^2 = H, R^3, R^4 = OEt, 70% yield
247m, R^1 =Ph, R^2 = Me, R^3, R^4 = OEt, 77% yield
247n, R^1 =4-$(Me)_2$NPh, R^2 = H, R^3 = OEt, R^4 = Ph, 68% yield

Scheme 103. *Selected examples of the synthesis of alkylphosphonates **247** via the one-pot three-component reaction*

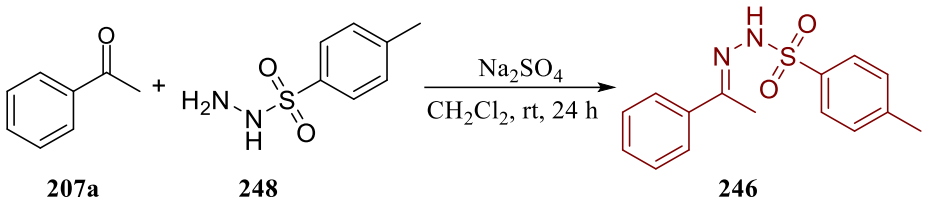
Given the crucial role of hydrazones as substitutes for imines in the synthesis of racemic alkylphosphonates, α-hydrazinophosphonates, and their related derivatives, along with the limited presence of information in the literature regarding their asymmetric variants, their study holds significant importance.

In the course of my Ph.D., I attempted to develop a diastereoselective protocol for synthesizing alkylphosphonates via the copper-catalyzed reductive coupling of *N*-tosylhydrazones **246** with (*R*,*R*)-**29**. Also in this chapter, I presented a diastereoselective protocol for the hydrophosphonylation of *N*-acylhydrazones **243** using (*R*,*R*)-**29** as a nucleophilic agent, resulting in the formation of α-hydrozinophosphonates **244**. This protocol gave the products with moderate to high yields and satisfactory diastereoselectivity. In both protocols, I hypothesized that the presence of the phosphorus-containing chiral auxiliary could play a vital role in inducing and controlling the diastereoselectivity of the final products.

2.0. Results and discussion

2.1. Synthesis of starting *N*-tosylhydrazone

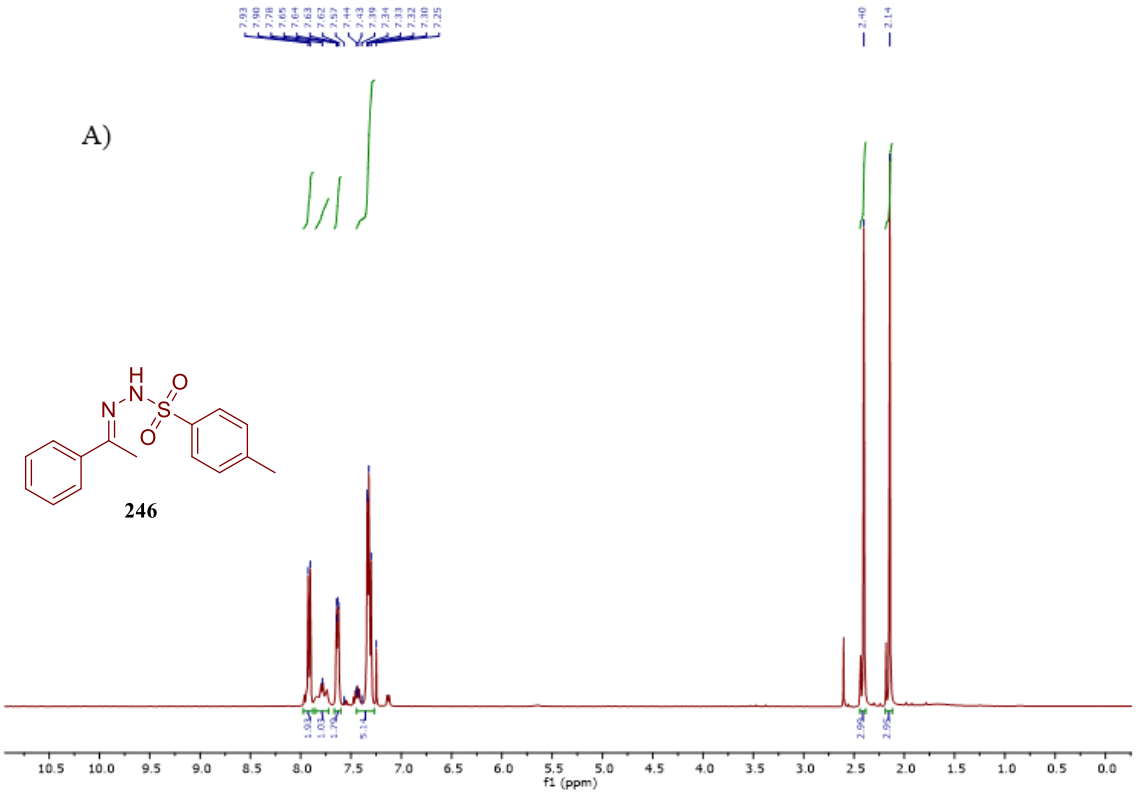
The preparation of the hydrazone was done according to the literature[300]. At 60 °C, a solution of pure *p*-toluenesulfonyl hydrazide ($TsNHNH_2$) **248** in methanol with stirring, followed by the addition of acetophenone, and the mixture was refluxed for an hour, cooled down, and filtered (Scheme104).



207a **248** **246**

Scheme 104. *Synthesis of N-tosylhydrazone* ***246***

The obtained white residue was washed with petroleum ether and dried with vacuum to give a 77% yield of *N-tosylhydrazone* that was employed in finding the optimal reaction conditions. The confirmation of the structure of the hydrazone **246** was accomplished through ^{1}H and ^{13}C NMR spectra analysis (Figure 34). The obtained spectra were identical to those reported in the literature[307]



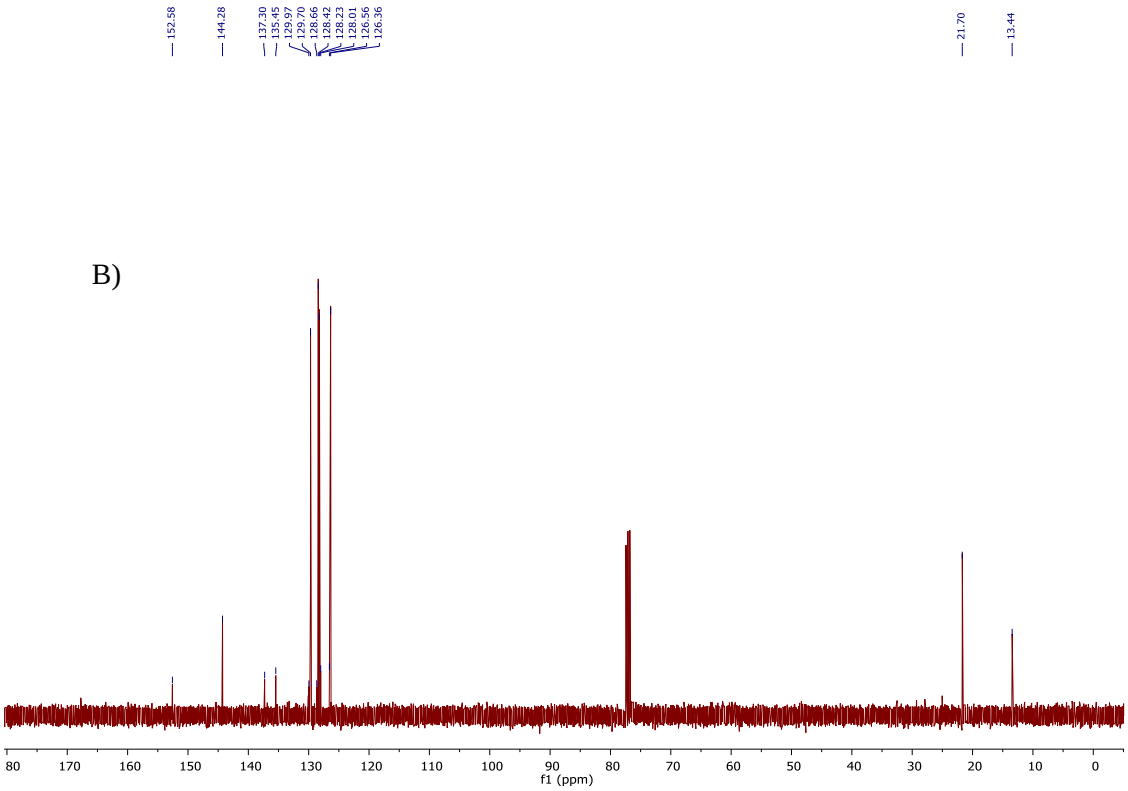


Figure 34. *The N-tosylhydrazones* ***246*** *spectra registered with Jeol 400yh apparatus. A)* ^{1}H *NMR (400 MHz,* $CDCl_3$*). B)* ^{13}C *NMR (101 MHz,* $CDCl_3$*).*

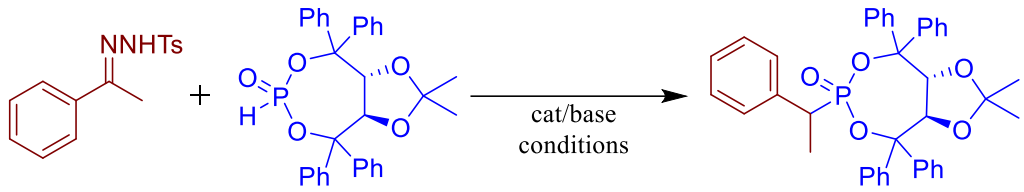
2.2. The reductive coupling of *N*-tosylhydrazone with TADDOL-derived *H*-phosphonate *(R,R)*-29

I initiated this work based on the publications of Wu et al.[299] and Miao et al.[300], where the authors carried out the non-asymmetric copper-catalyzed reductive coupling reaction to obtain the P-C(sp^3) alkylphosphonates **247** as a racemic mixture (Schemes 102 and 103). Inspired by these strategies, I envisioned that the introduction of a chiral nucleophile containing phosphorus could lead to an asymmetric version of this reductive coupling.

I initiated the investigation by performing the nucleophilic addition of (*R,R*)-**29** to *N*-tosylhydrazones **246** in the absence of either catalyst, base, or both in DME at 80 °C. Under such conditions, no reactivity was observed (Table 13, entries 1–3). The reductive coupling was tested by applying similar conditions to what has been reported by Miao et al.[300] (Scheme 103). Pleasingly, a complete conversion of (*R,R*)-**29** to the desired alkylphosphonate **247** was observed, albeit with a poor diastereomeric ratio of 42:52 (Table 13, entry 4). The investigation of reaction conditions was extended by experimenting with different inorganic and organic

bases (Table 13, entries 4-8). In particular, no reactivity was observed when using Et_3N (Table 13, entry 5) or quinine (Table 13, entry 8).

Table 13. Optimization of the reaction condition of the synthesis alkylphosphonates[a]



246 (*R,R*)-**29** **247**

Entry	Solvent	Cat[b]	Base[c]	Temp (°C)	Time (h)	Conv.[d] (%)	dr[d]
1	DME	-	-	80	4	-	-
2	DME		Cs_2CO_3	80	4	-	-
3	DME	CuI	-	80	4	-	-
4	DME	CuI	Cs_2CO_3	80	2	100	42:58
5	DME	CuI	Et_3N	80	2	-	-
6	DME	CuI	NaH	80	2	100	44:56
7	DME	CuI	DBU	80	2	100	48:52
8	DME	CuI	Quinine	80	2	-	-
9	DME	CuCl	Cs_2CO_3	80	2	100	43:57
10	DME	$CuCl_2$	Cs_2CO_3	80	2	100	43:57
11	DME	CuBr	Cs_2CO_3	80	2	100	44:56
12	DME	$NiBr_2$	Cs_2CO_3	80	4	24	43:57
13	CH_3CN	CuI	Cs_2CO_3	80	2	100	50:50
14	Dioxane	CuI	Cs_2CO_3	80	2	100	49:50
15	THF	CuI	Cs_2CO_3	80	2	100	50:50
16	DMF	CuI	Cs_2CO_3	80	2	100	46:54
17	Toluene	CuI	Cs_2CO_3	80	2	20	51:49
18	DME	CuI	Cs_2CO_3	60	2	-	-
19	DME	CuI	Cs_2CO_3	40	6	-	-
20	DME	CuI	Cs_2CO_3	rt	8	-	-
21[e]	DME	CuI	Cs_2CO_3/L	80	2	100	45:55

*[a]The reaction conditions: reactions were performed in 1.0 mL of the solvent on a 0.10 mmol scale of **246** and 0.10 mmol of (R,R)-**29**. [b]20 mol% of the catalyst. [c]1.5 equivalent of the base used (unless otherwise stated). [d]dr and conversion were determined based on ^{31}P NMR analysis of the crude reaction. [e]The reaction performed with 1.0 equiv of the Ligand (L = 1,10-phenanthroline).*

Among the bases considered, Cs_2CO_3 emerged as the preferred reaction base for subsequent optimizations, as it gave the best results in terms of diastereoselectivity. The two diastereoisomers were clearly distinguishable on the ^{31}P spectrum. One of the diastereoisomers gave a singlet at a chemical shift of $\delta_{minor} = 23.71$ and the other one at a chemical shift of δ_{major}

= 22.74 ppm. The NMR experiments were carried out in $CDCl_3$ and the crude reaction mixtures were analyzed (Table 13, entry 4 and Figure 35).

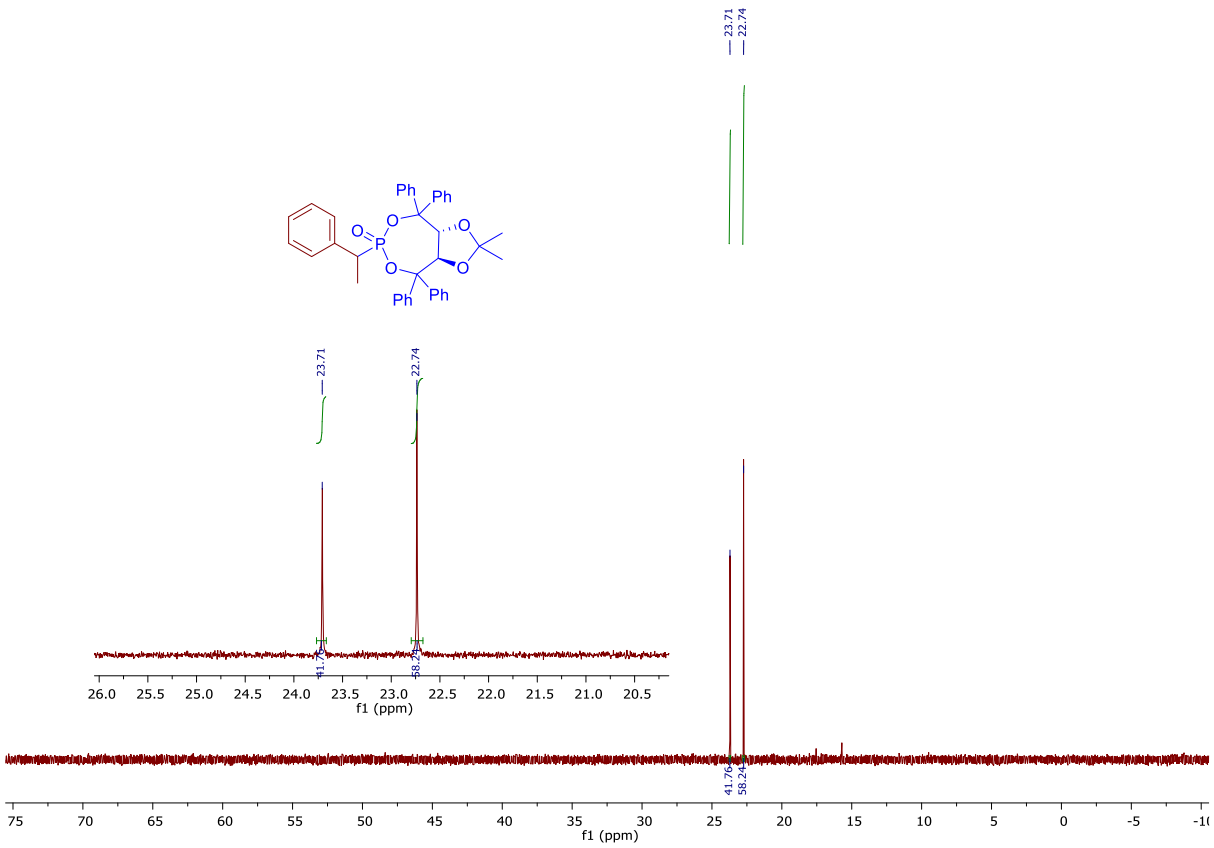
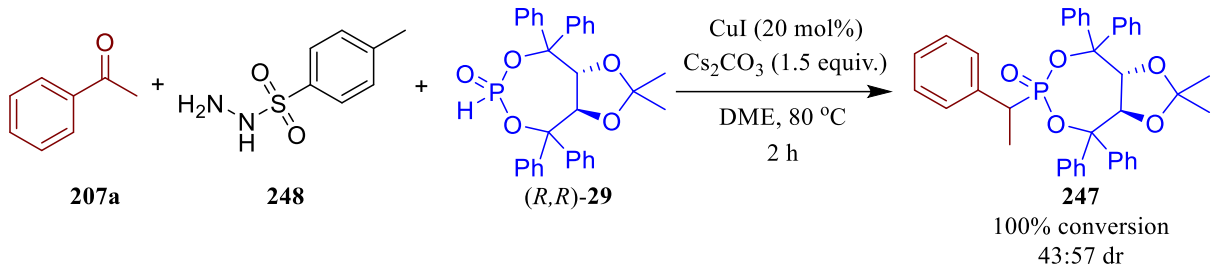


Figure 35. *^{31}P NMR (162MHz, $CDCl_3$ using Jeol 400yh apparatus) spectrum showing reductive coupling of N-tosylhydrazones **246** with (R,R)-**29** in the presence of CuI and Cs_2CO_3(Table 14, entry 4).*

The reaction proceeded smoothly with complete conversion when I examined other copper salts like CuCl, $CuCl_2$, and $CuBr_2$, but without success in improving the diastereoselectivity (Table 13, entries 9–11). When I conducted the reaction with $NiBr_2$, it resulted in poor reactivity and diastereoselectivity (Table 13, entry 12). In my continued effort to enhance diastereoselectivity, I tested a variety of solvents, but regrettably, the diastereomeric ratios were not improved (Table 13, entries 13–17). Likewise, I examined the influence of temperature on the reactivity and diastereoselectivity of the reaction system. However, no reactivity was observed when the reaction was executed at different temperatures, specifically 60°C, 40°C, and even at room temperature (Table 13, entries 18-20). The obtained results align well with the mechanism put forth by Wu et al. regarding the generation of alkylphosphonate **247**[299]. According to their proposal, *N*-tosylhydrazones **246** undergo oxidation in the presence of a base and heat to produce the diazo compound crucial for the *in-situ* reduction of Cu (II) to Cu (I) (refer to Figure 33 for more detail). Consequently, these results imply that elevated temperatures are essential for facilitating the progression of this reaction. Finally, I performed the reductive coupling in

the presence of base, catalyst, and 1,10-phenanthroline acting as a ligand at 80 °C. The reaction proceeded with complete conversion, but diastereoselectivity was still poor (Table 13, entry 21). I made several attempts to enrich one of the diastereoisomers of entry 4 by crystallization and chromatography but my efforts were unsuccessful.

Under the best optimized reaction conditions, I also tested the one-pot, three-component reductive coupling of acetophenone **49** with *p*-toluenesulphonyl hydrazide **248** and the *H*-phosphonate **29** catalyzed by copper (II) iodide in the presence of Cs_2CO_3 in dimethoxyethane (DME). The reaction proceeded with 100% conversion to give the desired product **247**, but with poor diastereoselectivity (43:57 dr) (Scheme 105).



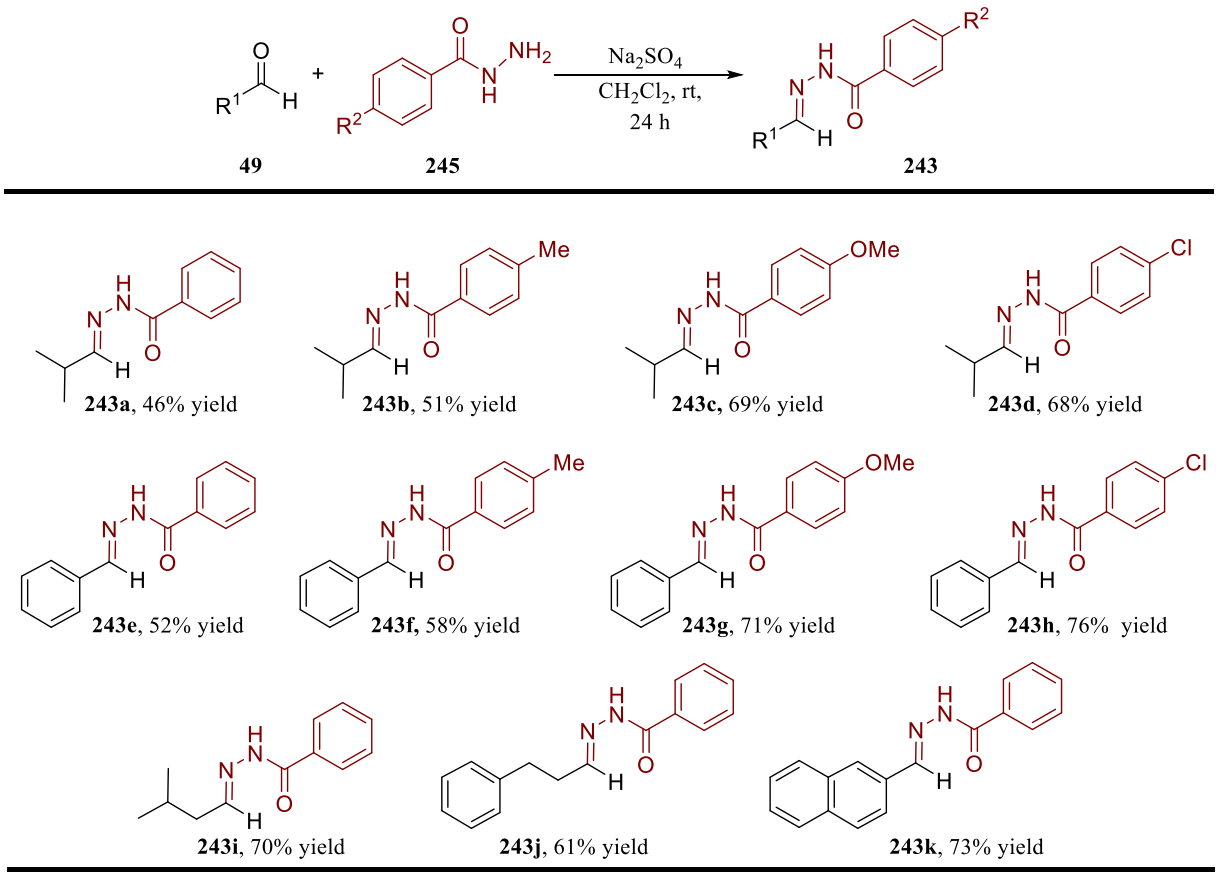
Scheme 105. *One pot Cu-catalyzed synthesis of alkylphosphonate **247***

Here I wish to emphasize that I didn't proceed with the substrate scope of this reductive coupling because finding the optimal conditions that afford the product with good diastereoselectivity was unsuccessful instead I turned my attention to the use of a different type of hydrazone to carry out the hydrophosphonylation reaction.

2.3. Synthesis of *N*-acylhydrazones and optimizations of the hydrophosphonylation reaction

Inspired by the research conducted by Herrera et al[298], where they performed the uncatalyzed hydrophosphonylation of *N*-acylhydrazones **243** with diphenyl *H*-phosphonate **150** to give the α-hydrazinophosphonates **244** as a racemic mixture (Scheme 100). In their work, the authors showed one example where they performed the first asymmetric hydrophosphonylation in the presence of cinchonidine. The reaction afforded product **244** but with low enantioselectivity (56% ee). Therefore, I envisioned that performing the nucleophilic addition of TADDOL-derived *H*-phosphonate **29** acting as a chiral auxiliary in the reaction system could play a crucial role in inducing high diastereoselectivity in the desired products. Before testing this hypothesis, I carried out the synthesis of the *N*-acylhydrazones **243** following the protocol described by Herrera[298]. Under mild reaction conditions, the direct condensation of benzohydrazide **245** with aldehydes in CH_2Cl_2 resulted in the formation of *N*-acylhydrazones

243. The subsequent crystallization of the crude product in ethanol gave the pure *N*-acylhydrazones (11 compounds) in the form of a white solid with yields ranging from 46% to 76% (Scheme 106).



Scheme 106. *Synthesis of N-acylhydrazones* ***243***

The ^{1}H NMR, ^{13}C NMR, and HRMS analyses were carried out on the pure isolated *N*-acylhydrazones **243** to elucidate and confirm their respective structures. The obtained data agreed with the data reported in the literature[298,308,309]. Figure 36 shows the NMR spectra, with *N*-acylhydrazones **243d** as a representative example.

During the optimization process, I used the *N*-acylhydrazone **243d** as model substrate and encountered a lack of reactivity when conducting the hydrophosphonylation reaction with (*R*,*R*)-**29** without a base (Table 14, entry 1). However, when the reaction was carried out in the presence of solid inorganic bases such as K_2CO_3 or KOH, as well as a liquid organic base (Et_3N), it resulted in product formation with satisfactory conversion but only moderate diastereoselectivity (Table 14, entries 2-4). In the presence of bifunctional alkaloid organocatalysts **II-III**, which functioned as both a base and a catalyst, the reaction proceeded with good conversion and diastereoselectivity (Table 14, entries 5-6).

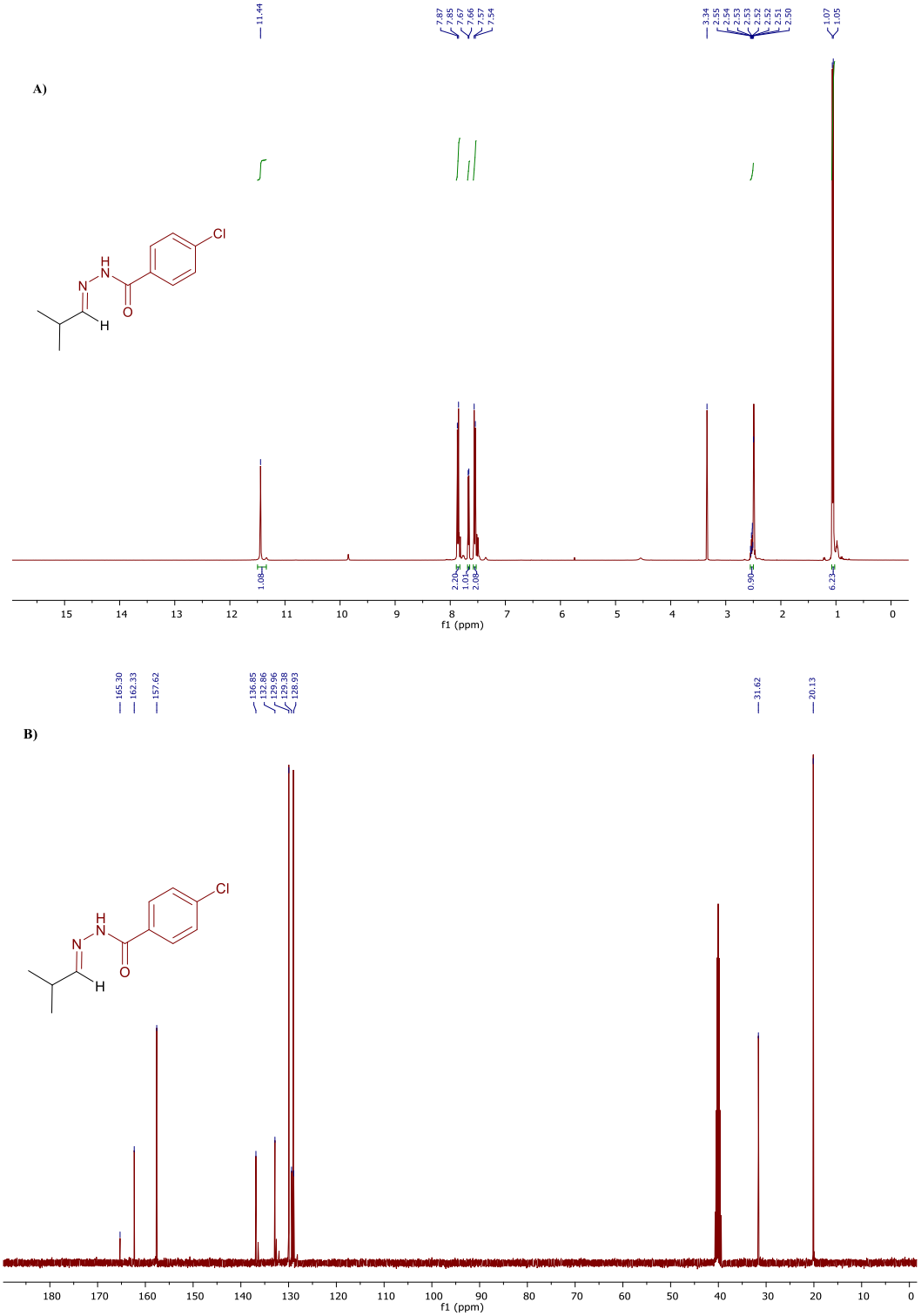
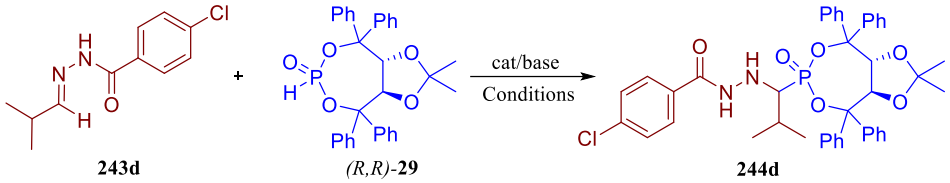
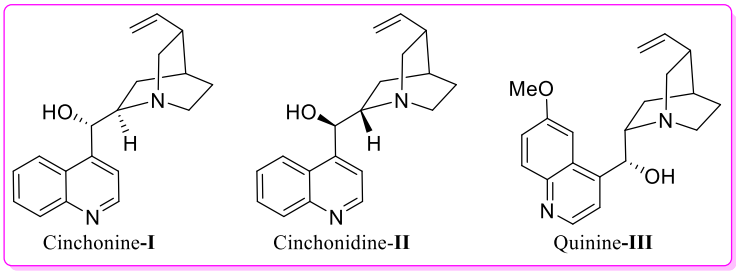


Figure 36. *N-acylhydrazone* ***243d*** *spectra registered with the use of Jeol 400yh instrucment. A)* ^{1}H *NMR (400 MHz, DMSO-*d_6*). B)* ^{13}C *NMR (101 MHz, DMSO-*d_6*).*

Table 14. Hydropphosphonylation of reaction of *N*-acylhydrazone **243d** with *(R,R)*-**29**: optimizations.





Entry	Solvent[a]	Base[b]/Cat.	Temp (°C)	Time (h)	Conv[c]. (%)	dr[c]
1	Toluene	-	rt	96	-	-
2	Toluene	Et_3N	rt	96	63	59:41
3	Toluene	K_2CO_3	rt	96	100	73:27
4	Toluene	KOH	rt	96	90	51:49
5	Toluene	**III** (0.5 equiv)	rt	96	87	17:83
6	Toluene	**II** (0.5 equiv)	rt	96	94	39:61
7	Toluene	**I** (0.5 equiv)	rt	96	34	91:9
8	Toluene	**I** (0.5 equiv)	80	50	98	80:20
9	Toluene	**I** (0.5 equiv)	60	50	95	84:16
10	CH_2Cl_2	**I** (0.5 equiv)	60	50	52	77:22
11	THF	**I** (0.5 equiv)	60	50	37	79:21
12	MeOH	**I** (0.5 equiv)	60	50	80	67:33
13	Dioxane	**I** (0.5 equiv)	60	50	29	79:21
14	EtOAc	**I** (0.5 equiv)	60	50	56	77:23
15	DME	**I** (0.5 equiv)	60	50	-	-
16	Toluene	**I** (0.3 equiv)	60	50	80	86:16
17	Toluene	**I** (0.2 equiv)	60	50	79	85:15
18	Toluene	**I** (0.1 equiv)	60	50	73	86:16

*[a]The reaction conditions: reactions were performed in 1.0 mL of the solvent on a 0.10 mmol scale of **243d** and 0.10 mmol of (R,R)-**29**. [b]1.0 equivalent of the base used (unless otherwise stated). [c]dr and conversion were determined based on ^{31}P NMR analysis of the crude product.*

Analyzing the ^{31}P NMR spectrum in entry 5 of Table 14, the chemical shift of the signal corresponding to the starting TADDOL-derived *H*-phosphonate **29** (δ_P = -3.09 ppm, in $CDCl_3$) markedly differed from that of the two diastereoisomers in the reaction product **244** (signal corresponding to the minor diastereomer at 22.12 ppm and that of the major diastereomer at

21.62 ppm, as registered in $CDCl_3$). This difference allowed me to precisely determine the conversion and the diastereomeric ratio of the reaction (Figure 37).

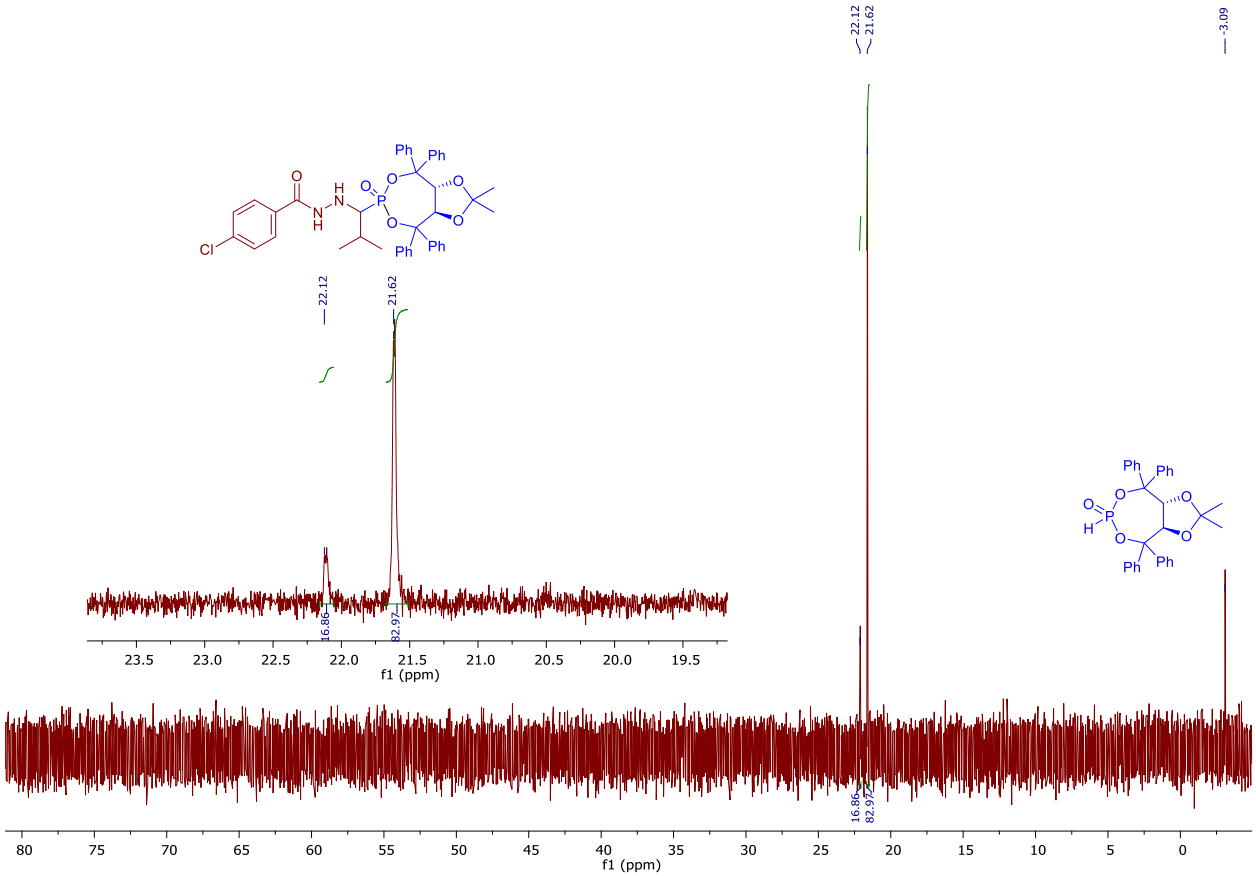


Figure 37. *^{31}P NMR (162MHz, $CDCl_3$ using Jeol 400yh apparatus) spectrum showing the crude product of hydrophosphonylationv reaction of N-acylhydrazone **243d** with (R,R)-**29** (Table 14, entry 5).*

In the presence of cinchonine (**I**) under the same reaction conditions, low conversion was achieved, albeit with satisfactory diastereoselectivity, and an inversion of the two diastereoisomers was also observed based on the ^{31}P NMR spectrum. (Table 14, entry 7). In my pursuit to enhance the conversion, I carried out the reaction at elevated temperatures of 80°C and 60°C (entries 8–9). The most favorable outcome, with the best result in term of conversion and diastereoselectivity, was achieved when the reaction was performed at 60°C for 50 hours in the presence of cinchonine (**I**). Therefore, this temperature was selected as the optimal one for subsequent optimization efforts (Table 14, entry 9, and figure 38). Subsequently, I explored the influence of solvents on the reaction system (Table 14, entries 9–15). Out of all the solvents examined, toluene gave the most favorable results (Table 14, entry 9). Finally, I delved into the impact of varying the catalyst loading by altering the quantity used in the reaction (Table 14, entries 16–18). The most optimal outcome, characterized by superior reactivity and

diastereoselectivity, was achieved when employing 0.5 equivalents of cinchonine (Table 14, entry 9).

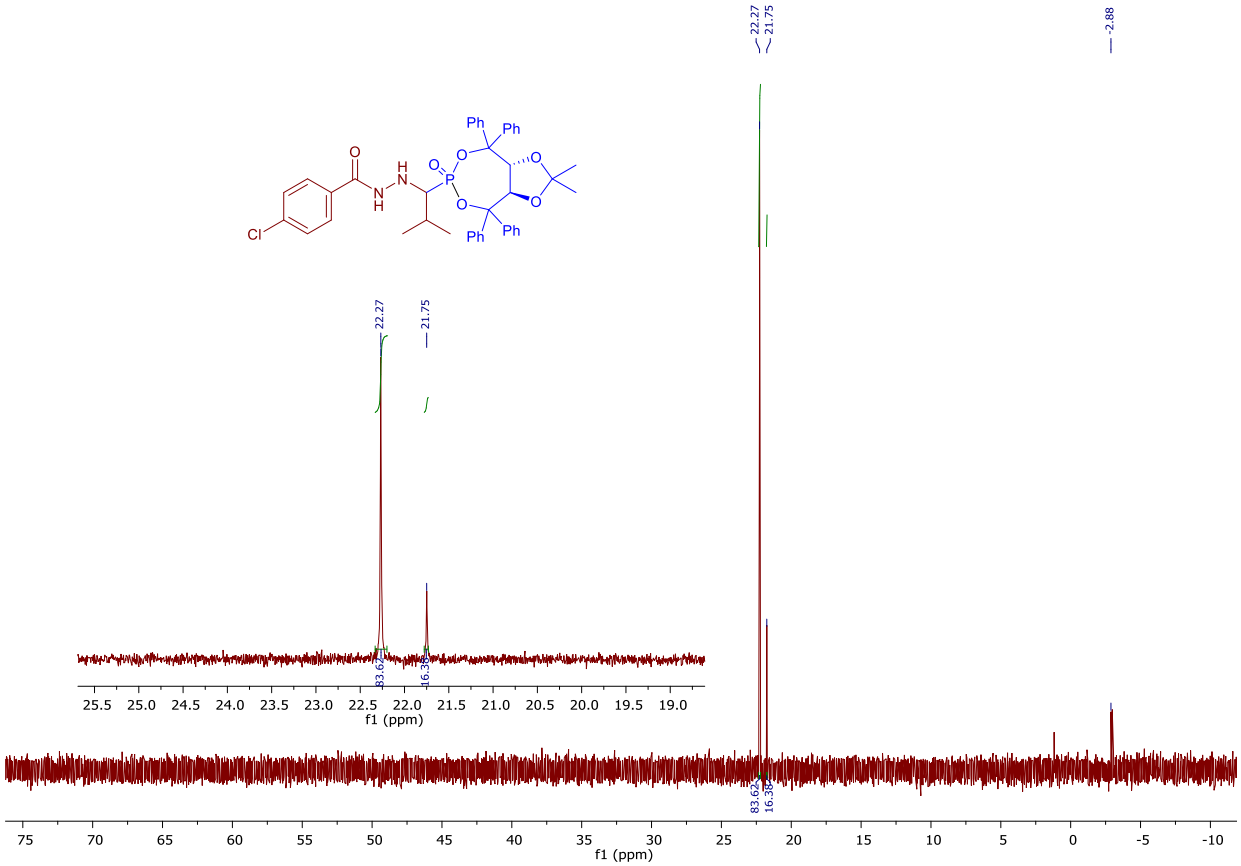
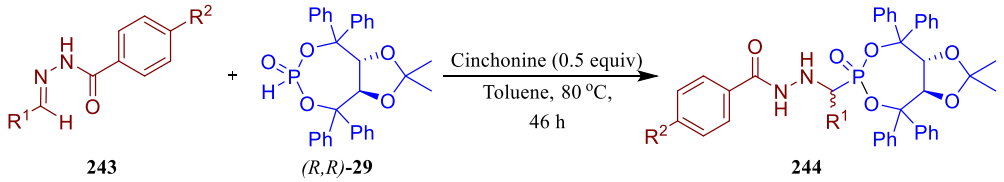
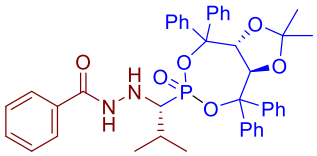


Figure 38. *^{31}P NMR (162MHz, $CDCl_3$ using Jeol 400yh apparatus) spectrum showing an inverse distribution of the two diastereoisomers in the presence of cinchonine (Table 14, entry 9).*

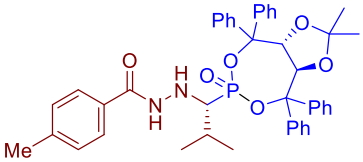
With the optimized reaction conditions in hand, I proceeded to investigate the methodology's scope to assess its suitability and constraints in the hydrophosphonylation process involving various hydrazones **243a-j**. The resulting products **244a–j**, were successfully synthesized with yields ranging from moderate to high (51–91%) and satisfactory diastereoselectivity (up to >99:1 dr) (Scheme 107). The hydrophosphonylation reaction proceeded seamlessly when utilizing aliphatic *N*-acylhydrazones, both with and without electron-donating or electron-withdrawing groups on the benzyl ring of the hydrazide fragment **243a-d**. This resulted in the formation of products **244a-d** with high yields ranging from 80% to 85% and excellent diastereoselectivity after column chromatography (>99:1). When working with aromatic hydrazones, whether with electron-donating or electron-withdrawing substituents or without any substituent on the benzyl ring of the hydrazide part, it became evident that a prolonged reaction time was necessary to achieve complete conversion.



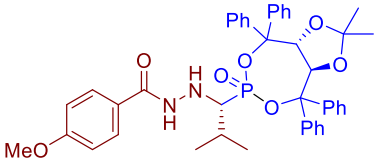
243 *(R,R)*-**29** **244**



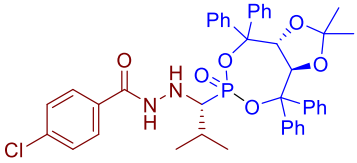
244a, 85% yield, dr:87:13 (>99:1)



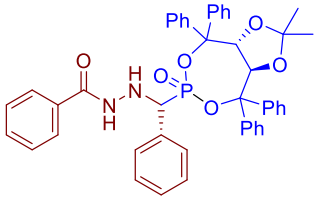
244b, 80% yield, dr:83:17 (>99:1)



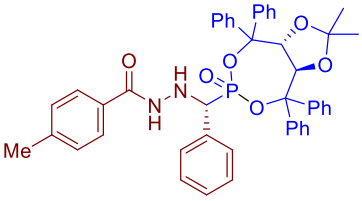
244c, 83% yield, dr:86:14 (>99:1)



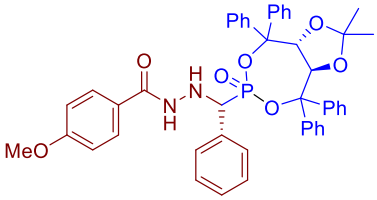
244d, 85% yield, dr:84:16 (>99:1)



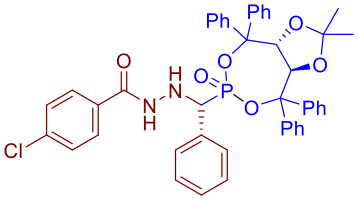
244e[a], 60% yield, dr:87:13 (90:10)



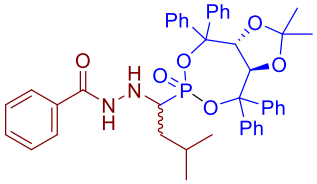
244f[a], 81% yield dr:88:12 (94:6)



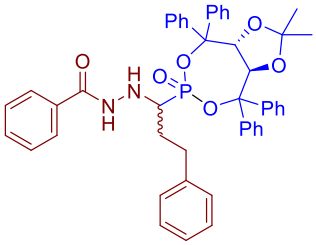
244g[a]. 51% yield, dr:: 95:5 (>99:1)



244h[a], 59% yield, dr:90:10 (>99:1)



244i[a], 86% yield, dr:30:70 (18:82)



244j[a], 79% yield, dr:35:65 (25:75)

Scheme 107*. Scope of the hydrophosphonylation reaction of N-acylhydrazones* ***243*** *with (R,R)-****29*** *in the formation α-hydrozinophosphonate* ***244****. [a]96 h of reaction time. The dr in parenthesis was after either column chromatography or crystallization.*

This extended reaction time led to the formation of α-hydrazinophosphonates **244e-h** with yields spanning from 51% to 86% while maintaining a commendable level of diastereoselectivity. In the case of products **244i-j**, which resulted from reactions involving hydrazones derived from aliphatic aldehydes with longer branched chains and 3-phenylpropionaldehyde, satisfactory yields were achieved. However, the diastereoselectivity was moderate, and there was also a notable occurrence of inversion of the chemical shift between the major and minor diastereoisomers.

Under the optimized conditions, I conducted a one-pot condensation reaction involving benzohydrazide **245**, an aldehyde **49**, and (*R*,*R*)-**29**. This reaction resulted in a mixture of both α-hydrazinophosphonate **244** and α-hydroxyphosphonate **205** as confirmed by the ^{31}P NMR analysis of the crude reaction mixture (Figure 39).

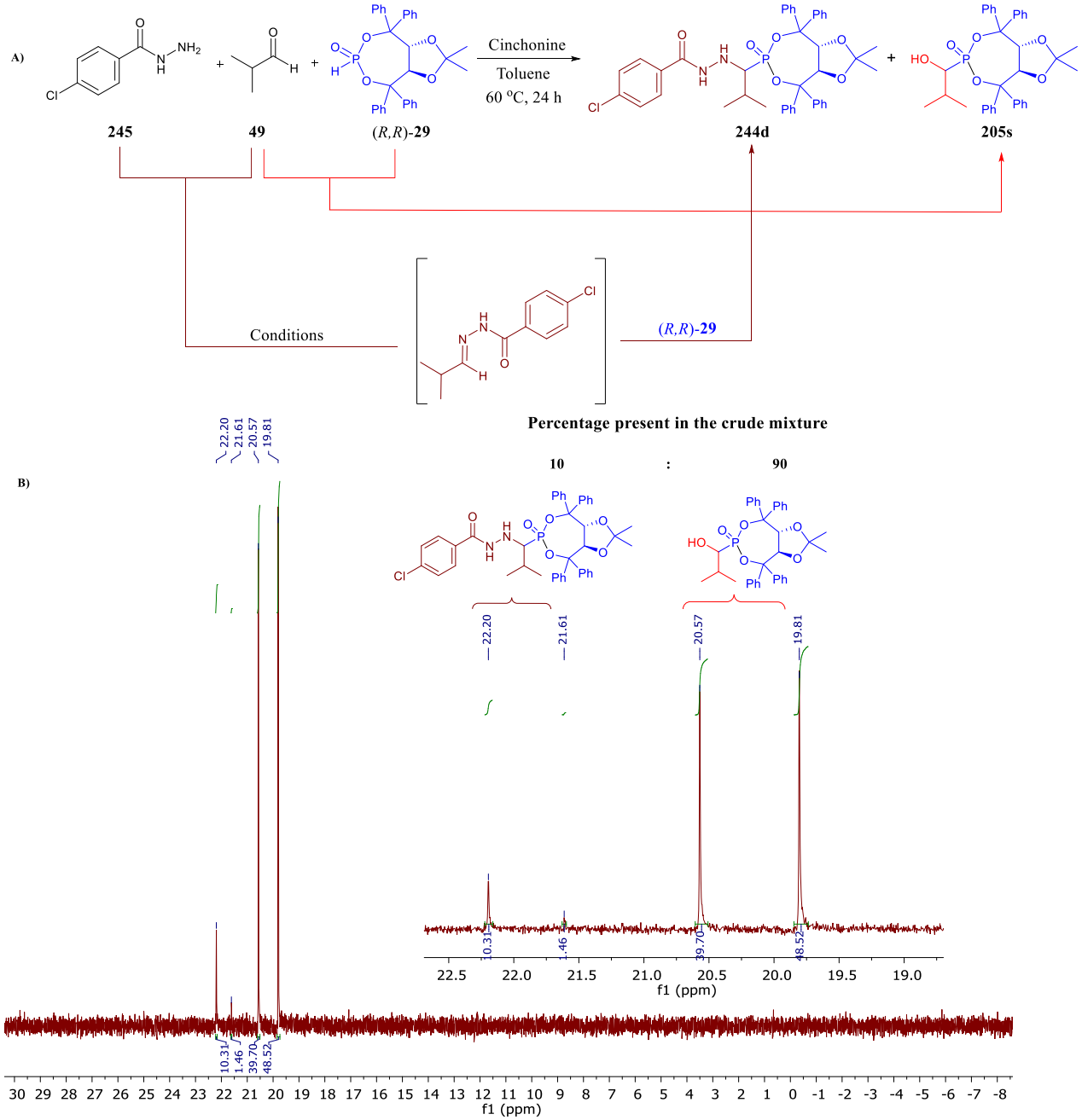
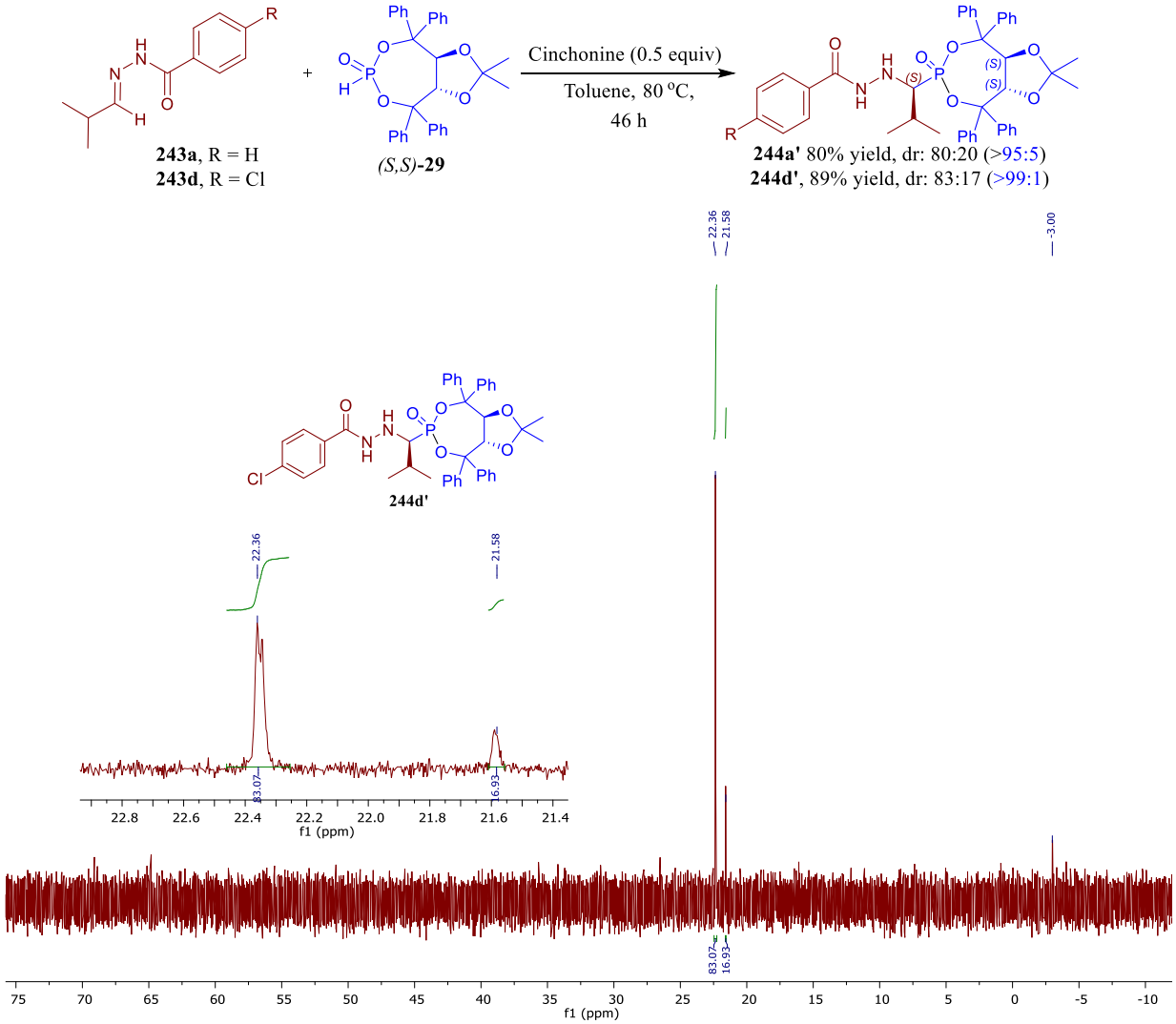


Figure 39. *^{31}P NMR (162MHz, $CDCl_3$ Jeol 400hy apparatus) spectrum of the crude product of the one-pot, three-component condensation of benzohydrazide **245** with isobutyraldehyde **49** and (R,R)-**29**.*

The signals observed at chemical shifts of δ_P = 22.20 ppm and δ_P = 21.61 ppm corresponded to the major and minor diastereoisomers of α-hydrazinophosphonate **244d**, whereas the signals at δ_P = 20.57 ppm and δ_P = 19.81 ppm represented the major and minor diastereoisomers of α-

hydroxyphosphonate **205s**. (Figure 39). Additionally, the HR-MS analysis confirmed the presence of both products in the crude reaction mixture. This result was predictable and could be attributed to the simultaneous presence of two nucleophiles: the benzohydrazide **245** and the *H*-phosphonate derived from TADDOL (*R*,*R*)-**29** competing for one electrophilic species (aldehyde **49**).



Scheme 108**. The hydrophosphonylation reaction of N-acylhydrazones **243d** with (S,S)-**29** and the ^{31}P NMR (162MHz, $CDCl_3$ using Jeol 400yh apparatus) spectrum of the crude product **244d'** of the hydrophosphonylation of N-acylhydrazone **243d** with (S,S)-**29.

Additionally, I opted to examine the hydrophosphonylation reaction of *N*-acylhydrazone **243a** with the enantiomerically opposite variant of the chiral phosphorus auxiliary, specifically (*S*,*S*)-**29**, using the previously determined optimal conditions. This led to the synthesis of crude product **244a**' and **244d'** with good diastereoselectivities (80:20 and 84:17 dr respectively). Following column chromatography, an impressive, isolated yields of

80% (for **244a'**) and 89% (for **244d'**) were achieved, along with exceptional diastereoselectivities (Scheme 108).

To delve deeper into the enantiomeric characteristics of the substances (*R,R,R*)-**244a** and (*S,S,S*)-**244a'**, circular dichroism (CD) measurements were performed as illustrated in Figure 40. The CD spectra derived from the solutions of these substances revealed a mirror-image correlation between (*R,R,R*)-**244a** and (*S,S,S*)-**244a'**, affirming their enantiomeric nature.

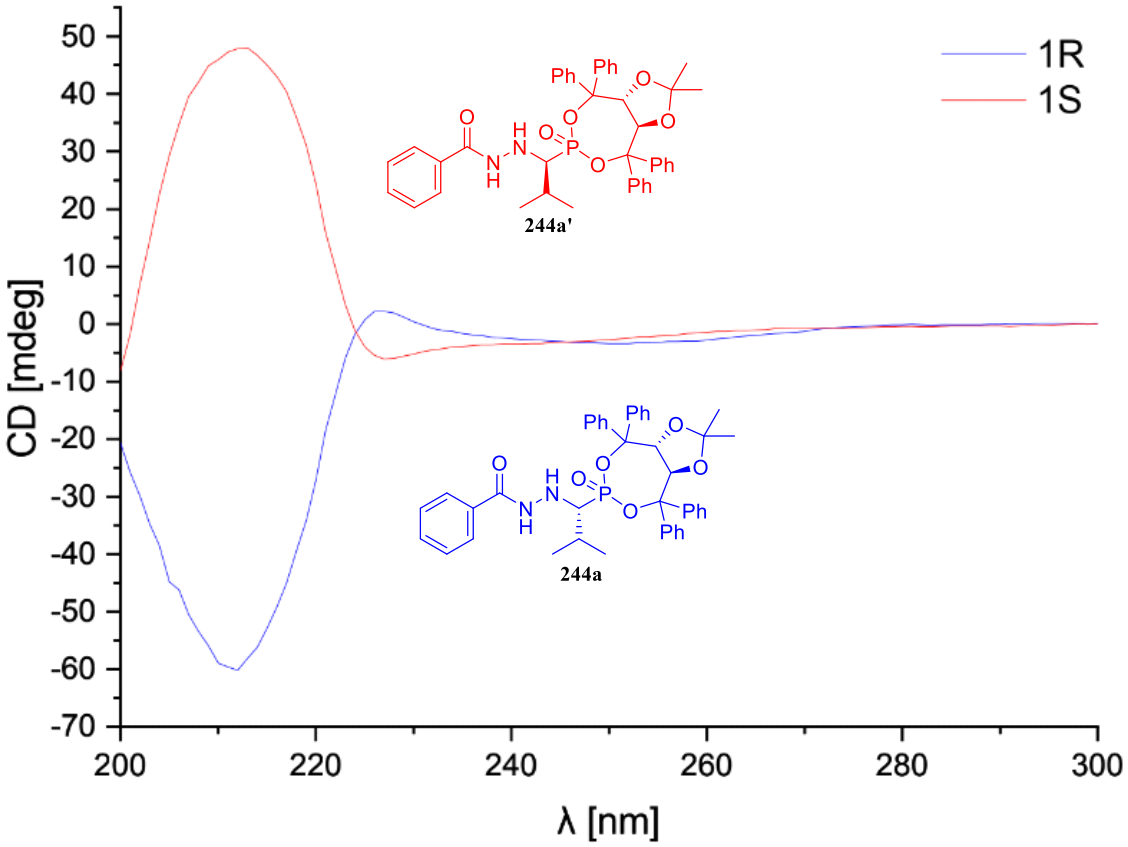


Figure 40. *Circular dichroism spectrum showing the enantiomeric nature of (R,R,R)-**244a** and (S,S,S)-**244a'** Experimental conditions: ECD spectra were recorded in the 200-300 nm range with a Jasco J-1500 1500spectropolarimeter (Jasco Inc, USA). Before use, the optical chamber of the CD spectrometer was deoxygenated with dry nitrogen and was held under a nitrogen atmosphere during the measurements. All optical measurements were performed in quartz cell cuvettes with conventional path length of 10 mm. The sample solutions in n-hexane HPLC were of concentration 4.8x10-5 M.*

3.0. Conclusions

In summary, the study of the reductive coupling of *N*-tosylhydrazones with (*R*,*R*)-**29** began with the aim of achieving an asymmetric version of this reaction, inspired by previous non-asymmetric copper-catalyzed reactions. I have managed to optimize the conditions that enable the reaction to proceed with excellent reactivity but unfortunately with low diastereoselectivity. I made several efforts to enhance the reaction conditions by exploring different solvents, bases, catalysts, and varying reaction temperatures, yet improving the product diastereoselectivity proved to be a persistent challenge. Furthermore, I made efforts to enrich one of the diastereoisomers in the crude reaction mixture using chromatography and/or crystallization techniques, capitalizing on the chiral auxiliary attached to the phosphorus atom, which could potentially favor the separation of the diastereoisomers. Regrettably, all these endeavors yielded rather disappointing results in terms of diastereoselectivity. Under the best reaction conditions, I tried the one-pot, three-component reductive coupling of acetophenone **49** with *p*-toluenesulphonyl hydrazide **248** and (*R*,*R*)-**29**. Unfortunately, the observed diastereoselectivity remained unchanged.

I further explored the hydrophosphonylation reaction of *N*-acylhydrazones **243** with (*R*,*R*)-**29**. Under the optimized reaction conditions, I investigated the scope of the methodology with various hydrazones (all the 10 substrates were synthesized separately), resulting in the successful synthesis of α-hydrazinophosphonates **244** with moderate to high yields (up to 91%) and satisfactory diastereoselectivity (up to >99:1 dr), depending on the nature of the hydrazone substrate. The reaction proceeded without complications when the opposite enantiomer of the chiral phosphorus nucleophile, (*S*,*S*)-**29**, was subjected to nucleophilic addition to the hydrazone. This led to the synthesis of α-hydrazinophosphonates **244a** in high yield and with remarkable diastereoselectivity. Additionally, I attempted to perform the reaction in one pot, however, the resulting crude product contained a mixture of both α-hydrazinophosphonate and the undesired α-hydroxyphosphonate as a side product. This outcome can be attributed to the inherent challenge associated with this reaction, which arises from the simultaneous presence of two nucleophiles, namely benzohydrazide **245** and (*R*,*R*)-**29**, and one electrophilic species, the aldehyde.

Experimental Part

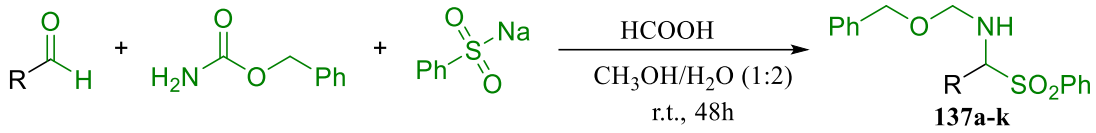
General information

All substrates and solvents bought from commercial suppliers (Sigma-Aldrich and POCh), were of analytical grade and were utilized without additional purification but when necessary, the solvents were purified and dried using standard procedures. Solvents were removed via a rotary evaporator unless otherwise stated. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were collected on a Jeol 400yh instrument (400 MHz for ^{1}H NMR, 162 MHz for ^{31}P NMR and 101 MHz for ^{13}C NMR) and were processed using dedicated software (MestReNova). Samples of the product were diluted with $CDCl_3$ or DMSO-d_6 with reference to the respective residual ^{1}H or ^{13}C signals of the solvents. Coupling constants are reported in hertz (Hz) and chemical shift in part per million (ppm). Multiplicities are reported with the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), tt (triplet of triplets), dt (doublet of triplets), td (triplet of doublets), ddd (doublet of doublets of doublets), dtd (doublet of triplets of doublets), qd (quartet of doublets), and m (multiplet) and the reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. For the characterization of diastereomeric mixtures, * represents the minor diastereoisomer, + indicates signal overlap from both diastereoisomers and the major diastereoisomer is characterized without additional denotation. The diastereomeric ratios (dr) values of the reactions were determined based on the ^{31}P NMR spectra of the crude reaction mixture. Analytical thin layer chromatography was performed on SIL G/UV254 plates and visualization was accomplished using UV light (254 nm). Column chromatography (FC) was performed using Sigma-Aldrich® silica gel high purity-grade (SiO_2 70–230 mesh). The optical rotations were measured on a Bellingham + Stanley ADP440 + polarimeter and $[\alpha]_D^T$ values are given in deg $cm^3\ g^{-1}\ dm^{-1}$; concentrations, c, are listed in 0.05 g/5 mL^{-1}. Mass spectra were recorded using a Waters LCT Premier XE mass spectrometer (electrospray ionization, ESI) (Waters, Milford, MA, USA) and melting points were determined using SRS melting point apparatus OptiMelt MPA 100 (Stanford Research System, Sunnyvale, CA, USA) and are reported at the Faculty of Chemistry, Wroclaw University of Science and Technology.

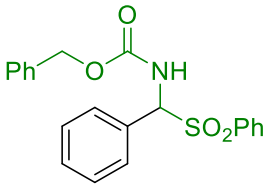
Asymmetric hydrophosphonylation of α-amido sulphones

1.0. General procedure for the preparation of the α-amido sulfones and compounds characterization

The synthesis of the sulphones was carried out according to the protocol reported by Tillman et al[185]. In a 100 mL flask, the corresponding aldehyde (9.4 mmol, 1.5 equiv.) was added to a rapidly stirred suspension of benzyl carbamate (6.3 mmol, 1 equiv.) and benzenesulfinic acid sodium salt (12.5 mmol, 2 equiv.) in methanol (6mL) and water (12mL), followed by formic acid (0.94 mL). The reaction mixture was stirred for 48 h at room temperature. The resulting precipitate formed during the reaction was filtered and washed with water and diethyl ether, then dried in vacuo to yield the α-amido sulfone **137** which was used without further purification. All of the synthesized sulphones are known and their spectral data agree with those previously reported in the literature[310-312].

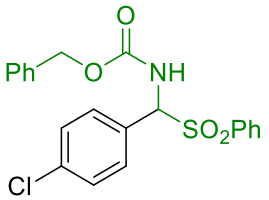


Benzyl (phenyl(phenylsulfonyl)methyl)carbamate (137a)



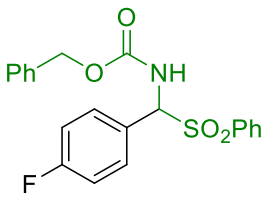
White solid; 1.98g, 55% yield; mp: 154-156 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 – 7.30 (m, 10H), 7.22 (brs, 2H), 6.16 (d, *J* = 10.7 Hz, 1H), 5.97 (d, *J* = 10.8 Hz, 1H), 4.96 – 4.88 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 154.77, 136.50, 135.57, 134.59, 134.23, 130.04, 129.82, 129.52, 129.10, 128.89, 128.67, 128.35, 124.94, 74.60, 67.77. HRMS (ESI) calculated for $C_{21}H_{19}NO_4SNa$ $[M^+Na]^+$: 404.0933 found 404.0933

Benzyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate (137b)



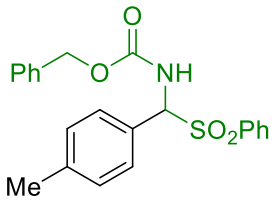
White solid; 1.48g, 38% yield; mp: 152-153 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.14 (d, *J* = 10.7 Hz, 1H), 7.80 (d, *J* = 7.4 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.24 (m, 3H), 7.15 (d, *J* = 6.5 Hz, 2H), 6.14 (d, *J* = 10.7 Hz, 1H), 4.85 (d, *J* = 12.5 Hz, 1H), 4.80 (d, *J* = 12.6 Hz, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6), δ: 155.67, 136.97, 136.78, 134.87 (d, *J* = 13.7 Hz), 132.02, 129.92 – 129.49 (m), 128.90, 128.75, 128.24, 125.01, 74.60, 66.64. HRMS (ESI) calculated for $C_{21}H_{18}ClNO_4SNa$ $[M^+Na]^+$: 438.0543 found 438.0544.

Benzyl ((4-fluorophenyl)(phenylsulfonyl)methyl)carbamate (137c)



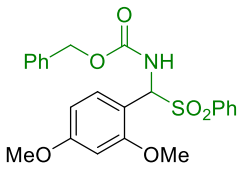
White solid; 1.64g, 44% yield; mp: ;162-164 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.12 (d, *J* = 10.7 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.74 – 7.63 (m, 3H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.13 (m, 7H), 6.12 (d, *J* = 10.7 Hz, 1H), 4.94 – 4.78 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 164.52, 162.07, 155.68, 137.02, 136.79, 134.74, 132.48 (d, *J* = 8.5 Hz), 129.63 (d, *J* = 6.7 Hz), 128.90, 128.49, 128.26, 128.07, 127.97, 127.13, 124.79, 115.67 (d, *J* = 21.7 Hz), 74.54, 66.62. HRMS (ESI) calculated for $C_{21}H_{18}FNO_4SNa$ $[M^+Na]^+$: 422.0838 found 422.0829.

Benzyl ((phenylsulfonyl)(p-tolyl)methyl)carbamate (137d)



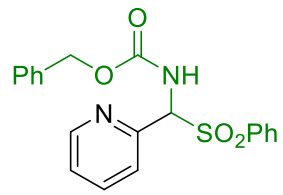
White solid; 2.20g, 59% yield, mp: 157-158 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.08 (d, *J* = 10.7 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.24 (m, 3H), 7.19 – 7.10 (m, 4H), 6.00 (d, *J* = 10.7 Hz, 1H), 4.87 – 4.77 (m, 2H), 2.28 (s, 3H).; **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 155.73, 139.49, 137.30, 136.85, 134.62, 130.27, 130.10, 129.62, 129.56, 129.25, 128.89, 128.46, 128.21, 127.68, 75.24, 66.54, 21.36. HRMS (ESI) calculated for $C_{22}H_{21}NO_4SNa$ $[M^+Na]^+$: 418.1089 found 418.1091.

Benzyl ((2,4-dimethoxyphenyl)(phenylsulfonyl)methyl)carbamate (137e)



White solid; 2.40g, 58% yield; mp:130-132 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.09 (d, *J* = 10.5 Hz, 1H), 7.823– 7.71 (m, 3H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.29-7.18 (m, 3H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.01 (d, *J* = 10.5 Hz, 1H), 4.99 – 4.77 (m, 2H), 3.76 (s, 3H), 3.69 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6), δ: 157.13, 155.72, 154.71, 150.12, 148.77, 137.89, 134.53, 131.91, 129.51, 128.86, 128.23,126.69, 126.01, 125.01, 122.73, 111.79, 109.89, 75.52, 66.60, 65.39, 56.41, 56.03; HRMS (ESI) calculated for $C_{23}H_{22}NO_6SNa$ $[M^+Na]^+$: 463.112 found 463.115.

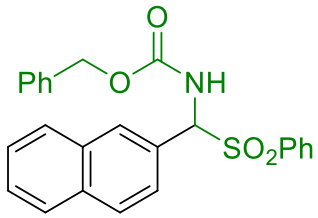
Benzyl ((phenylsulfonyl)(pyridin-2-yl)methyl)carbamate (137f)



137f, 42% yield

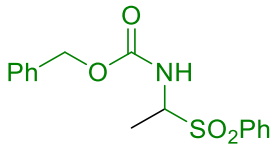
White solid; 1.51g, 42% yield; mp: 144-146 °C. **^{1}H NMR** (400 MHz, , $CDCl_3$) δ 8.52 (d, *J* = 4.5 Hz, 1H), 7.77 (t, *J* = 6.7 Hz, 4H), 7.66 – 7.55 (m, 3H), 7.41 (t, *J* = 7.8 Hz, 3H), 7.38 – 7.29 (m, 5H), 7.25 (d, *J* = 5.7 Hz, 2H), 7.05 (d, *J* = 9.1 Hz, 1H), 6.08 (d, *J* = 9.2 Hz, 1H), 5.03 – 4.89 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 155.73, 150.35, 149.53, 137.50, 137.12, 136.84, 134.81, 129.68, 129.59, 128.90, 128.47, 128.20, 125.16, 125.02, 76.86, 66.74. HRMS (ESI) calculated for $C_{20}H_{18}N_2O_4SNa$ $[M^+Na]^+$: 405.885 found 405.0892.

Benzyl (naphthalen-2-yl(phenylsulfonyl)methyl)carbamate (137g)



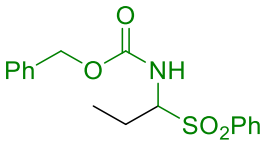
White solid; 2.52g; 62% yield; mp:152-154 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.26 (d, *J* = 10.7 Hz, 1H), 8.16 (s, 1H), 7.95 – 7.79 (m, 5H), 7.77 – 7.63 (m, 2H), 7.60 – 7.50 (m, 2H), 7.29 (dd, *J* = 8.7, 6.4 Hz, 3H), 7.16 (d, *J* = 6.6 Hz, 2H), 6.24 (d, *J* = 10.7 Hz, 1H), 4.95 – 4.77 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6), δ:157.14, 155.78, 137.91, 137.19, 136.3, 135.11, 134.36, 133.59, 132.77, 130.11, 129.81, 129.52, 128.84, 128.53, 128.22, 127.79, 127.57, 127.16, 125.02, 122.83, 75.59, 66.62, 65.39; HRMS (ESI) calculated for $C_{25}H_{21}NO_4SNa$ $[M^+Na]^+$: 454.1102 found 454.1100.

Benzyl (1-(phenylsulfonyl)ethyl)carbamate (137h)



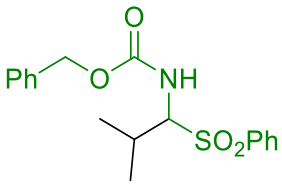
White solid; 1.35g, 45% yield; mp: 102-106 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.24 (m, 3H), 7.22 – 7.06 (m, 2H), 5.36 (d, *J* = 10.5 Hz, 1H), 5.11 – 4.95 (m, 1H), 4.85 (s, 2H), 1.61 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 154.63, 136.32, 135.74, 134.16, 129.39, 129.12, 128.63, 128.44, 128.25, 67.44 (d, *J* = 15.9 Hz), 13.15. HRMS (ESI) calculated for $C_{16}H_{17}NO_4SNa$ $[M^+Na]^+$: 342.0776 found 342.0785

Benzyl (1-(phenylsulfonyl)propyl)carbamate (137i)



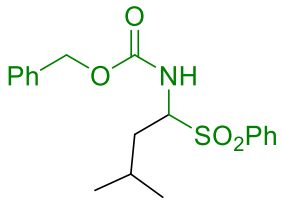
White solid; 2.15g, 68% yield; mp: 96-98 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.24 (m, 3H), 7.21 – 7.13 (m, 2H), 5.28 (d, *J* = 10.8 Hz, 1H), 4.93 – 4.74 (m, 3H), 2.36 – 2.22 (m, 1H), 1.84 – 1.68 (m, 1H), 1.06 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.17, 136.73, 135.76, 134.09, 129.52 – 128.96 (m), 128.70 – 127.98 (m), 72.76, 67.39, 20.22, 10.01. HRMS (ESI) calculated for $C_{17}H_{19}NO_4SNa$ $[M^+Na]^+$: 356.0933 found 356.0931

Benzyl (2-methyl-1-(phenylsulfonyl)propyl)carbamate (137j)



White solid; 1.99g, 61% yield; mp: 116-118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.24 (m, 3H), 7.21 – 6.96 (m, 2H), 5.40 (d, *J* = 11.2 Hz, 1H), 4.92 – 4.73 (m, 3H), 2.81 – 2.71 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.25, 137.74, 135.69, 133.97, 132.01, 129.09, 128.94, 128.66, 128.48, 128.28, 127.96, 126.72, 125.02, 75.00, 67.50, 26.93, 20.77, 16.98. HRMS (ESI) calculated for $C_{18}H_{21}NO_4SNa$ $[M^+Na]^+$: 370.1089 found 370.1095.

Benzyl (3-methyl-1-(phenylsulfonyl)butyl)carbamate (137k)

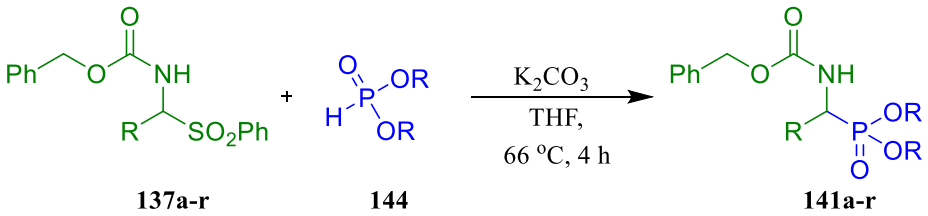


White solid; 1.94g; 57% yield; mp: 138-140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.24 (m, 3H), 7.20 – 7.03 (m, 2H), 5.30 (d, *J* = 10.8 Hz, 1H), 4.99 – 4.75 (m, 3H), 2.04 – 1.96 (m, 1H), 1.81 – 1.69 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.83, 136.59, 135.71, 134.06, 129.46, 129.32, 129.16, 129.05, 128.62, 128.43, 128.23, 128.03, 125.07, 70.24, 67.40, 34.70, 24.76, 23.34, 21.19. HRMS (ESI) calculated for $C_{19}H_{23}ClNO_4SNa$ $[M^+Na]^+$: 384.1245 found 384.1237.

2.0. General procedure for the hydrophosphonylation of α-amido sulfones

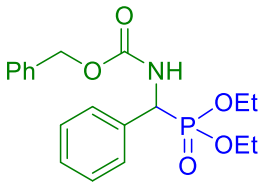
In a 50 mL flask, the corresponding amount of dialkyl *H*-phosphonate **144** (2.4mmol, 1 equiv.) was added to a solution of α-amido sulfone **137** (2.4mmol, 1 equiv.) and K_2CO_3 (9.6 mmol, 4 equiv.) in THF (15 mL). The mixture was heated 66 °C for 4 h and then cooled and filtered.

The solvent was removed under reduced pressure using a rotatory evaporator. The crude product was crystallized from diethyl ether in the case of solids. Oily products were purified by filtration through a pad of silica gel (eluent: Hexane/ethyl acetate = 5:1 to 3:1) to obtain the pure products **141**. The Spectral data agreed with those previously reported in the literature[313-315].



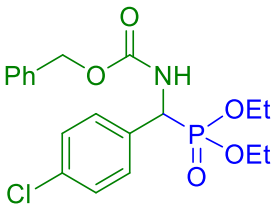
137a-r **144** **141a-r**

Benzyl ((diethoxyphosphoryl)(phenyl)methyl)carbamate (141a)



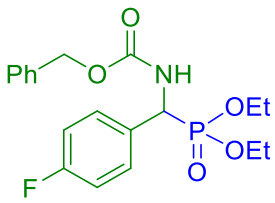
White solid; 860mg, 95% yield; mp: 112-114 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 8.43 (d, *J* = 10.8 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.22 (m, 8H), 5.11 – 4.96 (m, 3H), 4.02 – 3.71 (m, 4H), 1.10 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H**); ^{13}C NMR** (101 MHz, DMSO-d_6) δ: 156.48 (d, *J* = 8.6 Hz), 137.38 , 136.24 , 128.86, 128.74, 128.69, 128.64, 128.40, 128.31, 128.13 126.01, 66.38, 62.99 (d, *J* = 7.1 Hz), 62.77 (d, *J* = 6.8 Hz), 52.72 (d, *J* = 153.6 Hz), 16.72 (d, *J* = 5.4 Hz), 16.58 (d, *J* = 5.6 Hz); **^{31}P NMR** (162 MHz, DMSO-d_6) δ: 21.97. HRMS (ESI) calculated for $C_{19}H_{24}NO_5PNa$ $[M^+Na]^+$: 400.1290 found 400.1289

Benzyl ((4-chlorophenyl)(diethoxyphosphoryl)methyl)carbamate (141b)



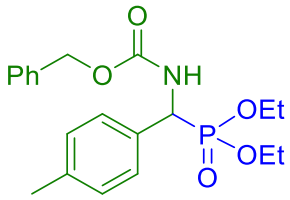
White solid; 938mg, 95% yield; mp: 116-117 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39 – 7.24 (m, 9H), 5.98 (s, 1H, NH), 5.17 – 4.99 (m, 3H), 4.13 – 3.98 (m, 2H), 3.98 – 3.88 (m, 1H), 3.82 – 3.70 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.82 (d, *J* = 12.9 Hz), 136.09, 134.19 (d, *J* = 3.3 Hz), 134.01, 129.25 (d, J = 2.0 Hz), 128.56, 128.24, 128.02 (d, J = 6.0), 129.57 – 127.99 (m), 67.46 (s), 63.54 (d, *J* = 6.9 Hz), 63.35 (d, *J* = 7.2 Hz), 52.02 (d, *J* = 156.0 Hz), 16.44 (d, *J* = 5.7 Hz), 16.27 (d, *J* = 5.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.38 (s); HRMS (ESI) calculated for $C_{19}H_{23}ClNO_5PNa$ $[M^+Na]^+$: 434.0900 found 434.0899.

Benzyl ((diethoxyphosphoryl)(4-fluorophenyl)methyl)carbamate (141c)



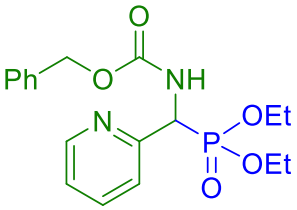
White solid; 808mg; 82% yield; mp: 124-126 ^{0}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40 (brs, 2H), 7.31 (brs, 5H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.05 (brs, 1H), 5.17 – 5.01 (m, 3H), 4.14 – 3.99 (m, 2H), 3.98 – 3.87 (m, 1H), 3.79 – 3.68 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.82 (d, *J* = 11.1 Hz), 136.13, 131.30, 129.77, 128.59, 128.33, 128.22, 115.74 (d, *J* = 2.0 Hz), 115.53 (d, *J* = 2.0 Hz), 67.42, 63.48 (d, *J* = 6.9 Hz), 63.26 (d, *J* = 7.1 Hz), 51.90 (d, *J* = 155.6 Hz), 16.43 (d, *J* = 5.7 Hz), 16.25 (d, *J* = 5.7 Hz).; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.66. HRMS (ESI) calculated for $C_{19}H_{23}FNO_5PNa$ $[M^+Na]^+$: 418.1196 found 418.1190

Benzyl ((diethoxyphosphoryl)(p-tolyl)methyl)carbamate (141d)



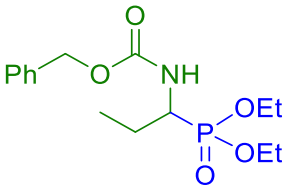
White solid; 771mg, 83% yield; mp: 115-117 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.36 – 7.24 (m, 7H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.74 (brs, 1H), 5.16 – 5.00 (m, 3H), 4.13 – 4.00 (m, 2H), 3.97 – 3.87 (m, 1H), 3.78 – 3.65 (m, 1H), 2.32 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.75 (d, *J* = 11.0 Hz), 138.08, 136.22, 132.20, 129.43, 128.58, 128.28, 127.89, 67.33, 63.45 (d, *J* = 6.9 Hz), 63.16 (d, *J* = 7.1 Hz), 52.25 (d, *J* = 154.7 Hz), 21.25 (s), 16.45 (d, *J* = 5.8 Hz), 16.26 (d, *J* = 5.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.14. HRMS (ESI) calculated for $C_{20}H_{26}NO_5PNa$ $[M^+Na]^+$: 414.1446 found 414.1448

Benzyl ((diethoxyphosphoryl)(pyridin-2-yl)methyl)carbamate (141e)



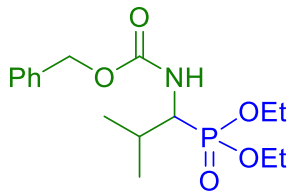
white solid; 790mg, 87% yield, mp: 110-112 ^{o}C.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.48 (d, *J* = 4.7 Hz, 1H), 8.21 (d, *J* = 9.8 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.24 (m, 5H), 5.25 (dd, *J* = 21.7, 10.0 Hz, 1H), 5.10-4.98 (m, 2H), 4.02 – 3.79 (m, 4H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.86, 167.53, 156.42 (d, *J* = 8.0 Hz), 155.71, 149.18, 137.33, 132.26, 128.85, 128.39, 128.28, 123.47 (d, *J* = 2.4 Hz), 123.33 (d, *J* = 3.9 Hz), 66.48, 63.07 (d, *J* = 6.8 Hz), 62.91 (d, *J* = 6.7 Hz), 54.91 (d, *J* = 148.0 Hz), 16.69 (d, *J* = 5.5 Hz), 16.56 (d, *J* = 5.6 Hz); ^{31}P NMR (162 MHz, DMSO-d_6) δ: 20.97. HRMS (ESI) calculated for $C_{19}H_{24}NO_5PNa$ $[M^+Na]^+$: 401.1294 found 401.1291

Benzyl (1-(diethoxyphosphoryl)propyl)carbamate (141f).



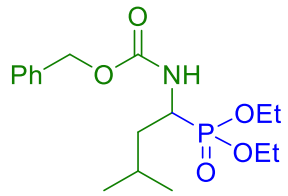
Colourless oil; 585mg, 62% yield. **^{1}H NMR** (400 MHz,) δ 7.65 – 7.06 (m, 5H), 5.17 – 5.02 (m, 3H), 4.14 – 3.91 (m, 4H), 1.94 – 1.84 (m, 1H), 1.63 – 1.51 (m, 1H), 1.25 (dt, *J* = 17.9, 7.1 Hz, 6H), 0.99 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz,) δ 156.29 (d, *J* = 6.2 Hz), 136.41 (s), 128.64 – 128.10 (m), 67.16 (s), 62.67 (d, *J* = 7.1 Hz), 62.49 (d, *J* = 6.7 Hz), 49.11 (d, *J* = 155.8 Hz), 23.35 (s), 16.41 (s), 10.49 (s); **^{31}P NMR** (162 MHz,) δ 25.41 (s). HRMS (ESI) calculated for $C_{15}H_{24}NO_5PNa$ $[M^+Na]^+$: 352.1290 found 352.1286

Benzyl (1-(diethoxyphosphoryl)-2-methylpropyl)carbamate (141g)



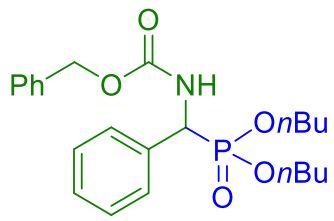
Yellowish oil; 588mg, 77% yield. **^{1}H NMR** (400 MHz,) δ 7.35 – 7.24 (m, 5H), 5.19 – 5.04 (m, 3H), 4.13 – 3.94 (m, 4H), 2.23 – 2.13 (m, 1H), 1.32 – 1.19 (m, 6H), 1.02 – 0.95 (m, 6H); **^{13}C NMR** (101 MHz,) δ 156.46 (d, *J* = 6.5 Hz), 136.39 (s), 129.44 – 127.29 (m), 67.23 (s), 62.42 (m), 52.68 (d, *J* = 152.9 Hz), 29.03 (d, *J* = 4.5 Hz), 20.51 (d, *J* = 12.7 Hz), 17.78 (d, *J* = 4.2 Hz), 16.42 (d, *J* = 6.0 Hz); **^{31}P NMR** (162 MHz,) δ 24.83 (s). HRMS (ESI) calculated for $C_{16}H_{26}NO_5PNa$ $[M^+Na]^+$: 366.1446 found 366.1450

Benzyl (1-(diethoxyphosphoryl)-3-methylbutyl)carbamate (141h)



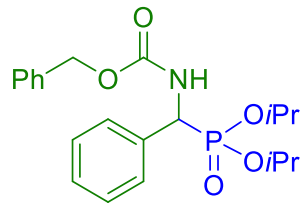
White solid; 497mg, 58% yield; 88-90 ºC. **^{1}H NMR** (400 MHz,) δ 7.34 – 7.24 (m, 5H), 5.17 – 4.93 (m, 3H), 4.17 – 3.99 (m, 4H), 1.72 (m, 1H), 1.58 – 1.51 (m, 2H), 1.24 (dt, *J* = 19.6, 7.1 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (101 MHz,) δ 156.04 (d, *J* = 5.0 Hz), 136.43 (s), 128.56 (s), 128.24 (s), 128.14 (s), 62.67 (d, *J* = 7.1 Hz), 62.49 (d, *J* = 6.6 Hz), 46.00 (d, *J* = 156.4 Hz), 38.61 (s), 24.47 (d, *J* = 13.3 Hz), 23.40 (s), 21.20 (s), 16.45 (dd, *J* = 5.8, 3.7 Hz); **^{31}P NMR** (162 MHz,) δ 26.00 (s). HRMS (ESI) calculated for $C_{17}H_{28}NO_5PNa$ $[M^+Na]^+$: 380.1603 found 380.1603

Benzyl ((dibutoxyphosphoryl)(phenyl)methyl)carbamate (141i)



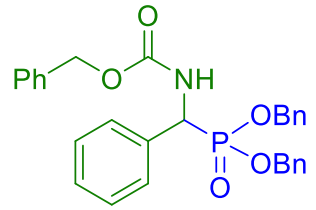
White solid; 905mg, 87% yield; mp: 104-106 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.23 (m, 8H), 5.89 (s, 1H, NH), 5.20 – 5.00 (m, 3H), 4.07 – 3.93 (m, 2H), 3.90 – 3.80 (m, 1H), 3.67 – 3.57 (m, 1H), 1.63 – 1.51 (m, 2H), 1.44 – 1.27 (m, 4H), 1.24 – 1.13 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.74 (d, *J* = 12.1 Hz), 136.19, 135.41, 128.70 (d, *J* = 2.0 Hz), 128.59, 128.33 – 128.14 (m), 127.97 (d, *J* = 5.8 Hz), 67.35, 67.05 (d, *J* = 7.1 Hz), 66.85 (d, *J* = 7.3 Hz), 52.51 (d, *J* = 153.3 Hz), 32.56 (d, *J* = 5.8 Hz), 32.35 (d, *J* = 5.9 Hz), 18.62 (d, *J* = 13.1 Hz), 13.61 (d, *J* = 7.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.94. HRMS (ESI) calculated for $C_{23}H_{32}NO_5PNa$ $[M^+Na]^+$: 456.1916 found 456.1819.

Benzyl ((diisopropoxyphosphoryl)(phenyl)methyl)carbamate (141j)



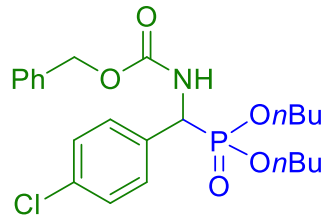
White solid; 919mg, 94% yield; mp: 102-103 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.24 (m, 8H), 5.85 (s, 1H NH), 5.17 – 4.99 (m, 3H), 4.70 – 4.59 (m, 1H), 4.47 – 4.37 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.80 (d, *J* = 9.5 Hz), 128.27 (d, *J* = 3.8 Hz), 128.18 – 128.05 (m), 72.31 (d, *J* = 7.2 Hz), 71.87 (d, *J* = 7.4 Hz), 67.31, 53.12 (d, *J* = 154.1 Hz), 24.28 (d, *J* = 3.1 Hz), 24.19 (d, *J* = 3.5 Hz), 23.79 (d, *J* = 5.2 Hz), 23.21 (d, *J* = 5.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 20.18. HRMS (ESI) calculated for $C_{21}H_{28}NO_5PNa$ $[M^+Na]^+$: 428.1603 found 428.1613.

Benzyl ((bis(benzyloxy)phosphoryl)(phenyl)methyl)carbamate (141k)



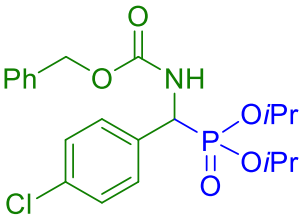
White solid; 1101mg, 91% yield; mp: 124-125 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.49 -7.20 (m, 18H), 7.09 (dd, *J* = 6.3, 2.8 Hz, 2H), 6.02 (s, 1H, NH), 5.27 (dd, *J* = 21.8, 9.6 Hz, 1H), 5.12 – 4.92 (m, 4H), 4.83 (dd, *J* = 11.7, 7.2 Hz, 1H), 4.60 (dd, *J* = 11.6, 8.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.73 (d, *J* = 11.3 Hz), 136.14, 135.78, 135.03, 128.81 (d, *J* = 2.1 Hz), 128.68 – 128.00 (m), 127.95, 68.67 (d, *J* = 6.7 Hz), 68.52 (d, *J* = 7.1 Hz), 67.40, 52.77 (d, *J* = 154.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.89. HRMS (ESI) calculated for $C_{29}H_{28}NO_5PNa$ $[M^+Na]^+$: 524.1603 found 524.1605

Benzyl ((4-chlorophenyl)(dibutoxyphosphoryl)methyl)carbamate (141l)



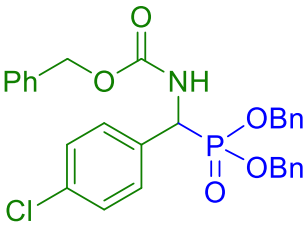
White solid; 921mg; 82% yield; mp: 95-96 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39 – 7.23 (m 9H), 5.89 (brs, 1H), 5.16 – 5.01 (m, 3H), 4.06 – 3.94 (m, 2H), 3.92 – 3.83 (m, 1H), 3.73 – 3.64 (m, 1H), 1.61 – 1.52 (m, 2H), 1.47 – 1.39 (m, 2H), 1.37 – 1.27 (m, 2H), 1.26 – 1.16 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.74 (d, *J* = 12.4 Hz), 136.06, 134.20 , 129.32, 128.87, 128.62, 128.37, 128.22, 67.48, 67. 13 (d, *J* = 7.1 Hz), 67.03 (d, *J* = 7.5 Hz), 51.98 (d, *J* = 156.2 Hz), 32.54 (d, *J* = 5.8 Hz), 32.37 (d, *J* = 5.8 Hz), 18.68, 18.58, 13.63, 13.56; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.35. HRMS (ESI) calculated for $C_{23}H_{31}ClNO_5PNa$ $[M^+Na]^+$: 490.1526 found 490.1534.

Benzyl ((4-chlorophenyl)(diisopropoxyphosphoryl)methyl)carbamate (141m)



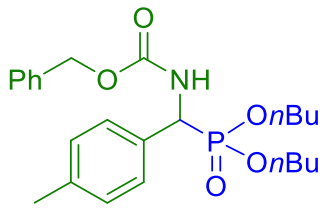
white solid; 938mg; 95% yield; mp:132-134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.45 – 7.14 (m, 9H), 5.91 (brs, 1H), 5.16 – 4.97 (m, 3H, CHP and CH2Ph), 4.69 – 4.59 (m, 1H), 4.52 – 4.42 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.83 (d, *J* = 9.6 Hz), 136.15, 134.46, 134.02, 129.47, 128.71, 128.60, 128.35, 128.27, 72.39 (d, *J* = 7.2 Hz), 72.12 (d, *J* = 7.4 Hz), 67.42, 52.58 (d, *J* = 157.0 Hz), 24.21 (d, *J* = 3.3 Hz), 24.16 (d, *J* = 3.5 Hz), 23.78 (d, *J* = 5.2 Hz), 23.36 (d, *J* = 5.6 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 19.47; HRMS (ESI) calculated for $C_{21}H_{27}ClNO_5PNa$ $[M^+Na]^+$: 462.1213 found 462.1208.

Benzyl ((bis(benzyloxy)phosphoryl)(4-chlorophenyl)methyl)carbamate (141n)



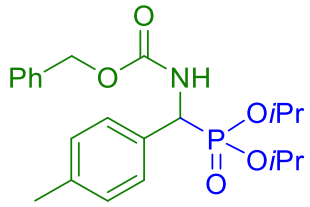
White solid; 1221mg; 95% yield; mp: 148-150 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 – 7.20 (m, 17H), 7.10 (dd, *J* = 7.3, 1.9 Hz, 2H), 5.94 (brs, 1H), 5.18 (dd, *J* = 22.2, 9.4 Hz, 1H), 5.09 – 4.91 (m, 4H), 4.83 (dd, *J* = 11.7, 7.7 Hz, 1H), 4.70 (dd, *J* = 11.6, 9.1 Hz, 1H); **^{13}C NMR** (101 MHz, DMSO), δ: 156.48 (d, *J* = 8.5 Hz), 137.21, 136.78 (d, *J* = 14.4 Hz), 135.08, 133.10, 130.65, 129.13 – 127.82 (m, aromatic carbon atoms), 68.17 (d, *J* = 6.9 Hz), 67.91 (d, *J* = 6.6 Hz), 66.56, 52.23 (d, *J* = 154.0 Hz,); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.38. HRMS (ESI) calculated for $C_{29}H_{27}ClNO_5PNa$ $[M^+Na]^+$: 558.1213 found 538.1221

Benzyl ((dibutoxyphosphoryl)(p-tolyl)methyl)carbamate (141o)



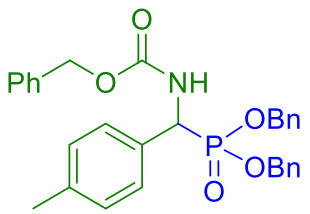
White solid; 835mg; 74% yield; mp: 108-110 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 – 7.22 (m, 7H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.77 (brs, 1H), 5.20 – 4.96 (m, 3H), 4.06 – 3.95 (m, 2H), 3.86 (1H), 3.69 – 3.58 (m, 1H), 2.32 (s, 3H), 1.64 – 1.53 (m, 2H), 1.46 – 1.28 (m, 4H), 1.26 – 1.14 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 155.70 (d, *J* = 10.7 Hz), 138.03, 136.23, 132.33, 129.97 – 127.77 (m), 67.31, 67.04 (d, *J* = 7.1 Hz), 66.81 (d, *J* = 7.4 Hz), 52.20 (d, *J* = 154.7 Hz), 32.57 (d, *J* = 5.8 Hz), 32.37 (d, *J* = 5.8 Hz), 21.22, 18.64 (d, *J* = 11.8 Hz), 13.62 (d, *J* = 7.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$), δ: 22.13. HRMS (ESI) calculated for $C_{24}H_{34}NO_5PNa$ $[M^+Na]^+$: 470.2072 found 470.2079

Benzyl ((diisopropoxyphosphoryl)(p-tolyl)methyl)carbamate (141p)



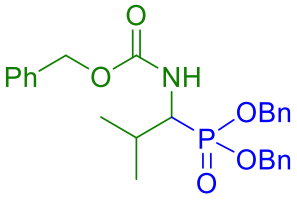
White solid; 812mg; 77% yield; mp: 126-128 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.37 – 7.22 (m, 7H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.77 (brs, 1H), 5.20 – 4.95 (m, 3H), 4.71 – 4.59 (m, 1H), 4.51 – 4.36 (m, 1H), 2.31 (s, 3H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 155.78 (d, *J* = 11.0 Hz), 137.85, 136.30, 132.68, 130.19 – 127.62 (m), 72.21 (d, *J* = 7.2 Hz), 71.80 (d, *J* = 7.5 Hz), 67.24, 52.82 (d, *J* = 156.8 Hz), 24.29 (d, *J* = 3.1 Hz), 24.19 (d, *J* = 3.4 Hz), 23.80 (d, *J* = 5.3 Hz), 23.27 (d, *J* = 5.7 Hz), 21.23; **^{31}P NMR** (162 MHz, $CDCl_3$), δ: 20.35. HRMS (ESI) calculated for $C_{22}H_{30}NO_5PNa$ $[M^+Na]^+$: 442.1759 found 442.1758

Benzyl ((bis(benzyloxy)phosphoryl)(p-tolyl)methyl)carbamate (141q)



white solid; 1115mg; 91% yield; mp: 128-138 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 – 7.22 (m, 15H), 7.15 – 7.07 (m, 4H), 5.84 (brs, 1H), 5.21 (dd, *J* = 21.5, 9.6 Hz, 1H), 5.11 – 4.92 (m, 4H), 4.83 (dd, *J* = 11.7, 7.3 Hz, 1H), 4.62 (dd, *J* = 11.7, 8.5 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.75 (d, *J* = 10.8 Hz), 138.15, 136.33 – 135.70 (m), 132.00, 129.52, 128.84 – 127.69 (m, aromatic carbon atom), 68.64 (d, *J* = 6.9 Hz), 68.47 (d, *J* = 7.2 Hz), 52.50 (d, *J* = 155.7 Hz), 21.27; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 23.08. HRMS (ESI) calculated for $C_{30}H_{30}NO_5PNa$ $[M^+Na]^+$: 538.1759 found 538.1765

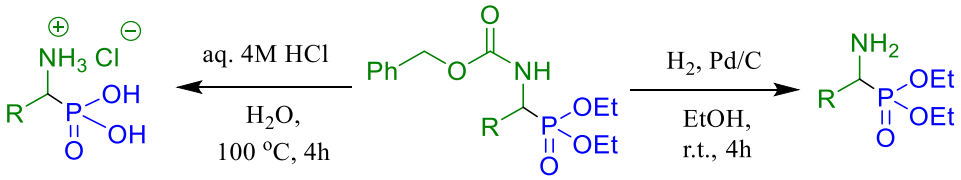
Benzyl (1-(bis(benzyloxy)phosphoryl)-2-methylpropyl)carbamate (141r)



White solid; 728mg, 62% yield; mp: 82-84 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.37 – 7.21 (m, 15H), 5.13 – 5.03 (m, 3H), 5.02 – 4.92 (m, 4H), 4.19 – 4.06 (m, 1H), 2.26 – 2.15 (m, 1H), 1.04 – 0.93 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.40 (d, *J* = 6.5 Hz), 136.35 – 136.05 (m), 128.74 – 128.02 (m), 67.85 (t, *J* = 6.8 Hz), 67.29, 53.00 (d, *J* = 152.4 Hz), 29.07 (d, *J* = 4.6 Hz), 20.51 (d, *J* = 12.8 Hz), 17.87 (d, *J* = 4.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 25.77. HRMS (ESI) calculated for $C_{25}H_{30}NO_5PNa$ $[M^+Na]^+$: 490.1759 found 490.1760.

3.0. General procedure for the deprotection of aminophosphonates

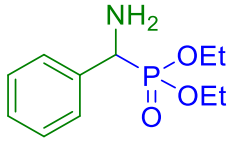
a. 20 mL of 4M aqueous HCl was added to a flask containing 0.5 g of **141** or **(*R*,*R*,*R*)-148** (for the asymmetric variant) and stirred at 100 °C for 4 h. The resulting mixture was then allowed to cool to room temperature and was evaporated to dryness. The obtained crude product was purified by crystallization from $CHCl_3$ to afford the free α-aminophosphonic acid salt **146** (see section 5 for the spectra characterization of **146**).



146 **141** **147**

b. To obtain pure compound **147**, a solution was prepared by dissolving 0.5 g of α-aminophosphonate **141** in 20 mL of ethanol, and then Pd/C (0.01g) was added to the solution. The mixture was stirred at room temperature under hydrogen gas for 4 hours, and then filtered through celite and concentrated. The resulting crude product was subjected to crystallization from Et_2O.

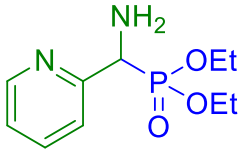
Diethyl (amino(phenyl)methyl)phosphonate (147e)



White solid; 264mg, 89% yield; **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 7.38 (d, *J* = 8.9 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.19 (m, 1H), 4.17 (d, *J* = 18.1 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.88 – 3.71 (m, 2H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 139.77 (d, *J* = 2.3 Hz), 128.38 (dd, *J* = 6.5, 4.2 Hz), 127.60 (d, *J* = 3.1 Hz), 62.54 (d, *J* =

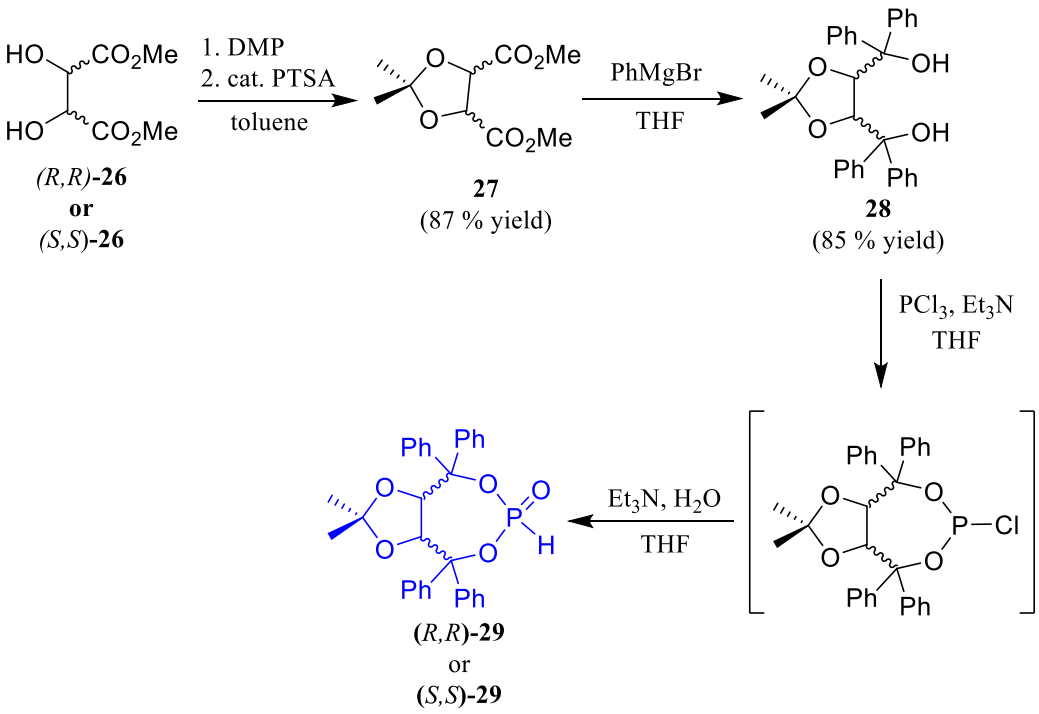
7.0 Hz), 62.28 (d, *J* = 7.0 Hz), 53.70 (d, *J* = 147.8 Hz), 16.84 (d, *J* = 5.4 Hz), 16.68 (d, *J* = 5.4 Hz); **^{31}P NMR** (162 MHz, DMSO-d_6) δ: 26.08.

Diethyl (amino(pyridin-2-yl)methyl)phosphonate (147a)



White solid, 178mg, 92% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 4.1 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 6.9 Hz, 1H), 7.17 (t, *J* = 5.3 Hz, 1H), 4.38 (d, *J* = 17.5 Hz, 1H), 4.08 – 3.93 (m, 4H), 1.24-1.19 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.32, 149.13, 136.40, 123.28 (d, *J* = 4.7 Hz), 122.70 (d, *J* = 3.1 Hz), 62.95 (d, *J* = 7.0 Hz), 62.80 (d, *J* = 7.1 Hz), 55.51 (d, *J* = 143.9 Hz), 16.47 (d, *J* = 3.0 Hz), 16.41 (d, *J* = 3.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 24.51.

4.0. Preparation of TADDOL derived *H*-phosphonate



(R,R)-**26**
or
(S,S)-**26**

27
(87 % yield)

28
(85 % yield)

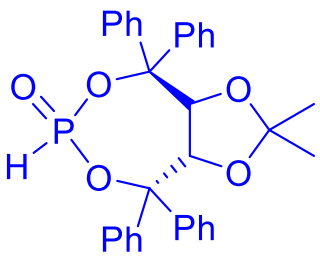
(*R,R*)-29
or
(*S,S*)-29

The 2,2-Dimethoxypropane (8.8g, 84.2 mmol, 1.5 equiv) was introduced into a solution containing the (*R,R*)-enantiomer of dimethyl tartrate (10.0g, 56.1 mmol, 1.0 equiv) and *p*-toluenesulfonic acid (0.10g) in dry toluene (120 mL), and the resulting mixture was heated under reflux for 8 h. Subsequently, the mixture was allowed to cool to room temperature, followed by the addition of $NaHCO_3$ (1.2 g) with simultaneous stirring for 15 min. Water (100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (60 mL twice). The combined organic layers were washed with water, brine (aqueous

NaCl), dried (Na_2SO_4), and concentrated to give compound **27** (11.92 g) as a yellowish oil. The crude product obtained was used for subsequent reactions without further purification. Under a nitrogen atmosphere in an ice cooling bath, Grignard reagent (37.27g, 4.5 equiv. of 2.0 M solution in THF) was added to a solution of **27** (11.92g, 54.65 mmol, 1 equiv) in THF (30 mL). After completion of the addition, the reaction mixture was refluxed for 1.5 hours and then cooled to room temperature. An aqueous saturated ammonium chloride solution (300 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (200 mL once, 100 mL twice). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellowish foam. The crude product was crystallized from methanol to afford (*R*,*R*)-TADDOL-**28.**

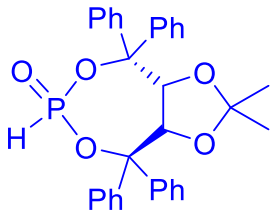
Under nitrogen at 0 ^oC achieved in an ice bath, a solution of freshly distilled PCl_3 (1.12 mL, 12.86 mmol, 2.0 equiv) in dry THF (15 mL) was slowly added to a flask containing a solution of TADDOL-**28** (3.0g, 6.43 mmol, 1.0 equiv) and Et_3N (2.7 mL, 19.29 mmol, 3.0 equiv) in dry THF (15 mL). The reaction mixture was stirred at the same temperature (0 ^oC) for 1 hour. To the resulting mixture, Et_3N (0.89 mL, 6.43 mmol, 1 equiv) and H_2O (0.12 mL, 6.43 mmol, 1.0 equiv) were added via a syringe at 0 ^oC. The mixture was then allowed to warm to room temperature and stirred for 1 hour. Solid triethylammonium chloride was removed by filtration through a pad of $MgSO_4$, and the filtrate was dried using a rotary evaporator. The obtained crude product was purified by column chromatography using hexane and ethyl acetate as the eluent in a ratio of 5:1 to 3:1 to afford the (*R*,*R*)-TADDOL *H*-phosphonate **29**. The procedure was repeated with the (S,S)-enantiomer of dimethyl tartrate to afford the (*S*,*S*)-TADDOL *H*-phosphonate **29**[185]

(3aR,8aR)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepine 6-oxide, (*R*,*R*)-29.



White solid, 2.93g; 89% yield; $[\alpha]_D^{20}$ = -273.0 (c = 1.0, CH_2Cl_2)**^{1}H NMR** (400 MHz, $CDCl_3$) δ:7.99 (s, 1H), 7.64 – 7.55 (m, 4H), 7.46 – 7.23 (m, 16H), 6.17 (s, 1H), 5.36 (d, *J* = 8.0 Hz, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 0.76 (s, 3H), 0.57 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ: 143.75, 143.23, 139.30, 139.00, 128.88, 128.79, 128.74, 128.57, 128.40, 128.28, 128.07, 127.97, 127.61, 127.43, 126.96, 126.88, 114.46, 88.84, 80.17 (d, *J* = 2.9 Hz), 79.89 (d, *J* = 2.0 Hz), 26.84, 26.35; **^{31}P NMR** (162 MHz, $CDCl_3$) δ:-3.27; **HRMS (ESI)** calculated for $C_{31}H_{29}O_5PNa$ $[M^+Na]^+$: 535.1650 found 535.1653

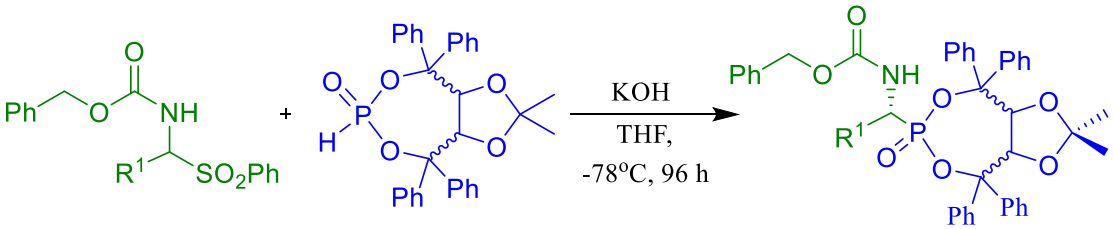
(3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepine 6-oxide, (*S*,*S*)-29.



White solid, 2.80g; 85% yield; $[\alpha]_D^{20}$ = +277.0 (c = 1.0, CH_2Cl_2)the **^{1}H, ^{13}C,** and **^{31}P NMR** Characteristics is similar to that of (*R*,*R*)-**29.** ; **HRMS (ESI)** calculated for $C_{31}H_{29}O_5PNa$ $[M^+Na]^+$: 535.1650 found 535.1660

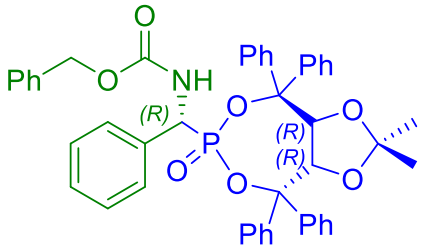
5.0. General procedure of the asymmetric hydrophosphonylation of α-amido sulphones

In a 50 mL flask, TADDOL derived *H*-phosphonate **29** (1 equiv.) was added to a solution of the corresponding α-amido sulphone **137a-j** (1 equiv.) in 15 mL of THF. After the resulting mixture was cooled to −78 °C, finely ground KOH (3 equiv.) was added in one portion to the mixture. The reaction mixture was stirred at the same temperature without any precaution to exclude air or moisture. After 96h, saturated aq. NH_4Cl (15 mL) was added, and then the mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted three times with toluene (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated to give the crude product. The concentrated crude product was then purified by column chromatography using CH_2Cl_2 (100%) to CH_2Cl_2/MeOH 97:3 to afford the desired pure products **148a-j**.



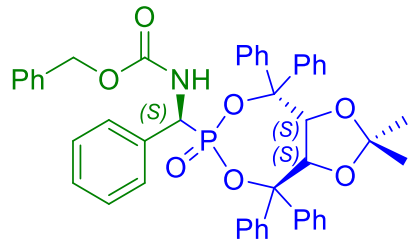
137 *(R,R)*-**29** or (*S,S*)-**29** *(R,R,R)*-**148** or (*S,S,S*)-**148**

Benzyl (((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(phenyl)methyl)carbamate (*R*,*R*,*R*)-148a



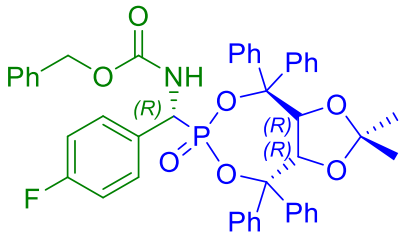
White solid; 187mg, 85% yield; mp: 123-125°C; $[\alpha]_D^{20}$ = -145.8 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ: 7.58 – 7.53 (m, 2H), 7.52 – 7.47 (m, 2H), 7.42 – 7.15 (m, 24H), 7.02 – 6.97 (m, 2H), 5.73(br, s, 1H), 5.51 (d, *J* = 7.9 Hz, 1H), 5.36 – 4.96 (m, 4H) 0.81 (s, 3H), 0.53 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$), δ: 155.70 (d, $^1J_{CO}$ = 14.0 Hz), 144.14, 143.31, 139.33 (d, *J* = 9.9 Hz), 135.15, 129.82, 129.62, 128.63, 128.57, 128.54, 128.24, 128.12, 127.97, 127.91, 127.78, 127.40, 127.30, 126.62, 114.10, 90.93 (d, *J* = 12.6 Hz), 87.39 (d, *J* = 8.2 Hz), 79.94, 79.08, 67.40, 53.91 (d, $^1J_{CP}$ = 161.2 Hz), 27.02, 26.53; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.07; **HRMS (ESI)** calculated for $C_{46}H_{42}NO_7PNa$ $[M^+Na]^+$: 774.2596 found 774.2600.

Benzyl (((3aS,8aS)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(phenyl)methyl)carbamate (*S*,*S*,*S*)-148a



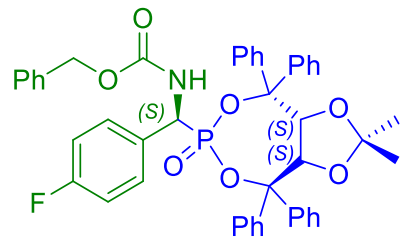
White solid; 194mg, 88% yield; mp: 124-126 °C ; $[\alpha]_D^{20}$ = +171.0 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ: 7.58 – 7.53 (m, 2H), 7.52 – 7.44 (m, 2H), 7.42 – 7.13 (m, 24H), 7.03 – 6.96 (m, 2H), 5.70 (br, s, 1H), 5.51 (d, *J* = 7.9 Hz), 5.36 – 4.96 (m, 4H), 0.80 (s, 3H), 0.53 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 155.69 (d, $^1J_{CO}$ = 12.6 Hz), 144.22, 143.31, 139.34 (d, $^2J_{CP}$ = 9.9 Hz), 135.17, 129.63, 128.64, 128.62, 128.56, 128.54, 128.23, 128.12 , 128.09, 127.90, 127.77, 127.39, 127.29, 126.61, 114.10, 90.94 (d, $^2J_{CP}$ = 13.0 Hz), 87.37 (d, $^2J_{CP}$ = 9.7 Hz), 79.91, 79.05, 67.39, 53.92 (d, $^1J_{CP}$ = 161.9 Hz), 27.01, 26.54; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.05 **HRMS (ESI)** calculated for $C_{46}H_{42}NO_7PNa$ $[M^+Na]^+$: 774.2596 found 774.2594.

Benzyl(((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(4-fluorophenyl)methyl)-carbamate (*R*,*R*,*R*)-148b



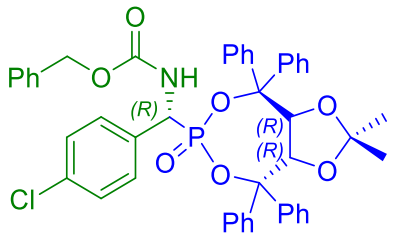
White solid; 210mg, 93% yield; mp: 174-176°C; $[\alpha]_D^{20}$ = -139.2 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ: 7.54 – 7.48 (m, 2H), 7.47-7.41 (m, 2H), 7.38 – 7.12 (m, 21H), 7.03 – 6.88 (m, 4H), 5.64 (br, s, 1H), 5.49 (d, *J* = 7.6, 1H), 5.33 – 4.89 (m, 4H), 0.76 (s, 3H), 0.50 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 163.87 (d, J_{CF} = 3.1 Hz), 161.41 (d, $^1J_{CO}$ = 3.3 Hz), 144.05 (d, $^2J_{CP}$ = 6.2 Hz), 143.14, 139.21 (d, $^3J_{CF}$= 9.9 Hz), 131.11, 129.78, 129.57, 128.68, 128.64, 128, 56, 128.48, 128.36, 128.26, 128.17, 127.95, 127.87, 127.39, 127.30, 127.25, 126.60, 115.51 (d, $^2J_{CF}$ = 21.7 Hz), 114.22, 91.14 (d, $^2J_{CP}$ = 11.7 Hz), 87.57 (d, $^2J_{CP}$ = 10.4 Hz), 79.68, 78.93, 67.45, 53.21 (d, J_{CP} = 161.4 Hz), 26.96, 26.52; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.69; **HRMS (ESI)** calculated for $C_{46}H_{41}FNO_7PNa$ $[M^+Na]^+$: 791.790 found 791.796

Benzyl (((3aS,8aS)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e] [1,3,2] dioxaphosphepin-6-yl)(4-fluorophenyl)methyl)carbamate (*S*,*S*,*S*)-148b



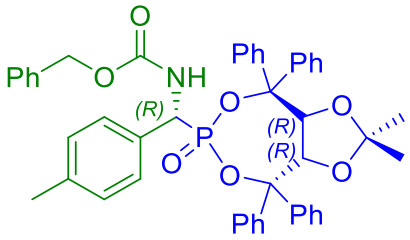
White solid; 205mg, 91% yield; mp:208-210 °C; $[\alpha]_D^{20}$ = +169.2 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ: 7.56 – 7.51 (m, 2H), 7.49 – 7.43 (m, 2H), 7.41 – 7.15 (m, 21H), 7.01 – 6.91 (m, 2H), 5.70 (br, s 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 5.31 – 4.94 (m, 4H), 78, 0.52; **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 163.87 (d, $^1J_{CF}$ = 3.1 Hz), 161.42 (d, $^1J_{CO}$ = 3.1 Hz), 155.68, 144.10 (d, $^2J_{CP}$ = 6.2 Hz), 143.16, 139.25 (d, $^3J_{CF}$ = 9.9 Hz), 131.12, 129.59, 128.68, 128.64, 128.57, 128.50, 128.36, 128.25, 127.94, 127.88, 127.40, 127.31, 127.26, 126.62, 115.50 (d, $^2J_{CF}$ = 19.5 Hz), 114.22, 91.15 (d, $^2J_{CP}$ = 13.5 Hz), 87.54 (d, $^2J_{CP}$ = 9.0 Hz), 79.77, 78.95, 67.45, 53.24 (d, $^1J_{CP}$ = 167.8 Hz), 26.98, 26.54; ; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 14.65; **HRMS (ESI)** calculated for $C_{46}H_{41}FNO_7PNa$ $[M^+Na]^+$: 791.790 found 791.793.

Benzyl((4-chlorophenyl)((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8tetraphenyltetrahydro [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)methyl)carbamate (*R*,*R*,*R*)- 147c



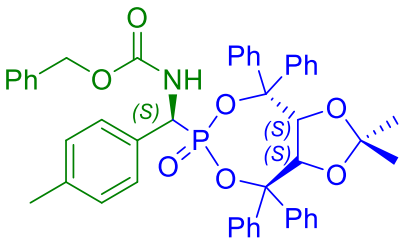
White solid; 219mg, 95% yield; mp: 236-238 °C; $[\alpha]_D^{20}$ = -135.5 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 – 7.49 (m, 2H), 7.49 – 7.43 (m, 2H), 7.41 – 7.14 (m, 23H), 6.94 – 6.89 (m, 2H), 5.70 (s, br, 1H), 5.48 (d, *J* = 7.9 Hz, 1H), 5.29 – 4.94 (m, 4H), 0.77 (s, 3H), 0.52 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$), δ: 155.71 (d, $^1J_{CO}$ = 14.1 Hz), 144.06 (d, J_{CCl} = 6.2 Hz), 143.11, 139.19 (d, $^2J_{CCl}$ = 9.9 Hz), 136.08, 134.03 (d, $^2J_{CP}$ = 3.6 Hz), 129.84, 129.62, 129.13, 128.73, 128.59, 128.50, 128.40, 128.28, 127.93 (d, $^3J_{CP}$ = 6.2 Hz), 127.40, 127.32, 126.61, 114.26, 92.02 (d, $^1J_{CP}$ = 13.5 Hz), 91.33 (d, $^1J_{CP}$ = 12.7 Hz), 79.66, 78.90, 67.49, 53.46 (d, J_{CP} = 161.5 Hz), 26.98, 26.55; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 14.51; **HRMS (ESI)** calculated for $C_{46}H_{41}ClNO_7PNa$ $[M^+Na]^+$: 808.2207 found 808.2220

Benzyl (((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(p-tolyl)methyl)carbamate (*R*,*R*,*R*)-148d



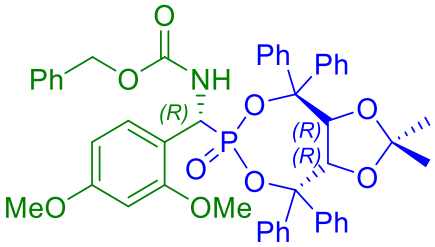
White solid; 204mg, yield = 91%; mp: 128-130 °C; $[\alpha]_D^{20}$ = -122.7 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.58 – 7.52 (m, 2H), 7.50-7.45 (m, 2H), 7.40 – 7.14 (m, 21H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 6.9 Hz, 2H), 5.65 (br, s, 1H), 5.50 (d, *J* = 7.9 Hz, 1H), 5.37 – 4.97 (m, 4H), 2.35 (s, 3H), 0.80 (s, 3H), 0.53 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.62 (d, $^1J_{CO}$ = 12.3 Hz), 144.18 143.36, 139.38 (d, *J* = 9.9 Hz), 137.80 132.12, 129.62, 129.31, 128.59, 128.51, 128.21, 127.88, 127.75, 127.37, 127.27 (d, $^3J_{CP}$ = 4.5 Hz), 126.63, 114.06, 90.80 (d, $^2J_{CP}$ = 14.2 Hz), 87.29 (d, $^3J_{CP}$ = 9.2 Hz), 79.96, 79.09, 67.33, 53.64 (d, $^1J_{CP}$ = 165.6 Hz), 27.01, 26.53, 21.28; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.23; **HRMS (ESI)** calculated for $C_{47}H_{44}NO_7PNa$ $[M^+Na]^+$: 788.2753 found 788.2749

Benzyl (((3aS,8aS)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(p-tolyl)methyl)carbamate (*S,S,S*)-148d



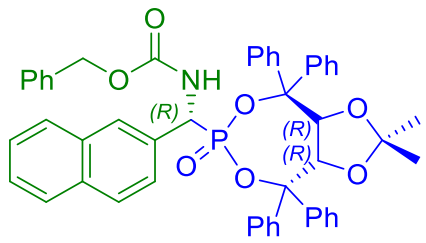
White solid; 208mg, 93% yield; mp: 154-156 °C; $[\alpha]_D^{20}$ = +142.2 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.57 – 7.51 (m, 2H), 7.50-7.45 (m, 2H), 7.40 – 7.12 (m, 21H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 2H), 5.61 (br, s, 1H), 5.48 (d, *J* = 7.9 Hz, 1H), 5.50 – 4.99, (m, 4H), 2.34 (s, 3H), 0.79 (s, 3H), 0.52 (s, 3H);); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:155.62 (d, $^1J_{CO}$ = 12.4 Hz), 144.16, 143.38, 139.37 (d, $^2J_{CP}$ = 9.9 Hz), 137.85, 132.11, 129.62 , 129.28, 128.58, 128.50, 128.21, 127.87, 127.73, 127.36 127.26, 127.24, 126.61, 114.05, 90.82 (d, $^2J_{CP}$ = 9.9 Hz), 87.27 (d, $^2J_{CP}$ = 7.9 Hz), 79.93, 79.07, 67.33, 53.61 (d, $^1J_{CP}$ = 162.8 Hz), 27.00, 26.52, 21.26; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.21; **HRMS (ESI)** calculated for $C_{47}H_{44}NO_7PNa$ $[M^+Na]^+$: 788.2753 found 788.2757

Benzyl ((2,5-dimethoxyphenyl)((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetra hydro[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)methyl)carbamate (*R,R,R*)-148e



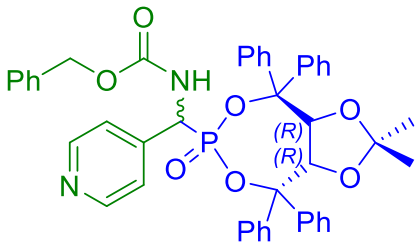
White solid; 212mg, 89% yield; mp: 120-122 °C $[\alpha]_D^{20}$ = -133.5 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.57 – 7.52 (m, 2H), 7.50 – 7.46 (m, 2H), 7.38 – 7.15 (m, 19H), 7.07 – 7.03 (m, 2H), 6.95 – 6.84 (m, 2H), 6.79 (d, *J* = 6.7 Hz, 1H), 5.68-5.58 (br, s, 1H), 5.51 (d, *J* = 8.0 Hz), 5.30 – 4.93 (m, 4H), 3.86 (s, 3H), 3.69 (s, 3H), 0.82 (s, 3H), 0.52 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.63 (d, $^1J_{CO}$ = 13.6 Hz), 149.09 (d, $^3J_{CP}$ = 2.0 Hz), 149.03 (d, $^3J_{CP}$ = 2.7 Hz), 129.47, 128.63, 128.53, 128.47, 128.17, 127.90, 127.82, 127.42, 127.29, 127.14, 126.61, 120.57 (d, $^2J_{CP}$ = 7.2 Hz), 113.92, 111.08, 90.60 (d, $^1J_{CP}$ = 11.7 Hz), 87.21 (d,$^1J_{CP}$ = 11.5 Hz), 80.35, 79.09, 67.39, 56.01,, 55.90, 53.50 (d, $^1J_{CP}$ = 164.1 Hz), 26.99, 26.47; **^{31}P NMR** (162 MHz, $CDCl_3$) δ:15.29; **HRMS (ESI)** calculated for $C_{48}H_{46}NO_9PNa$ $[M^+Na]^+$: 834.2808 found 834.2809

Benzyl (((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(naphthalen-2-yl)methyl)carbamate (*R*,*R*,*R*)-148f



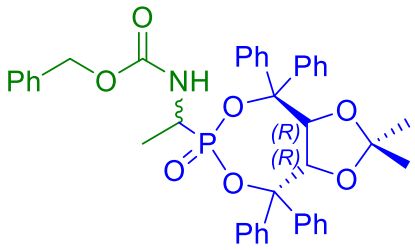
White solid; 211mg, 90% yield; mp: 126-128 ^{o}C ; $[\alpha]_D^{20}$ = -119.0 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 5.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.60 (m, 2H), 7.58 – 7.07 (m, 24H), 7.06 – 6.91 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 2H), 5.77(s, br, 1H), 5.49 (d, *J* = 7.7 Hz, 1H), 5.41 – 4.94 (m, 4H), 0.77 (s, 3H), 0.49 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:155.76 (d, $^{1}J_{CO}$ = 14.0 Hz), 144.18, 143.23, 139.25, 133.20 (d, $^{2}J_{CP}$ = 10.6 Hz), 129.65, 128.61, 128.47, 128.24, 127.92, 127.70, 127.39, 127.16, 126.83, 126.60, 126.32, 125.58, 114.14, 91.15 (d, $^{2}J_{CP}$ = 13.6 Hz), 87.43 (d, $^{2}J_{CP}$ = 8.9 Hz), 79.77, 78.98, 67.46 , 54.21 (d, $^{1}J_{CP}$ = 162.9 Hz), 26.98, 26.54; **^{31}P NMR** (162 MHz, $CDCl_3$) δ:15.05; **HRMS (ESI)** calculated for $C_{50}H_{44}NO_7PNa$ $[M^+Na]^+$: 824.2753 found 824.2769.

benzyl (((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)(pyridin-4-yl)methyl)carbamate (148g)



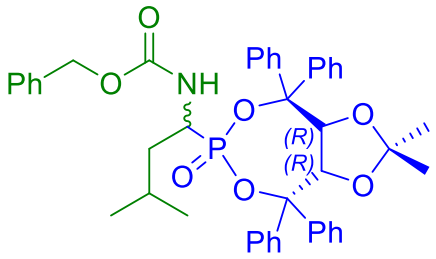
Yellowish solid; 167mg, yield: 76%; mp: 126-128 ^{o}C ; dr = 68:32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: $^{+}$8.14 (d, *J* = 8.5 Hz, 4H), 7.62 (d, *J* = 10.4 Hz, 2H), 7.48 – 7.12 $^{+}$(m, 32H), 6.98 $^{+}$(d, *J* = 7.3 Hz, 3H), 5.87 (s, br, 1H), *5.54 (s, br, 1H), *5.50 (d, *J* = 7.7 Hz, 1H), 5.47 (d, *J* = 7.8 Hz, 1H), $^{+}$5.41 – 4.93 (m, 7H), *0.73 (s, 2H), , 0.70 (s, 3H), *0.56 (s, 2H), 0.54 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:155.61 (d, $^{1}J_{CO}$ = 13.2 Hz), 148.31, 142.85, 139.01, 137.59, 134.37, 129.80, 129.63, 129.51, 129.08, 128.86, 128.69, 128.65, 128.61, 128.48, 128.41, 128.37, 128.16, 128.07, 127.51, 127.42, 127.32, 127.23, 126.69, 126.60, 123.40, 123.12, *92.48 (d, $^{2}J_{CP}$ = 13.3 Hz), 91.98 (d, $^{2}J_{CP}$ = 13.2 Hz), *88.11 (d, $^{2}J_{CP}$ = 9.1 Hz), 87.69 (d, $^{2}J_{CP}$ = 8.3 Hz), *67.78, 67.70 53.38 (d, $^{1}J_{CP}$ = 160.6 Hz), *53.09 (d, $^{1}J_{CP}$ = 158.2 Hz) 26.97, *26.88, 26.64 *26.32; **^{31}P NMR** (162 MHz, $CDCl_3$) δ:13.52, *12.75; **HRMS (ESI)** calculated for $C_{45}H_{41}N_2O_7PNa$ $[M^+Na]^+$: 775.7864 found 776.7861

Benzyl (1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo [4,5-e] [1,3,2]dioxaphosphepin-6-yl)ethyl)carbamate (148h)



White solid; 131mg, 65% yield; mp: 156-158 ^{o}C ;dr = 90:10; $[\alpha]_D^{20}$ = -163.7 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.60 – 7.46 (m, 4H), 7.45 – 7.13 (m, 21H), 5.54 (d, *J* = 7.9 Hz, 1H), 5.35 – 4.93 (m, 4H), 4.34 – 4.18 (m, 1H), 1.38 (dd, *J* = 17.7, 7.3 Hz, 3H), 0.77 (s, 3H), 0.58 (s, 3H);); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 155.64 (d, $^{1}J_{CO}$ = 6.4 Hz), *155.41 (d, $^{1}J_{CO}$ = 8.8 Hz), 144.44, 143.73, 143.38, 139.55, 136.24, 129.75, 128.84, 128.76, 128.64, 128.58, 128.39, 128.36, 128.28, 128.22, 128.12, 127.92, 127.83, 127.39, 127.33, 127.20, 127.08, 126.87, 126.65, *114.4, 114.12, 90.87 (d, $^{2}J_{CP}$ = 13.5 Hz), 86.87 (d, $^{2}J_{CP}$ = 8.8 Hz), 79.68, 78.99, 67.19, *67.02, 45.04 (d, ^{1}JCP = 167.66 Hz), *44.44 (d, $^{1}J_{CP}$ = 166.65 Hz), 26.94 (d, $^{2}J_{CP}$ = 6.3 Hz), *26.66 (d, $^{2}J_{CP}$ = 7.9 Hz), 16.20, 15.71; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 19.38, *18.88; **HRMS (ESI)** calculated for $C_{41}H_{40}NO_7PNa$ $[M^+Na]^+$: 712.2440 found 721.2435.

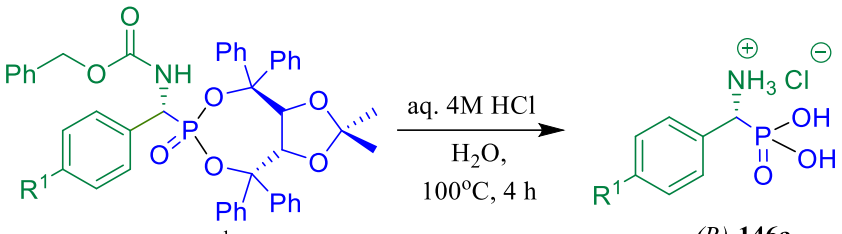
Benzyl (1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo [4,5-e] [1,3,2] dioxaphosphepin-6-yl)-3-methylbutyl)carbamate (184i)



White solid; 161mg, 75% yield; mp: 114-116 ^{o}C ;dr = 90:10; $[\alpha]_D^{20}$ = -153.8 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.61 – 7.48 (m, 4H), 7.42 – 7.06 (m, 21H), 5.54 (d, *J* = 7.9 Hz, 1H), 5.27 – 5.07 (m, 2H), 5.01 (d, *J* = 10.5 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.30 – 4.16 (m, 1H), 1.77 – 1.56 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H), 0.74 (s, 3H), 0.60 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 156.03 (d, $^{1}J_{CO}$ = 4.3 Hz), *155.73 (d, $^{1}J_{CO}$ = 5.1 Hz), 144.69 (d, $^{3}J_{CP}$= 7.2 Hz), *144.52 (d, $^{3}J_{CP}$ = 5.8 Hz), 143.78, 139.56, 136.26, 129.82, 128.94, 128.73, 128.65, 128.60, 128.54, 128.44, 128.39, 128.35, 128.26, 128.17, 128.06, 127.77, 127.36, 127.32 , 127.23, 126.95, 126.67, *114.33, 114.16, 91.10 (d, $^{2}J_{CP}$ = 13.8 Hz), *90.61 (d, $^{2}J_{CP}$ = 14.1 Hz), *87.07 (d, $^{2}J_{CP}$ = 9.1 Hz), 86.80 (d, $^{2}J_{CP}$ = 8.9 Hz), *80.21, 79.79, *79.49, 78.93, 67.23, *67.06, 47.97 (d, $^{1}J_{CP}$ = 165.64 Hz, *47.31 (d, $^{1}J_{CP}$ = 165.64 Hz), *38.36 (d, $^{2}J_{CP}$ = 4.1 Hz), 37.82 (d, $^{2}J_{CP}$ = 3.4 Hz), 26.94, *26.72, 24.63, *24.46, *24.32, *23.52, 23.48, *21.27, 21.18; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: *19.21, 18.90; **HRMS (ESI)** calculated for $C_{44}H_{46}NO_7PNa$ $[M^+Na]^+$: 754.2910 found 754.2913

6.0. General protocol for the cleavage of the chiral auxiliary and Cbz protecting group.

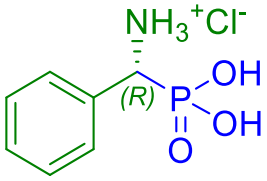
See section **3.0a** (page 189) for the procedure.



(R,R,R)-**148a**, R^1 = H
(R,R,R)-**148b**, R^1 = F

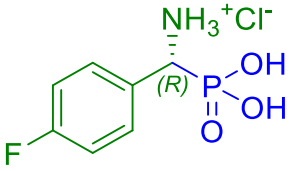
(R)-**146a**
(R)-**146b**

(*R*)-(Amino(phenyl)methyl)phosphonic acid salt (146a)



White solid; 134mg, 90% yield; mp: 224-226 °C; $[\alpha]_D^{20}$ = +19.0 (c = 1.0, 1M NaOH); **^{1}H NMR** (400 MHz, D_2O) δ: 7.25 (s, 5H), 4.29 (d, *J* = 16.4 Hz); **^{13}C NMR** (101 MHz, D_2O) δ 132.00 (d, $^2J_{CP}$ = 3.7 Hz), 129.07, 129.05, 129.03, 53.01 (d, $^1J_{CP}$ = 141.5 Hz); **^{31}P NMR** (162 MHz, D_2O) δ: 12.02

(*R*)-(Amino(4-fluorophenyl)methyl)phosphonic acid salt (146b)



White solid; 137mg, 87% yield; mp: 295-397 °C; $[\alpha]_D^{20}$ = +10.4 (c = 1.0, 1M NaOH); **^{1}H NMR** (400 MHz, D_2O) δ: 7.32 (s, 2H), 7.12 – 7.01 (m, 2H), 4.33 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (151 MHz, D_2O) δ 162.72 (d, $^1J_{CF}$ = 245.4 Hz), 129.84, 129.10, 128.48, 127.09, 115.88 (d, $^2J_{CP}$ = 21.9 Hz), 52.69 (d, $^1J_{CP}$ = 139.8 Hz); **^{31}P NMR** (162 MHz, D_2O) δ: 11.33.

Asymmetric hydrophosphonylation of imines

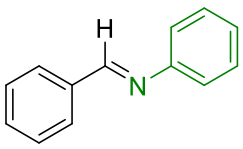
1.0. General procedure for the preparation of imines

The aldehyde **49** (3.0 mmol, 1 equiv)) was dissolved in CH_2Cl_2 (15 mL) and an appropriate amine **159** was added (3.0 mmol, 1 equiv). The mixture was stirred for 24 h (30 h in case of ketone) at room temperature and dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated to give the crude product which was crystallized from diethyl ether to afford the pure products **203**.

49 **159** **203**

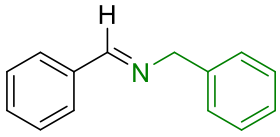
R^1 = H, CH_3

€-*N*,1-diphenylmethanimine (203a)



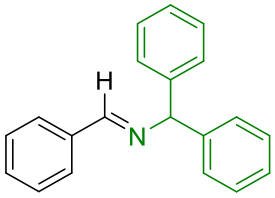
White solid; 392mg, 72% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.47 (s, 1H), 7.95-7.92 m, 2H), 7.54 – 7.38 (m, 5H), 7.28-7.24 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 160.57, 152.19, 136.33, 131.52, 129.29, 128.96, 128.91, 126.09, 121.02.

(E)-N-benzyl-1-phenylmethanimine (203b)



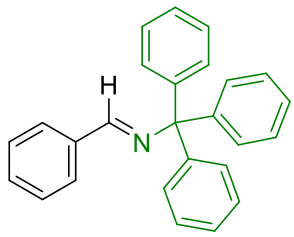
Yellowish oil; 474mg, 81% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ:8.43 (s, 1H), 7.93 – 7.79 (m, 2H), 7.55 – 7.26 (m, 8H), 4.88 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 162.24, 139.46, 136.30, 130.99, 128.81, 128.71, 128.50, 128.19, 127.20, 65.19.

(E)-*N*-benzhydryl-1-phenylmethanimine (203c)



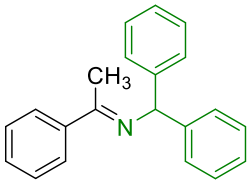
White solid; 651mg, 80% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H), 7.88-7.85 (m, 2H), 7.49 – 7.13 (m, 13H), 5.63 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 160.93, 144.00, 136.43, 130.89, 128.65, 128.59, 128.56, 127.80, 127.10, 78.00.

(E)-1-phenyl-*N*-tritylmethanimine (203d)



Yellowish solid; 823mg, 79% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.3 Hz, 1H), 7.92 – 7.80 (m, 4H), 7.53 – 7.41 (m, 4H), 7.31 – 7.14 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 159.75, 145.93, 136.85, 133.90, 130.86, 130.33, 129.92, 128.73, 128.67, 128.61, 127.87, 126.89, 78.39.

(E)-N-benzhydryl-1-phenylethan-1-imine (203e)



Colourless oil, 591mg, 69% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.1 Hz, 2H), 7.34 – 7.18 (m, 3H), 7.16 – 6.94 (m, 10H), 4.96 (s, 1H), 2.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:145.74, 144.96, 137.23, 133.22, 128.68, 128.5, 128.5, 128.42, 128.26, 127.68, 127.04, 127.00, 59.8, 26.73.

2.0. General procedure for the hydrophosphonylation of imine with TADDOL-derived *H*-phosphonate

The imine **203c** (1.0 equiv, 0.1 mmol) and Cs_2CO_3 (1.0 equiv) were dissolved in toluene (0.80 mL) followed by the addition of (*R*,*R*)-TADDOL-derived *H*-phosphonate **29** (1.0 equiv, 0.1 mmol) and the mixture was stirred at 100 °C for 10 h. The resulting crude product was isolated directly by column chromatography on silica gel (using a hexane/EtOAc eluent in ratios ranging from 5:1 to 3:1) to give the corresponding aminophosphonates **204c**.

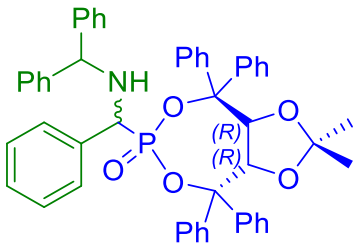
Note: The reaction with imine **203e** gave a poor conversion. Hence the obtained crude product **206** wasn't purified. The presence of products **204a, b, c** and **206** were confirmed by HRMS and analysis of the ^{31}P and ^{1}H NMR spectra of the crude reaction mixture (Table 7, page 110 and Table 9, page 117) .

3.0. General procedure for the one-pot synthesis of aminophosphonate

To 0.80 mL of toluene, 0.10 mmol of benzaldehyde **49**, 0.10 mmol of benzhydrylamine **159c** and 1.0 equiv. of a base were added under constant stirring and heating at 100 °C. After one hour, 0.10 mmol of the TADDOL-derived *H*-phosphonate (*R*,*R*)-**29** was added to the mixture. The resulting mixture was heated at the same temperature for 8 hours. At the end of the reaction, the mixture was cooled to room temperature and concentrated to give the crude

aminophosphonate **204c**, which was purified by column chromatography using a hex:EtOAc eluent gradient (from 5:1 to 3:1, v/v).

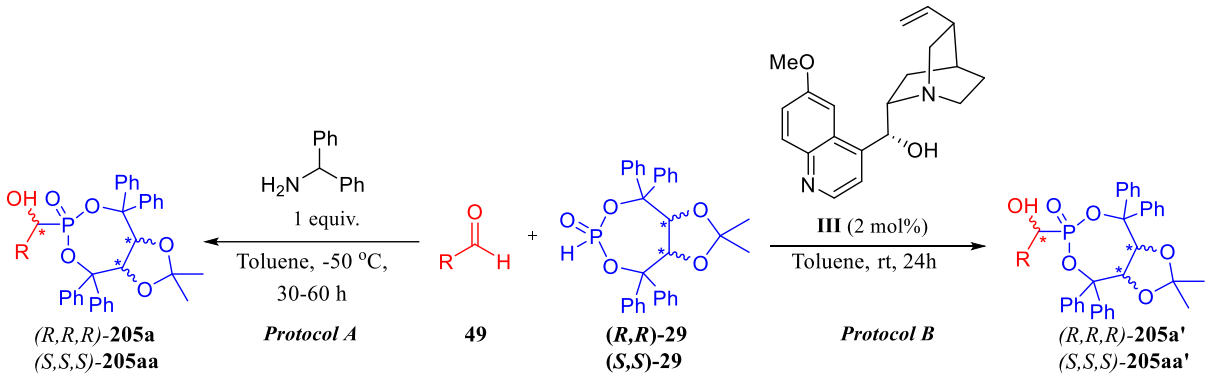
Benzyl (((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepin-6-yl)(phenyl)methyl)carbamate (204c)



White solid; 124mg, 81% yield, dr: 58:42 (62:38 dr after purification); **^{1}H NMR** (400 MHz, $CDCl_3$), δ: 7.77 (dd, *J* = 8.0, 1.5 Hz, 2H)$^{+}$, 7.65 – 7.55 (m, 3H)$^{+}$, 7.48-7.44 (m, 3H)$^{+}$, 7.40 – 7.16 (m, 38)$^{+}$, 5.56 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 7.9 Hz, 1H)*, 5.17 (d, *J* = 8.0 Hz, 1H)*, 5.03 (d, *J* = 8.0 Hz, 1H), 4.95 (s, 1H), 4.82 (s, 1H)*, 4.29 – 4.15 (m, 2H)$^{+}$, 0.95 (s, 3H), 0.83 (s, 1H)*, 0.64 (s, 1H)*, 0.48 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:145.04 (d, *J* = 7.2 Hz)*, 144.69 (d, *J* = 8.0 Hz), 144.04, 143.91, 143.72, 142.46, 142.35, 140.02, 139.97, 139.87, 139.83, 139.67, 135.58, 130.17, 130.03, 129.08, 128.90, 128.84, 128.79, 128.53, 128.40, 128.26, 128.17, 128.15, 128.13, 128.11, 127.94, 127.85, 127.75, 127.69, 127.52, 127.47, 127.41, 127.38, 127.32, 127.27, 127.24, 127.17, 126.71, 126.59, 113.74*, 113.48, 91.04 (d, $^{2}J_{CP}$ = 14.0 Hz)*, 90.28 (d, $^{2}J_{CP}$ = 13.5 Hz), 86.20 (d, $^{2}J_{CP}$ = 8.5 Hz), 86.16 (d, $^{2}J_{CP}$ = 8.8 Hz)*, 80.08 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.68 (d, $^{3}J_{CP}$ = 2.6 Hz)*, 79.40 (t, $^{3}J_{CP}$ = 2.3 Hz)$^{+}$, 58.60 (d, $^{1}J_{CP}$ = 161.7 Hz)*, 58.56 (d, $^{1}J_{CP}$ = 160.5 Hz), 27.29, 27.13*, 26.74*, 26.33; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 18.67, 17.24*; **HRMS (ESI)** calculated for $C_{51}H_{46}NO_5P$ $[M^{+}H]^{+}$: 784.3192 found 784.3184.

Asymmetric hydrophosphonylation of carbonyl compounds

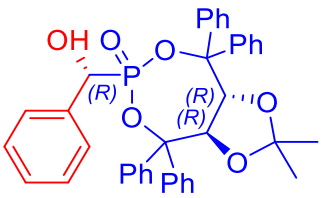
1.0. General procedure for the hydrophosphonylation of aldehydes



Protocol A: TADDOL derived *H*-phosphonate **29** (0.290 mmol, 1.0 equiv.) was added to the mixture of benzylhydryl amine and carbonyl compound, (0.290 mmol, 1.0 equiv.) in 2 mL of toluene at -50 °C. The reaction mixture was stirred at that temperature for 30-60 h to complete conversion (see Scheme 94, page 136 for the exact reaction time). Through crystallization from diethyl ether, the pure product was isolated.

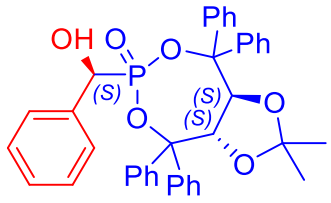
Protocol B: The carbonyl compound (0.290 mmol, 1.0 equiv) was added to a mixture of TADDOL derived *H*-phosphonate **29** (0.290 mmol, 1.0 equiv.) and quinine **III** (2 mol%) in toluene (2 mL). The reaction mixture was stirred at room temperature for 24 h to complete conversion. The pure product **205'** was isolated by crystallization using diethyl ether.

(3aR,8aR)-6-(hydroxy(phenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205a')



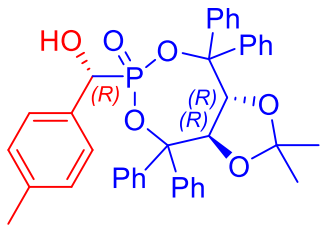
Protocol B: White solid, mass: 165mg, 91% yield; dr: 91:9 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -188.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.45 – 7.42 (m, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.22 – 7.11 (m, 11H), 7.05 – 7.01 (m, 6H), 6.94 (t, *J* = 7.5 Hz, 2H), 6.51 (d, *J* = 6.9 Hz, 2H), 5.21 (d, *J* = 7.9 Hz, 1H), 4.95 (d, *J* = 8.7 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 3.22 (bs, 1H), 0.59 (s, 3H), 0.31 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.34, 143.42, 139.53, 139.44, 135.16, 130.03, 128.63, 128.41, 128.28, 128.18, 128.13, 127.81, 127.67 , 127.54, 127.29, 127.15, 126.81, 126.57, 113.93, 91.35 (d, $^{2}J_{CP}$ = 14.5 Hz), 86.45 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.23 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.06 (d, $^{3}J_{CP}$ = 2.5 Hz), 71.16 (d, $^{1}J_{CP}$ = 158.3 Hz), 27.04, 26.50; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.61, dr: 91:9 (97:3); **HRMS (ESI)** calculated for $C_{38}H_{36}O_6P$ $[M^+H]^+$: 619.2250 found 619.2253

(3aS,8aS)-6-(hydroxy(phenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide, (205aa')



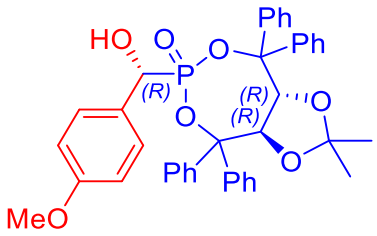
Protocol B: White solid, mass: 166mg, 91% yield; dr: 90:10, (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: +186.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** 7.47 – 7.42 (m, 2H), 7.35 (d, *J* = 6.9 Hz, 2H), 7.24 – 7.08 (m, 11H), 7.06 – 7.00 (m, 6H), 6.95 (t, *J* = 7.5 Hz, 2H), 6.51 (d, *J* = 6.7 Hz, 2H), 5.22 (d, *J* = 7.9 Hz, 1H), 4.95 (d, *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 3.44 (bs, 1H), 0.60 (s, 3H), 0.31 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.26, 143.43, 139.52, 139.43, 136.12, 130.02 128.63 , 128.42, 128.29, 128.14, 127.85, 127.81, 127.55, 127.29, 127.16, 126.81, 126.58, 113.94, 91.35 (d, $^{2}J_{CP}$ = 14.6 Hz), 86.47 (d, $^{2}J_{CP}$ = 9.6 Hz), 79.23 (d, $^{3}J_{CP}$ = 2.4 Hz), 79.06 (d, $^{3}J_{CP}$ = 2.6 Hz), 71.14 (d, $^{1}J_{CP}$ = 164.8 Hz), 27.04, 26.49; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.66; **HRMS (ESI)** calculated for $C_{38}H_{36}O_6P$ $[M^+H]^+$: 619.2250 found 619.2248

(3aR,8aR)-6-(hydroxy(p-tolyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide, (205b)



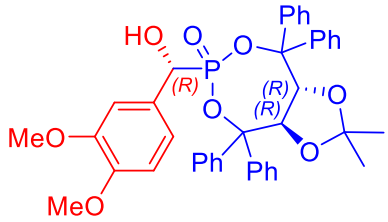
Protocol A: White solid, mass: 165mg, 89% yield; dr: 95:5, (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -186.4 (*c* 1.0, CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ: 7.61 – 7.54 (m, 2H), 7.49 – 7.23 (m, 13H), 7.20 – 7.13 (m, 1H), 7.11 – 6.96 (m, 6H), 6.67 (d, *J* = 7.3 Hz, 2H), 5.35 (d, *J* = 7.9 Hz, 1H), 5.05 (d, *J* = 8.2 Hz, 1H), 4.90 (d, *J* = 7.9 Hz, 1H), 3.27 (bs, 1H), 2.39 (s, 3H), 0.74 (s, 3H), 0.45 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.32, 143.44, 139.54, 139.44, 137.44, 133.12, 129.98, 128.89, 128.86, 128.70, 128.42, 128.28, 128.20, 127.84, 127.76, 127.55, 127.29, 127.08, 126.68, 126.62, 126.59, 113.94, 91.17 (d, $^{2}J_{CP}$ = 14.5 Hz), 86.46 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.24 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.15 (d, $^{3}J_{CP}$ = 2.6 Hz), 71.13 (d, $^{1}J_{CP}$ = 165.0 Hz), 27.04, 26.52, 21.34; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.67.); **HRMS (ESI)** calculated for $C_{39}H_{38}O_6P$ $[M^+H]^+$: 633.2406 found 633.2404

(3aR,8aR)-6-(hydroxy(4-methoxyphenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205c)



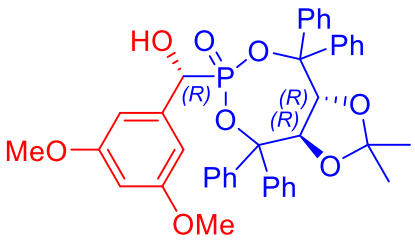
Protocol A: White solid, mass: 167mg, 88% yield; dr 90:10 (94:6 dr after crystallization); $[\alpha]^{D}_{20}$: -196.6 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: *7.67 – 7.61 (m, 1H), 7.45 – 7.40 (m,2H), 7.37 – 7.32 (m, 2H), $^{+}$7.25 – 6.92 (m, 17H), *6.83 – 6.73 (m, 1H), 6.66 – 6.52 (m, 4H), *5.43 (s, 1H), 5.22 (d, *J* = 7.9 Hz, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.78 (d, *J* = 7.9 Hz,1H), 3.69 (s, 3H), *3.20 (s, 1H), $^{+}$0.60 (s, 3H), *0.37 (s, 1H), 0.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 161.80, 160.17, 159.41, 144.40, 143.45, 139.50, 130.12, 129.98, 128.71, 128.49, 128.40, 128.29, 128.20, 128.12, 128.07, 127.84, 127.79, 127.61, 127.29, 127.13, 126.98, 126.61, 113.95, 113.51, 91.16 (d, $^{2}J_{CP}$ = 14.5 Hz), 86.49 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.23 (d, $^{3}J_{CP}$ = 2.4 Hz), 79.13 (d, $^{3}J_{CP}$ = 2.6 Hz), 70.89 (d, $^{1}J_{CP}$ = 166.3 Hz), 55.41, 27.03, 26.51; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.60, *15.06; **HRMS (ESI)** calculated for $C_{21}H_{19}NO_4SNa$ $[M^{+}Na]^{+}$: 671.2175 found 671.2170.

(3aR,8aR)-6-((3,4-dimethoxyphenyl)(hydroxy)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetra- hydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205d)



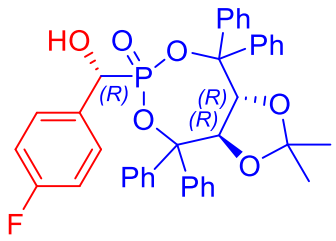
Protocol A: White solid, mass: 176mg, 87% yield dr 90:10 (96:4 dr after crystallization); $[\alpha]^{D}_{20}$: -195.8 (*c* 1.0, CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ: 7.62 – 7.54 (m, 2H), 7.48 – 7.26 (m, 13H), 7.22 – 7.11 (m, 3H), 6.99 (s, 1H), 6.83 – 6.79 (m, 2H), 6.63 – 6.60 (m, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 5.05 (d, *J* = 8.3 Hz, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 0.77 (s, 3H), 0.48 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:148.9, 148.80, 144.58, 143.48, 139.52, 129.87, 128.62, 128.55, 128.50, 128.31, 128.27, 128.18, 127.84, 127.71, 127.60, 127.32, 127.22, 127.13, 126.57, 119.55, 113.86, 110.68, 109.89, 91.06 (d, $^{2}J_{CP}$ = 14.4 Hz), 86.50 (d, $^{2}J_{CP}$ = 9.6 Hz), 79.52 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.22 (d, $^{2}J_{CP}$ = 2.5 Hz), 71.10 (d, $^{1}J_{CP}$ = 166.3 Hz), 56.04, 55.84, 27.02, 26.50; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.79, *15.09; **HRMS (ESI)** calculated for $C_{40}H_{39}O_8PNa$ $[M^{+}Na]^{+}$: 701.2280 found 701.2286

(3aR,8aR)-6-((R)-(3,5-dimethoxyphenyl)(hydroxy)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetra- hydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205e)



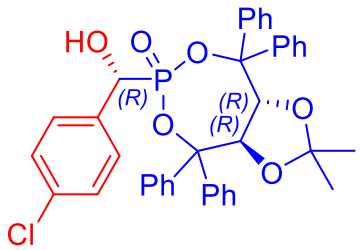
Protocol A : White solid, mass: 172mg, 85% yield; dr 94:6 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -189.4 (*c* 1.0, CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ: 7.61 – 7.55 (m, 2H), 7.48 – 7.40 (m, 3H), 7.40 – 7.11 (m, 14H), 6.83 (d, *J* = 7.2 Hz, 2H), 6.49 (t, *J* = 2.2 Hz, 1H), 6.44 – 6.42 (m, 1H), 5.41 (d, *J* = 7.9 Hz, 1H), 5.04 (d, *J* = 9.4 Hz, 1H), 4.94 (d, *J* = 8.0 Hz,1H), 3.59 (s, 6H), 0.80 (s, 3H), 0.49 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ:148.22, 143.93, 142.92, 138.90, 129.30, 128.05, 127.73, 127.70, 127.60, 127.27, 127.14, 127.03, 126.74, 126.65, 126.00, 118.99, 113.28, 110.10, 109.28, 90.48 (d, $^{2}J_{CP}$ = 14.4 Hz), 85.92 (d, $^{2}J_{CP}$ = 9.6 Hz), 78.95 (d, $^{3}J_{CP}$ = 2.4 Hz), 78.66 (d, $^{3}J_{CP}$ = 2.5 Hz), 70.52 (d, $^{1}J_{CP}$ = 166.3 Hz), 55.47, 55.27, 26.45, 25.92. **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.61; **HRMS (ESI)** calculated for $C_{40}H_{39}O_8PNa$ $[M^+Na]^+$: 701.2280 found 701.2286.

(3aR,8aR)-6-((4-fluorophenyl)(hydroxy)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205f)



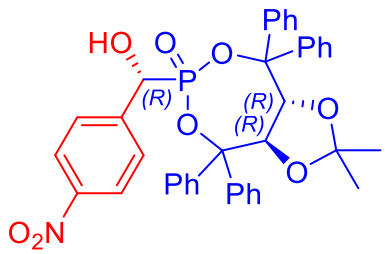
Protocol A: White solid; mass:168mg, 90% yield; dr 95:5 (single diatereomer after crystallization); $[\alpha]^{D}_{20}$: -197.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.46 – 7.39 (m, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.25 – 7.11 (m, 11H), 7.05-6.91 (m, 5H), 6.69 (t, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 7.4 Hz, 2H), 5.20 (d, *J* = 7.8 Hz, 1H), 4.92 (d, *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 3.66 (br, s, 1H), 0.57 (s, 3H), 0.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 162.44 (d, J_{CP} = 250.0 Hz), 144.23, 143.30, 139.42, 139.33, 131.99, 130.04, 128.58, 128.54, 128.50, 128.44, 128.34, 128.33, 128.23, 114.90 (d, J_{CF} = 21.5 Hz), 114.04, 91.60 (d, $^{2}J_{CP}$ = 14.7 Hz), 86.56 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.15 (d, $^{2}J_{CP}$ = 2.3 Hz), 78.88 (d, $^{2}J_{CP}$ = 2.6 Hz), 70.49 (d, $^{1}J_{CP}$ = 166.2 Hz), 27.00, 26.52; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.52.; **HRMS (ESI)** calculated for $C_{38}H_{35}FO_6P$ $[M^+Na]^+$: 637.2155 found 637.2157.

(3aR,8aR)-6-((4-chlorophenyl)(hydroxy)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205h')



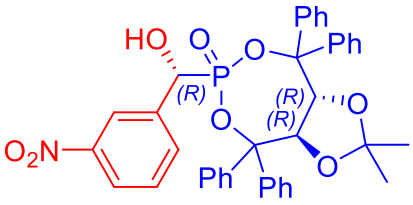
Protocol B: White solid, mass:174mg, 91% yield; dr 90:10 (single diastereomer after crystallization); $[\alpha]^{D}_{20}$: -184.2 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ:7.58 – 7.55 (m, 2H), 7.50 (d, *J* = 7.1 Hz, 2H), 7.43 – 7.27 (m, 11H), 7.22 – 7.02 (m, 7H), 6.60 (d, *J* = 7.3 Hz, 2H), 5.33 (d, *J* = 7.8 Hz, 1H), 5.06 (d, *J* = 8.7 Hz, 1H), 4.89 (d, *J* = 7.8 Hz, 1H), 391 (bs, 1H), 0.71 (s, 3H), 0.47 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.22, 143.28, 139.36, 139.21, 134.98, 133.44, 130.04, 129.83, 128.58, 128.53, 128.37, 128.33, 128.23, 128.20, 128.13, 128.07, 127.92, 127.84, 127.74, 127.32, 127.21, 126.58, 91.77 (d, $^{2}J_{CP}$ = 14.8 Hz), 86.61 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.13 (d, $^{3}J_{CP}$ = 2.4 Hz), 78.83 (d, $^{3}J_{CP}$ = 2.6 Hz), 70.42 (d, $^{1}J_{CP}$ = 166.2 Hz), 27.02, 26.53; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.17; **HRMS (ESI)** calculated for $C_{38}H_{34}ClO_6PNa$ $[M^{+}Na]^{+}$: 675.1679 found 675.1671.

(3aR,8aR)-6-((R)-hydroxy(4-nitrophenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205h)



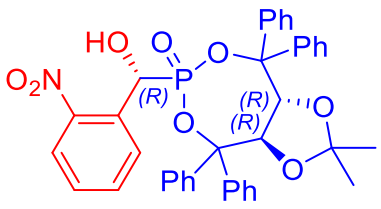
Protocol A: White solid, mass:173mg, 89% yield; dr 89:11 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -169.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ:7.83 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.30 (m, 6H), 7.23 – 7.03 (m, 12H), 6.97 (t, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 7.5 Hz, 2H), 5.21 (d, *J* = 7.8 Hz, 1H), 5.10 (bs, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 7.8 Hz, 1H), 0.58 (s, 3H), 0.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 147.35, 144.01, 143.89, 143.14, 139.22, 139.12, 130.10, 128.83, 128.58, 128.47, 128.40, 128.29, 128.01, 127.89, 127.63, 127.32, 127.24, 127.00, 126.53, 123.06, 114.25, 92.36 (d, $^{3}J_{CP}$ = 14.8 Hz), 86.84 (d, $^{2}J_{CP}$ = 9.3 Hz), 79.08 (d, $^{3}J_{CP}$ = 2.4 Hz), 78.51 (d, $^{3}J_{CP}$ = 2.8 Hz), 70.39 (d, $^{1}J_{CP}$ = 165.1 Hz), 26.97, 26.52; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.53. **HRMS (ESI)** calculated for $C_{38}H_{34}NO_8PNa$ $[M^{+}Na]^{+}$: 686.1920 found 686.1925.

(3aR,8aR)-6-((R)-hydroxy(3-nitrophenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205i)



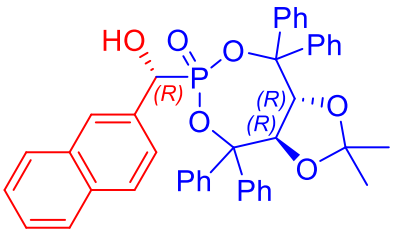
Protocol A: White solid, mass: 169mg, 87% yield; dr 86:14 (92:8 dr after crystallization); $[\alpha]^{D}_{20}$: -171.4 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.34 – 7.17 (m, 18), 7.09 – 7.04 (m, 2H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.49 (d, *J* = 8.0 Hz, 1H), 5.18 (s, 1H), 5.08 (d, *J* = 8.0 Hz, 1H), 0.92 (s, 3H), 0.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 147.35, 143.94 , 143.55, 139.49, 139.23, 133.37, 129.89, 129.43, 128.79, 128.62, 128.58, 128.34, 128.12, 128.09, 127.94, 127.83, 127.41, 127.37, 127.21, 127.09, 126.99, 126.56, 125.06, 113.74, 90.31 (d, $^{2}J_{CP}$ = 13.0 Hz), 87.66 (d, $^{2}J_{CP}$ = 9.1 Hz), 80.37 (d, $^{3}J_{CP}$ = 2.2 Hz), 79.43 (d, $^{3}J_{CP}$ = 2.3 Hz), 66.54 (d, $^{1}J_{CP}$ = 163.6 Hz), 59.75, 27.19, 26.03; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.13, *15.55; **HRMS (ESI)** calculated for $C_{38}H_{34}NO_8PNa$ $[M^{+}Na]^{+}$: 686.1920 found 686.1924.

(3aR,8aR)-6-((R)-hydroxy(2-nitrophenyl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205j)



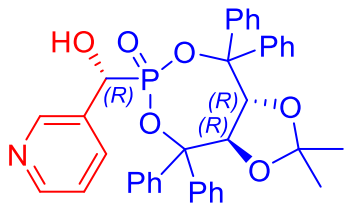
Protocol A: White solid, mass: 132mg, 68% yield; dr 73:27 (89:11 dr after crystallization); $[\alpha]^{D}_{20}$: -176.3 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** δ: 8.00 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 9.3 Hz, 3H), 7.33 – 7.18 (m, 20H)$^{+}$, 7.09 – 7.00 (m, 2H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.49 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 7.3 Hz, 1H), 0.92 (s, 3H), 0.36 (s, 3H), **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 147.35, 143.94, 143.55, 139.49, 139.23, 133.57, 133.37, 129.89, 128.83, 129.43, 128.79, 128.62, 128.58, 128.38, 128.34, 128.12, 128.09, 127.94, 127.83, 127.41, 127.37, 127.21, 127.09, 126.99, 126.56, 125.06, 113.74, 90.31 (d, $^{2}J_{CP}$ = 13.0 Hz), 87.66 (d, $^{2}J_{CP}$ = 9.1 Hz), 80.37 (d, $^{3}J_{CP}$ = 2.2 Hz), 79.43 (d, $^{3}J_{CP}$ = 2.3 Hz), 66.54 (d, $^{1}J_{CP}$ = 163.6 Hz), 27.19, 26.03; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.43, *15.85; **HRMS (ESI)** calculated for $C_{38}H_{34}NO_8PNa$ $[M^{+}Na]^{+}$: 686.1920 found 686.1916.

(3aR,8aR)-6-(hydroxy(naphthalen-2-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205k)



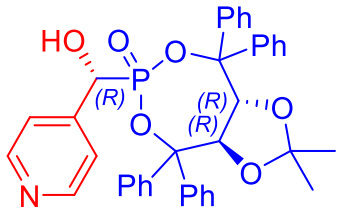
Protocol A: White solid, mass:178mg, 91% yield; dr 97:3 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$ -168.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 7.7 Hz,1H), 7.69 – 7.41 (m, 15H), 7.38 – 7.26 (m, 6H), 7.04 – 6.96 (m, 1H), 6.75 – 6.66 (m, 2H), 6.41 (d, *J* = 8.3 Hz, 2H), 5.34 (d, *J* = 7.9 Hz, 1H), 5.30 (d, *J* = 8.7 Hz, 1H), 4.79 (d, *J* = 7.9 Hz, 1H), 3.48 (bs, 1H), 0.71 (s, 3H), 0.40 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.45, 143.35, 139.45, 133.72, 133.13, 130.00, 128.51, 128.45, 128.39, 128.31, 128.27, 127.93, 127.88, 127.78, 127.65, 127.44, 127.31, 126.58, 126.08, 125.51, 124.63, 113.94 , 91.56 (d, $^{2}J_{CP}$ = 14.6 Hz), 86.52 (d, ^{2}JCP = 9.7 Hz), 79.17 (d, $^{3}J_{CP}$ = 2.6 Hz), 79.05 (d, $^{3}J_{CP}$ = 2.7 Hz), 71.44 (d, $^{1}J_{CP}$ = 164.1 Hz), 27.00, 26.49; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 16.44; **HRMS (ESI)** calculated for $C_{42}H_{37}O_6P$ $[M^{+}H]^{+}$: 669.2298 found 669.2313.

(3aR,8aR)-6-((R)-hydroxy(pyridin-3-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205l)



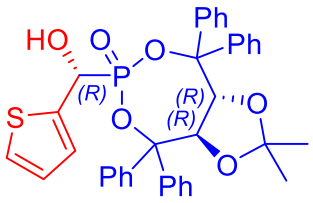
Protocol A: White solid mass: 147mg, 81% yield; dr: 89:11 (91:9 after crystallization); $[\alpha]^{D}_{20}$: -194.0 (*c* 1.0, CH_2Cl_2); dr **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.61 – 8.53 (m, 1H), 8.46 (s, 1H), $^{+}$7.57 – 7.27 (m, 18H), 7.22 – 7.12 (m, 4H), 7.09 – 7.02 (m, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.39 (d, *J* = 7.9 Hz, 1H), 5.10 (d, *J* = 9.8 Hz, 1H), 4.95 (d, *J* = 7.9 Hz, 1H), 3.74 (bs, 1H), *0.85 (s, 1H), 0.74 (s, 3H), *0.51 (s, 1H), 0.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 149.99, 146.44, 144.67, 143.86, 139.96, 129.36, 129.19, 129.11, 129.06, 129.00, 128.91, 128.61, 128.47, 127.97, 127.20, 122.42, 114.82, 92.92 (d, $^{2}J_{CP}$ = 13.4 Hz), 87.38 (d, $^{2}J_{CP}$ = 10.9 Hz), 79.81 (d, $^{3}J_{CP}$ = 2.7 Hz), 79.27 (d, $^{3}J_{CP}$ = 2.4 Hz), 70.38 (d, $^{1}J_{CP}$ = 168.3 Hz), 27.66, 27.20. **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.60, *14.013; **HRMS (ESI)** calculated for $C_{37}H_{34}NO_6P$ $[M^{+}H]^{+}$: 620.2202 found 619.2197

(3aR,8aR)-6-(hydroxy(pyridin-4-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205n')



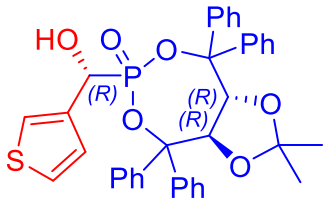
Protocol B: White solid; mass:161mg, 89% yield, dr: 91:9 (96:4 dr after crystallization); $[\alpha]^{D}_{20}$: -198.8 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.33 (d, *J* = 5.7 Hz, 2H), 7.64 – 7.51 (m, 5H), 7.48 – 7.31 (m, 10), 7.22 – 7.10 (m, 3H), 7.06 – 6.96 (m, 2H), 6.62 (d, *J* = 7.7 Hz, 2H), 5.33 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 0.70 (s, 3H), 0.47 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 149.31, 145.82, 144.06, 143.18, 139.33, 139.23, 130.13, 129.82, 128.68, 128.49, 128.43, 128.39, 128.32, 128.23, 127.93, 127.79, 127.30, 126.53, 92.25 (d, $^{3}J_{CP}$ = 14.8 Hz), 86.70 (d, $^{2}J_{CP}$ = 9.5 Hz), 79.13 (d, $^{3}J_{CP}$ = 2.3 Hz), 78.59 (d, $^{3}J_{CP}$ = 2.6 Hz), 69.70 (d, $^{1}J_{CP}$ = 165.9 Hz), 26.98, 26.52; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.69, *14.06; dr:88:12i (94:6); . **HRMS (ESI)** calculated for $C_{37}H_{34}NO_6P$ $[M^+H]^+$: 620.2202 found 620.2210

(3aR,8aR)-6-(hydroxy(thiophen-2-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205m)



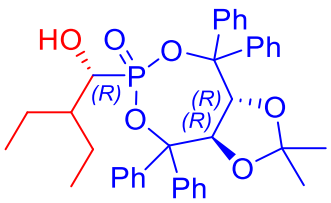
Protocol A: White solid mass:162mg, 88% yield; dr: 92:8 (97:3 after crystallization); $[\alpha]^{D}_{20}$: -233.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: δ 7.56 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.53 – 7.46 (m, 4H), 7.41 – 7.25 (m, 10), 7.22 – 7.13 (m, 3H), 6.93 – 6.83 (m, 3H), 6.61 (t, *J* = 3.4 Hz, 1H), 5.42 (d, *J* = 7.9 Hz, 1H), 5.30 (d, *J* = 9.2 Hz, 1H), 5.07 (d, *J* = 7.9 Hz, 1H), 3.42 (bs, H), 0.74 (s, 3H), 0.52 (s, 3H; **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.33, 143.29, 139.49, 139.34, 129.82, 128.65, 128.54, 128.43, 128.32, 127.88, 127.67, 127.56, 127.35, 127.23, 126.79, 126.67, 125.25, 125.19, 114.13, 91.29 (d, $^{2}J_{CP}$ = 14.1 Hz), 87.02 (d, $^{2}J_{CP}$ = 9.6 Hz), 79.37 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.22 (d, $^{3}J_{CP}$ = 2.4 Hz), 68.01 (d, $^{1}J_{CP}$ = 172.6 Hz), 26.98, 26.58; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 14.54, *12.69; **HRMS (ESI)** calculated for $C_{36}H_{33}O_6PSNa$ $[M^+Na]^+$: 647.1633 found 647.1627.

(3aR,8aR)-6-((R)-hydroxy(thiophen-3-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205n)



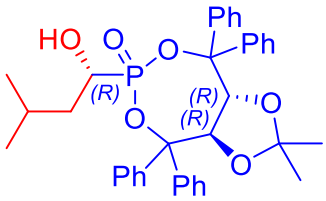
Protocol A: White solid mass: 168mg, 90% yield; dr: 95:5 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -213.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.50 – 7.15 (m, 17H), 7), 6.99 (t, *J* = 3.1 Hz, 1H), 6.89 – 6.79 (m, 2H), 5.39 (d, *J* = 7.9 Hz, 1H), 5.16 (dd, *J* = 8.7, 4.4 Hz, 1H), 5.01 (d, *J* = 7.9 Hz, 1H), 3.39 (bs, 1H), 0.73 (s, 3H), 0.49 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.49, 143.38, 139.57, 139.47, 137.08, 129.88, 129.13, 128.61, 128.52, 128.40, 128.32, 128.29, 127.85, 127.65, 127.32, 127.26, 126.62, 126.52, 125.32, 122.38, 114.06, 91.17 (d, $^{2}J_{CP}$ = 14.3 Hz), 86.69 (d, $^{2}J_{CP}$ = 9.7 Hz), 79.25 (d, $^{3}J_{CP}$ = 1.7 Hz), 79.23 (d, $^{3}J_{CP}$ = 1.4 Hz), 68.37 (d, $^{1}J_{CP}$ = 168.9 Hz), 27.01, 26.56; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 15.40; **HRMS (ESI)** calculated for $C_{36}H_{33}O_6PSNa$ $[M^+Na]^+$: 647.1633 found 647.1653.

(3aR,8aR)-6-((R)-2-ethyl-1-hydroxybutyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205o)



Protocol A: White solid, mass: 125mg, 76% yield; dr 74:26 (single diastereoisomer after crystallization); $[\alpha]^{D}_{20}$: -179.6 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ:7.59 – 7.50 (m, 6H), 7.43 – 7.20 (m, 14H), 5.50 (d, *J* = 7.9 Hz, 1H), 5.28 (d, *J* = 7.9 Hz, 1H), 3.94-3.88 (m, 1H), 1.84 – 1.74 (m, 1H), 1.59 – 1.19 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.70 (s, 3H), 0.56 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.83, 143.62, 140.07, 139.61, 129.82, 128.82, 128.70, 128.59, 128.32, 128.26, 127.80, 127.77, 127.33, 127.29, 127.06, 126.96, 114.24, 90.52 (d, $^{2}J_{CP}$ = 14.0 Hz), 86.97 (d, $^{2}J_{CP}$ = 10.2 Hz), 79.38 (d, $^{3}J_{CP}$ = 2.5 Hz), 78.93 (d, $^{3}J_{CP}$ = 2.7 Hz), 70.49 (d, $^{1}J_{CP}$ = 162.3 Hz), 26.94, 26.69, 21.86 (d, *J* = 10.2 Hz), 21.12 (d, *J* = 6.9 Hz), 11.31, 10.93; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 20.08; **HRMS (ESI)** calculated for $C_{37}H_{42}O_6P$ $[M^+H^+]^+$: 613.2672 found 613.262670.

(3aR,8aR)-6-((R)-1-hydroxy-3-methylbutyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (205p)

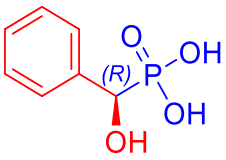


Protocol A: White solid, mass: 131mg, 70% yield; dr 69:31 (dr of 92:8 after column chromatography); $[\alpha]^{D}_{20}$: -182.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.57 – 7.50 (m, 6H), 7.42 – 7.24 (m, 14H), 5.50 (d, *J* = 7.9 Hz, 1H), 5.28 (d, *J* = 7.9 Hz, 1H), 3.91 (d, *J* = 5.3 Hz, 1H), 1.87 – 1.71 (m, 1H), 1.53 – 1.38 (m, 2H), 0.86 (d, *J* = 14.7 Hz, 3H), 0.80 (d, *J* = 14.8 Hz, 3H), 0.69 (s, 3H), 0.56 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 139.90, 139.81 , 139.58, 129.68, 128.64, 128.60, 128.32, 127.85, 127.80, 127.37, 127.30, 126.82, 90.44 (d, $^{2}J_{CP}$ = 13.9 Hz), 86.94 (d, $^{2}J_{CP}$ = 10.1 Hz), 79.28 (d, $^{3}J_{CP}$ = 2.5 Hz), 79.14 (d, $^{3}J_{CP}$ = 2.6 Hz), 67.10 (d, $^{1}J_{CP}$ = 166.0 Hz), *43.12, 39.75, 26.89, 26.69, *25.55, 24.30, 23.49, *22.52, 21.10; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 19.58, *19.38; **HRMS (ESI)** calculated for $C_{36}H_{39}O_6P$ $[M^+H]^+$: 599.2527 found 599.2525

2.0. Cleavage of the chiral auxiliary using bromotrimethylsilane (BrTMS)

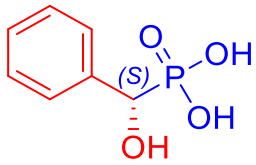
In CH_2Cl_2 (12 mL), pure α-hydroxyphosphonate (*R,R,R*)-**205a'** or (*S,S,S*)-**205aa'** (0.5 g, 0.81 mmol) was dissolved. Followed by the addition of bromotrimethylsilane (0.43 mL, 3.24 mmol) and resulting reaction mixture was stirred at room temperature for 24 h. After the evaporation of the solvent, MeOH (8 mL) was added to the resulting oily residue and stirred at room temperature for another 12 hours. The concentrated crude product was crystallized from chloroform to yield the (*R*)-(α-(hydroxy(phenyl)methyl)phosphonic acid **51a**. The same was followed by using the pure (*S,S,S*)-α-hydroxyphosphonate **205aa'** to give the (*S*)-(α-(hydroxy(phenyl)methyl) phosphonic acid **51aa**.

(R)-(hydroxy(phenyl)methyl)phosphonic acid (51a)



White solid, mass: 142mg, 93% yield; $[\alpha]^{D}_{20}$: -21.0 (*c* 1.0, H_2O); **^{1}H NMR** (400 MHz, D_2O) δ: 7.33-7.23 (m, 5H), 4.85 (d, *J* = 12.5 Hz, 1H); **^{13}C NMR** (101 MHz, D_2O) δ: 137.27, 128.56, 128.31, 128.28, 127.20, 127.14, 70.80 (d, $^{1}J_{CP}$ = 158.4 Hz); **^{31}P NMR** (162 MHz, D_2O) δ 20.37; **HRMS (ESI)** calculated for $C_7H_{10}O_4P$ $[M^+H]^+$: 189.0317 found 189.0315

(S)-(hydroxy(phenyl)methyl)phosphonic acid (51aa)

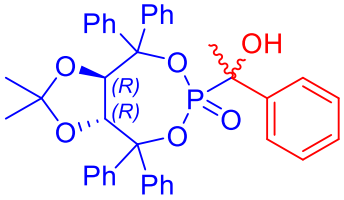


White solid, mass: 138mg, 91% yield; $[\alpha]^{D}_{20}$: +29.0 (*c* 1.0, H_2O); **HRMS (ESI)** calculated for $C_7H_{10}O_4P$ $[M^+H]^+$**:** 189.0317 found 189.0318

3.0. General procedure for the hydrophosphonylation of ketone with TADDOL-derived *H*-phosphonate

The ketone **207a** (1.0 equiv, 0.1 mmol) was added dropwise to a mixture of (*R*,*R*)-TADDOL-derived *H*-phosphonate **29** (1.0 equiv, 0.1 mmol) and quinine **III** (20 mol%) in dioxan (1.0 mL). The reaction mixture was stirred at room temperature for 70 h. Product **230a** was isolated by column chromatography using the eluent Hex:EtOAc in a ratio ranging from 1:5 to 1:3.

(3aR,8aR)-6-((R)-1-hydroxy-1-phenylethyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (230a)



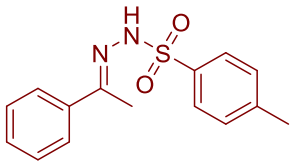
White solid, mass: 112mg, 62% yield; dr: 74:26 (76:24 dr after crystallization); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 – 7.44 (m, 3H)$^+$, 7.40-7.28 (m, 16)$^+$, 7.23 – 7.14 (m, 8H)$^+$, 7.05 (t, *J* = 7.8 Hz, 2H), 5.12 (bs, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 1.88 (s, 3H), 1.77 (s, 1H)*, 0.63 (s, 3H), 0.58 (s, 1H)*, 0.35 (s, 3H) 0.30 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 144.34, 144.01, 143.42, 140.53, 139.21, 135.16, 131. 04, 130, 83, 130.03, 128.81, 128.41, 128.32, 128, 20, 128.15, 128.11, 127.86, 127.71, 127.54, 127. 41, 127.29, 127. 18, 127.04, 126.83, 126.73, 126.47, 113.93, 113.46*, 90.65 (t, $^2J_{CP}$ = 14.5 Hz)$^+$, 87.45 (d, $^2J_{CP}$ = 9.5 Hz)*, 86.84 (d, $^2J_{CP}$ = 9.7 Hz), 79.34 (d, $^3J_{CP}$ = 2.5 Hz)*, 79.23 (d, $^3J_{CP}$ = 2.5 Hz), 79.14 (d, $^3J_{CP}$ = 2.4 Hz)*, 79.06 (d, $^3J_{CP}$ = 2.5 Hz), 71.43 (d, $^1J_{CP}$ = 160.1 Hz)*, 71.16 (d, $^1J_{CP}$ = 158.3 Hz), 27.74, 27.31* 26.33*, 26.07, 20.94, 20.77*; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 19.68, *18.91; **HRMS (ESI)** calculated for $C_{39}H_{37}O_6P$ $[M+H]^+$: 633.2406 found 633.2412.

Asymmetric hydrophosphonylation of hydrazones

1.0. Procedure for the synthesis of N-tosylhydrazones

Following the literature procedure[300], 5.0 mmol solution of *p*-toluenesulfonyl hydrazide ($TsNHNH_2$) in methanol (5.0 mL) was stirred and heated to 60°C until the $TsNHNH_2$ was completely dissolved, followed by the dropwise addition of the corresponding ketone (1.0 equiv, 5.0 mmol) to the solution. The resulting mixture was heated for 1.5 hours and then cooled to 0°C. The desired product was isolated by filtration, washed with petroleum ether, and then evaporated under vacuum to give the final pure product **246**.

(E)-4-methyl-N'-(1-phenylethylidene)benzenesulfonohydrazide (246)



White solid, 1110mg, 77% yield, **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.2 Hz, 2H), 7.68 – 7.55 (m, 2H), 7.38 – 7.23 (m, 5H), 2.40 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 152.58, 144.28, 137.30, 135.45, 129.97, 129.70, 128.66, 128.42, 128.23, 128.01, 126.56, 126.36, 21.70, 13.44.

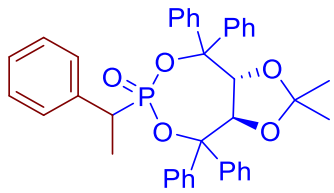
2.0. General procedure for the coupling of TADDOL-derived *H*-phosphonate with N-tosylhydrazone

TADDOL-derived *H*-phosphonate (1.0 equiv, 0.1 mmol), *N*-tosylhydrazone (1.0 equiv, 0.1 mmol), CuI (0.2 equiv), and Cs_2CO_3 (1.5 equiv) were added into an oven-dried vial and backfilled with nitrogen three times. Then 1 mL of DME was added to the vial, and the mixture was heated continuously with stirring at 80°C for 2 hours. The reaction mixture was then allowed to cool to room temperature and concentrated to give the crude product, which was purified by column chromatography using Hex:EtOAc (6:1 to 2:1, v/v) as the eluent.

3.0. Preparation of alkylphosphonate 247 from TADDOL derived *H*-phosphonates and benzophenone in one-pot

In a vial, $TsNHNH_2$ (1.10 mmol) was dissolved in DME (2.0 mL) by stirring and heating at 60°C. Ketone (1.10 mmol) was then added dropwise to the mixture and refluxed for 1 hour, followed by the addition of CuI (0.2 equiv), TADDOL-derived H-phosphonate (*R*,*R*)-**29** (1 equiv, 0.1 mmol) and Cs_2CO_3 (1.5 equiv) to the vial. The resulting mixture was then heated at 80°C for 2 hours with stirring. Upon completion of the reaction, the mixture was cooled to room temperature and concentrated to give the crude product 247 with 100% conversion and dr of 43:57. Note: I made attempt to purify and enrich the product by column chromatography using hex:EtOAc eluent gradient (from 6:1 to 2:1, v/v).

(3aR,8aR)-2,2-dimethyl-4,4,8,8-tetraphenyl-6-(1-phenylethyl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (247)

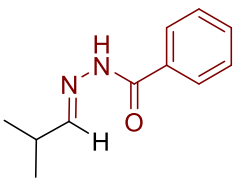


Yellowish solid, mass: 53mg; 86% yield; dr: 42:58 (40:60 dr after column chromatography) **^{1}H NMR** (400 MHz,) δ 7.68 – 7.57 (m, 4H)$^{+}$, 7.47 – 7.09 (m, 43H), 6.80 – 6.73 (m, 2H)$^{+}$, 5.50 (d, *J* = 8.0 Hz, 1H), 5.44 (d, *J* = 7.9 Hz, 1H)*, 4.95 (d, *J* = 8.1 Hz, 1H), 4.92 (d, *J* = 8.0 Hz, 1H)*, 3.47 – 3.27 (m, 2H)$^{+}$, 1.75 (d, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 7.4 Hz, 2H)*, 0.85 (s, 3H), 0.76 (s, 3H)*, 0.47 (s, 3H)*, 0.44 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 145.05 (d, *J* = 2.4 Hz), 144.97 (d, *J* = 1.9 Hz), 144.53, 144.02, 143.95, 140.14, 140.05, 139.97, 139.93, 138.16 (d, *J* = 8.7 Hz), 137.67 (d, *J* = 8.3 Hz), 134.00, 133.22, 130.21, 129.95, 129.52, 129.35, 129.01, 128.95, 128.79, 128.67, 128.44, 128.34, 128.25, 128.16, 128.10, 128.02, 127.84, 127.69, 127.64, 127.49, 127.21, 127.17, 127.12, 126.96, 126.70, 126.48, 113.56, 113.35*, 90.55 (d, $^{2}J_{CP}$ = 14.1 Hz)*, 89.79 (d, $^{2}J_{CP}$ = 13.2 Hz), 85.89 (d, $^{2}J_{CP}$ = 8.5 Hz)*, 85.87 (d, $^{2}J_{CP}$ = 8.4 Hz), 79.98 (d, $^{3}J_{CP}$ = 2.6 Hz)*, 79.27 (d, $^{3}J_{CP}$ = 2.6 Hz), 79.16 (d, $^{3}J_{CP}$ = 2.6 Hz), 78.87 (d, $^{3}J_{CP}$ = 2.8 Hz)*, 39.87 (d, $^{1}J_{CP}$ = 145.5 Hz)*, 39.36 (d, *J* = 143.8 Hz), 27.13, 27.09*, 26.53*, 26.33, 15.12 (d, $^{2}J_{CP}$ = 5.3 Hz), 14.81 (d, $^{2}J_{CP}$ = 4.7 Hz)*; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 24.22, 23.25*; **HRMS (ESI)** calculated for $C_{39}H_{37}O_5P$ $[M^{+}H]^{+}$: 617.2457 found 617.2468.

4.0. General procedure for the synthesis of N-benzoylhydrazones

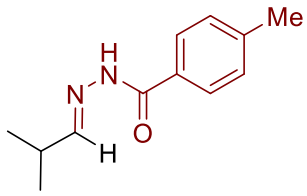
According to literature[299], Na_2SO_4 and the corresponding aldehyde (1.0 equiv, 3.0 mmol) were added to the corresponding solution of benzohydrazide (1.2 equiv, 3.6 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 1 day until complete consumption of the starting material. The mixture was then filtered and concentrated to give the corresponding hydrazones **243a-k**.

(E)-*N'*-(2-methylpropylidene)benzohydrazide (243a)



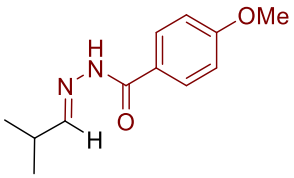
White solid; 315mg, 46% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.35 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 2H), 7.65 (d, *J* = 5.2 Hz, 1H), 7.58 – 7.37 (m, 3H), 2.65 – 2.22 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (101 MHz, MHz, DMSO-d_6) δ: 166.41, 163.44, 157.24, 134.19, 132.01, 128.90, 128.01, 127.47, 31.61, 20.17; **HRMS (ESI)** calculated for $C_{11}H_{14}N_2ONa$ $[M^{+}Na]^{+}$: 213.1004 found 213.0999.

(E)-4-methyl-*N'*-(2-methylpropylidene)benzohydrazide (243b)



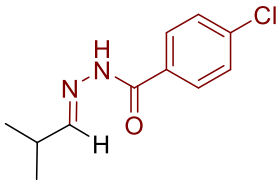
White solid; 375mg, 51% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 2H), 2.57 – 2.48 (m, 1H), 2.35 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (101 MHz, MHz, DMSO-d_6) δ: 167.97, 161.70, 146.75, 136.05, 134.18, 132.77, 36.36, 26.28, 24.97; **HRMS (ESI)** calculated for $C_{12}H_{16}N_2O$ $[M^+H]^+$: 205.1341 found 205.1334.

(E)-4-methoxy-*N'*-(2-methylpropylidene)benzohydrazide (243c)



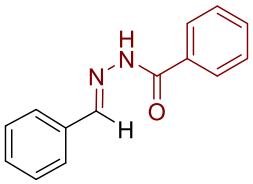
White solid; 547mg, 69% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.27 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 5.1 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.52-2.48 (m, 1H), 2.47, 2.31 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (101 MHz, MHz, DMSO-d_6) δ: 163.23, 156.92, 141.98, 141.42, 131.28, 129.42, 128.02, 127.51, 31.60, 21.51, 20.20; **HRMS (ESI)** calculated for $C_{12}H_{16}N_2O_2$ $[M^+H]^+$: 221.1290 found 221.1303.

(E)-4-chloro-*N'*-(2-methylpropylidene)benzohydrazide (243d)



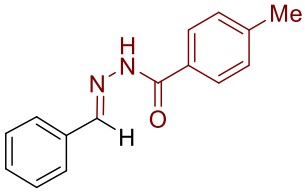
White solid; 550mg, 68% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.44 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 5.2 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 2.56 – 2.50 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (101 MHz, MHz, DMSO-d_6) δ: 165.30, 162.33, 157.62, 136.85, 132.86, 129.96, 129.38, 129.00, 31.62, 20.13; **HRMS (ESI)** calculated for $C_{11}H_{13}ClN_2O$ $[M^+H]^+$: 225.0795 found 225.0784.

(E)-*N'*-benzylidenebenzohydrazide (243e)



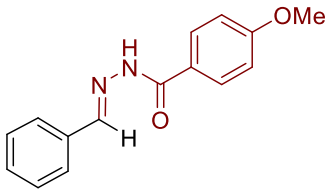
White solid; 420mg, 52% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.84 (s, 1H), 8.44 (s, 1H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.70 (d, *J* = 6.2 Hz, 2H), 7.58-1.41(m, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 163.69, 148.33, 134.87, 133.97, 132.30, 130.62, 129.38, 129.02, 128.16, 127.63; **HRMS (ESI)** calculated for $C_{14}H_{12}N_2O$ $[M^+H]^+$: 225.1028 found 225.1023.

(E)-*N'*-benzylidene-4-methylbenzohydrazide (243f)



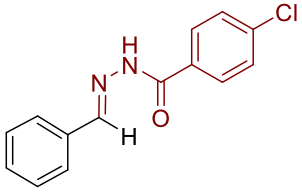
White solid; 498mg, 58% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.76 (s, 1H), 8.45 (s, 1H), 7.76 (d, *J* = 43.1 Hz, 4H), 7.62 – 7.19 (m, 5H), 2.37 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 163.45, 148.03, 142.36, 134.96, 131.08, 130.5, 129.55, 129.38, 128.18, 127.58, 21.57; **HRMS (ESI)** calculated for $C_{15}H_{14}N_2O$ $[M^+H]^+$: 239.1184 found 239.1174.

(E)-N'-benzylidene-4-methoxybenzohydrazide (243g)



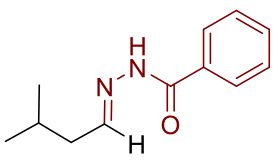
White solid; 650mg, 71% yield; **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.74 (s, 1H), 8.45 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 6.2 Hz, 2H), 7.62 – 7.19 (m, 5H), 3.62 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-D_6) δ: 163.76, 148.20, 144.26, 135.89, 132.11, 130.72, 129.87, 129.21, 128.78, 128.09, 51.04; **HRMS (ESI)** calculated for $C_{15}H_{14}N_2O_2$ $[M^+H]^+$: 255.1134 found 255.1144.

(E)-N'-benzylidene-4-chlorobenzohydrazide (243h)



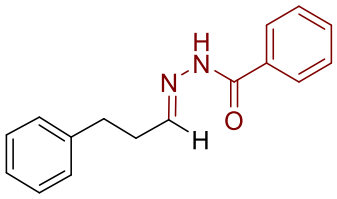
White solid; 708mg, 76% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.39 (s, 1H), 8.63 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.72, (d, *J* = 8.5 Hz, 2H), 7.52 – 7.27 (m, 5H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 163.25, 147.19, 143.13, 135.26, 133.42, 130.46, 129.98, 129.21, 128.88, 128.00, 127.65; **HRMS (ESI)** calculated for $C_{14}H_{11}ClN_2O$ $[M^+H]^+$: 259.0638 found 259.0647.

(E)-*N'*-(3-methylbutylidene)benzohydrazide (243i)



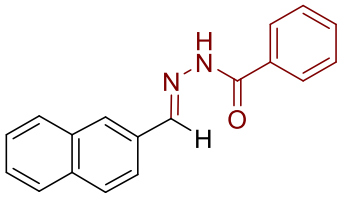
White solid; 515mg, 70% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.39 (s, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.71 (t, *J* = 5.8 Hz, 1H), 7.56 – 7.39 (m, 3H), 2.11 (t, *J* = 6.3 Hz, 2H), 1.86 – 1.72 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 63.28, 152.21 , 134.11, 132.04, 128.90, 128.01, 41.33, 26.82, 22.81; **HRMS (ESI)** calculated for $C_{12}H_{16}N_2O$ $[M^+H]^+$: 205.1341 found 205.1334.

(E)-*N'*-(3-phenylpropylidene)benzohydrazide (243j)



White solid; 554mg, 61% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 7.82 (d, *J* = 7.3 Hz, 2H), 7.75 (t, *J* = 5.0 Hz, 1H), 7.55-7.45 (m, 3H), 7.32 – 7.12 (m), 5H, 2.81 (t, *J* = 7.5 Hz, 2H), 2.59-2.51 (m, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 163.34, 151.89, 141.49, 134.08, 132.07, 128.95, 128.05, 126.52, 34.31, 32.56; **HRMS (ESI)** calculated for $C_{16}H_{16}N_2O$ $[M^+H]^+$: 253.1341 found 253.1340.

(E)-*N'*-(naphthalen-2-ylmethylene)benzohydrazide (243k)

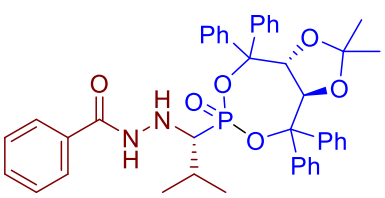


White solid; 721mg, 73% yield, **^{1}H NMR** (400 MHz, DMSO-d_6) δ:11.93 (s, 1H), 8.59 (s, 1H), 8.12 (s, 1H), 8.02 – 7.84 (m, 6H), 7.61 – 7.36 (m, 5H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 163.76, 148.25, 134.29, 134.01, 133.41, 132.64, 132.32, 129.28, 129.05, 128.88, 128.32, 128.21, 127.67, 127.30, 123.23; **HRMS (ESI)** calculated for $C_{18}H_{14}N_2O$ $[M^+H]^+$: 275.1184 found 275.1184.

5.0. General procedure for the diastereoselective hydrophosphonylation of benzohydrazide with TADDOL-derived *H*-phosphonate

The benzohydrazide (1.0 quiv, 0.1 mmol) and cinchonine (0.5 equiv) were dissolved in toluene (1.5 mL). To this solution, TADDOL-derived *H*-phosphonate (1.0 equiv, 0.1 mmol) was added and stirred at 60°C for 50 hours. The resulting crude product was isolated directly by column chromatography on silica gel (using a hexane/EtOAc eluent in ratios ranging from 4:1 to 2:1) to afford the product **244a-k**.

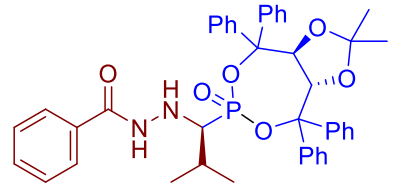
N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)benzohydrazide (244a)



Yellowish oil; 60mg, 85% yield, dr 87:13 (single diastereomer after column chromatography); $[\alpha]^{D}_{20}$: -129.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 6.3 Hz, 1H), 7.67 – 7.44 (m, 8H), 7.40 – 7.17 (m, 17H), 5.65 (d, *J* = 8.0 Hz, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 5.04 (d, *J* = 28.3 Hz, 1H), 3.26-3.22 (m, 1H), 2.37 – 2.25 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 3H), 0.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 165.96, 144.93, 143.93,

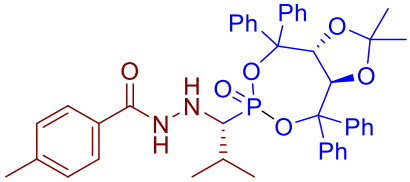
139.67, 132.49, 131.79, 129.83, 128.72 , 128.66, 128.36, 128.35, 128.17, 127.80, 127.35, 127.19, 127.04, 126.75, 113.82, 91.10 (d, $^{2}J_{CP}$ = 13.8 Hz), 86.95 (d, $^{2}J_{CP}$ = 8.8 Hz), 80.16 (d, $^{3}J_{CP}$ = 2.8 Hz), 78.81 (d, $^{3}J_{CP}$ = 2.8 Hz), 66.06 (d, $^{1}J_{CP}$ = 165.8 Hz), 28.58, 26.90, 26.57, 20.97, 19.01; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.89; **HRMS (ESI)** calculated for $C_{42}H_{43}N_2O_6P$ $[M^+H]^+$: 703.2937 found 703.2927.

N'-((S)-1-((3aS,8aS)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo[4,5-e] [1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)benzohydrazide (244a')



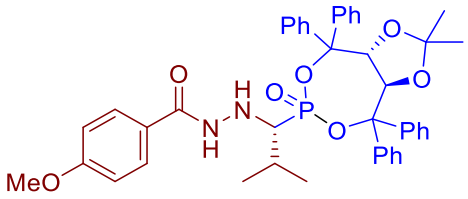
Yellowish oil; 55mg, 80% yield, dr 80:20 (>95:5 dr after column chromatography);); $[\alpha]^{D}_{20}$: +142.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** and **^{13}C NMR** spectra similar to that of **244a**; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.94, *20.97; **HRMS (ESI)** calculated for $C_{42}H_{43}N_2O_6P$ $[M^+H]^+$: 703.2937 found 703.2931.

N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)-4-methylbenzohydrazide (244b)



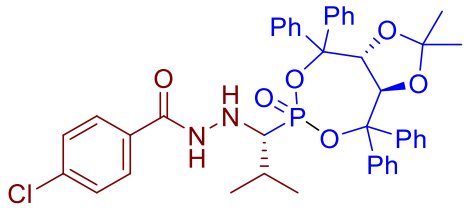
White solid; 57mg, 80% yield, dr 83:17 (single diastereomer after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 6.3 Hz, 1H), 7.65 – 7.49 (m, 8H), 7.41 – 7.17 (m, 16H), 5.65 (d, *J* = 8.1 Hz, 1H), 5.18 (d, *J* = 9.2 Hz, 1H), 5.01 (d, *J* = 29.1 Hz, 1H), 3.25-3.21 (m, 1H), 2.42 (s, 3H) 2.35 – 2.26 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 3H), 0.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 164.47, 144.43, 144, 15 143.55, 137.67, 130.57, 129.45, 124.01 128.56, 128.34, 128.15, 128.05, 128.02, 127.87, 127.55, 127.51, 127.03, 127.02, 126.83, 126.38, 113.54, 90.86 (d, *J* = 14.4 Hz), 86.70 (d, *J* = 8.7 Hz), 79.77 (d, *J* = 2.8 Hz), 78.48 (d, *J* = 2.6 Hz), 65.65 (d, *J* = 165.2 Hz), 28.16, 26.56, 26.21, 21.46 20.66, 18.69; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.16; **HRMS (ESI)** calculated for $C_{43}H_{45}N_2O_6P$ $[M^+H]^+$: 717.3026.2937 found 717.3012.

N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)-4-methoxybenzohydrazide (244c)



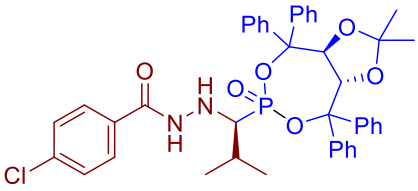
White solid; 61mg, 83% yield, dr: 86:14 (single diastereomer after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.31 (d, *J* = 6.3 Hz, 1H), 7.69 – 7.53 (m, 8H), 7.43 – 7.21 (m, 16H), 5.66 (d, *J* = 8.0 Hz, 1H), 5.20 (d, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 29.4 Hz, 1H), 3.90 (s, 3H), 3.26-3.323 (m, 1H), 2.37 – 2.21 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 3H), 0.57 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 165.01, 163.56, 144.97, 144.09, 138.21, 131.11, 129.99, 129.10, 128.88, 128.69, 128.59, 128.56, 128.41, 128.09, 128.05, 127.57, 127.56, 127.37, 126.92, 114.08, 91.40 (d, $^{2}J_{CP}$ = 14.3 Hz), 87.24 (d, $^{2}J_{CP}$ = 9.5 Hz), 80.31 (d, $^{3}J_{CP}$ = 2.6 Hz), 79.02 (d, $^{3}J_{CP}$ = 2.9 Hz), 66.19 (d, *J* = 165.1 Hz), 56.02, 28.70, 27.10, 26.75, 21.20, 19.23; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.11; **HRMS (ESI)** calculated for $C_{43}H_{45}N_2O_7P$ $[M^+H]^+$: 733.2937 found 733.2932.

4-chloro-N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro[1,3] dioxolo- [4,5-e][1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)benzohydrazide (244d)



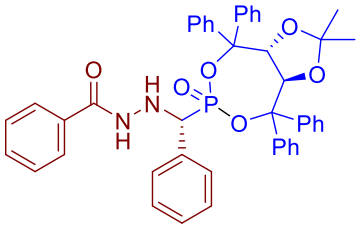
colourless oil; 63mg, 85% yield, dr 84:16 (single diastereomer after column chromatography); $[\alpha]^{D}_{20}$: -169.0 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 6.4 Hz, 1H), 7.65 – 7.49 (m, 8H), 7.39 – 7.19 (m, 16H), 5.65 (d, *J* = 8.0 Hz, 1H), 5.22 (d, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 30.7 Hz, 1H), 3.25-3.322 (m, 1H), 2.36 – 2.23 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 3H), 0.58 (s, H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 164.82, 144.85, 143.90, 139.72, 139.61, 138.02, 130.92, 129.80, 128.91, 128.69, 128.50, 128.40, 128.37, 128.22, 127.90, 127.86, 127.37, 127.18, 126.73, 113.89, 91.21 (d, $^{2}J_{CP}$ = 13.6 Hz), 87.05 (d, $^{2}J_{CP}$ = 8.7 Hz), 80.13 (d, $^{3}J_{CP}$ = 2.9 Hz), 78.83 (d, $^{3}J_{CP}$ = 2.6 Hz), 66.00 (d, $^{1}J_{CP}$ = 165.8 Hz), 28.52, 26.91, 26.56, 21.01, 19.04; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.18; **HRMS (ESI)** calculated for $C_{42}H_{42}ClN_2O_6P$ $[M^+H]^+$: 737.2547 found 737.2538.

4-chloro-N'-((S)-1-((3aS,8aS)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-2-methylpropyl)benzohydrazide (244d')



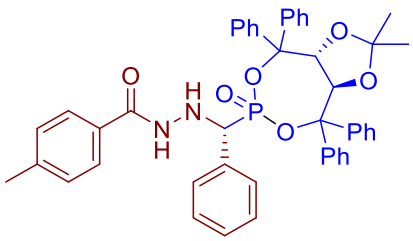
colourless oil; 66mg, 89% yield, dr 83:17 (single diastereomer after column chromatography); $[\alpha]^{D}_{20}$: +151.2 (*c* 1.0, CH_2Cl_2); **HRMS (ESI)** calculated for $C_{42}H_{42}ClN_2O_6P$ $[M^+H]^+$: 737.2547 found 737.2535.

N'-(((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)(phenyl)methyl)benzohydrazide 244e



White solid; 44mg, 60% yield, dr 87:13 (90:10 after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 5.4 Hz, 1H),7.65 – 7.54 (m, 10H), 7.42 – 7.06 (m, 18H), 6.65 (d, *J* = 7.4 Hz, 2H), 5.39 (d, *J* = 7.9 Hz, 1H), 5.11 – 5.04 (m, 1H), 4.84 (d, *J* = 7.9 Hz, 1H), 4.54 (d, *J* = 14.7 Hz, 1H), 0.80 (s, 3H), 0.49 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 164.99, 150.30, 148.16, 143.71, 139.40, 137.97, 133.79, 130.87, 130.46, 129.91, 129.14, 128.91, 128.72, 128.63, 128.36, 128.33, 128.20, 127.75, 127.33, 127.19, 126.96, 126.56, 125.40, 113.93, 91.42 (d, $^2J_{CP}$ = 13.5 Hz), 86.78 (d, $^2J_{CP}$ = 8.6 Hz), 79.36 (d, $^3J_{CP}$ = 2.2 Hz), 79.20 (d, $^3J_{CP}$ = 2.5 Hz), 64.34 (d, $^1J_{CP}$ = 171.2 Hz), 27.11, 26.31; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 20.23 *19.46; **HRMS (ESI)** calculated for $C_{45}H_{41}N_2O_6P$ $[M^+H]^+$: 737.2781 found 751.2782.

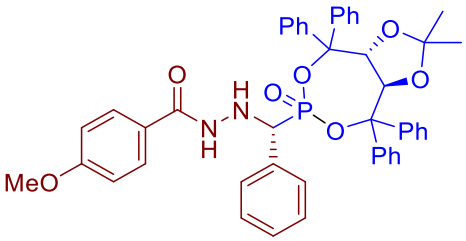
N'-(((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)(phenyl)methyl)-4-methylbenzohydrazide (244f)



White solid; 61mg, 81% yield, dr 88:12 (94:6 dr after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.42 (d, *J* = 4.7 Hz, 1H),7.69 – 7.58 (m, 10H), 7.48 – 7.23 (m, 17H), 6.74 (d, *J* = 7.3 Hz, 2H), 5.39 (d, *J* = 7.7 Hz, 1H), 4.86 (d, *J* = 7.9 Hz, 1H), 4.50 (d, *J* = 14.7 Hz, 1H), 2.39 (s, 3H), 0.79 (s, 3H), 0.50 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 166.01, 151.34, 148.94, 145.70, 141.42, 138.89, 134.66, 131.47, 130.93, 130.15, 129.93, 129.73, 129.64, 129.38, 129.22, 128.76, 128.35, 128.20, 127.94, 127.57, 126.42, 114.98, 92.48 (d, $^2J_{CP}$ = 13.3 Hz), 85.99 (d, $^2J_{CP}$ = 8.5 Hz), 81.38 (d, $^3J_{CP}$ = 2.2 Hz), 81.23 (d, $^3J_{CP}$ = 2.3 Hz), 62.73 (d, $^1J_{CP}$ = 165.02 Hz), 27.44.13, 25.44, 21.59.**^{31}P NMR** (162

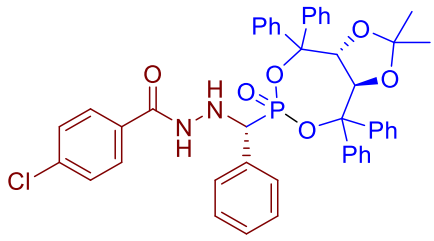
MHz, $CDCl_3$) δ: 21.19, *20.26; **HRMS (ESI)** calculated for $C_{46}H_{43}N_2O_6P$ $[M^+H]^+$: 751.2937 found 751.2944.

N'-(((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)(phenyl)methyl)-4-methoxybenzohydrazide (244g)



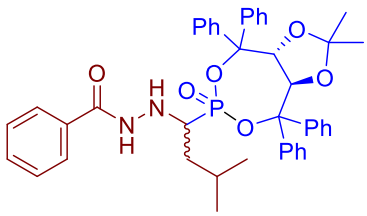
White solid; 39mg, 51% yield, dr 95:5 (single diastereomer after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.77 (d, *J* = 4.4 Hz, 1H),7.70 – 7.68 (m, 9H), 7.56 – 7.32 (m, 18H), 6.88 (d, *J* = 7.1 Hz, 2H), 5.42 (d, *J* = 7.9 Hz, 1H), 4.87 (d, *J* = 7.9 Hz, 1H), 4.53 (d, *J* = 13.4 Hz, 1H), 3.94 (s, 3H), 0.78 (s, 3H), 0.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 166.10, 152.31, 145.75, 141.66, 138.81, 137.99 134.71, 131.21, 130.89, 130.05, 129.91, 129.64, 129.22, 129.04, 128.98, 128.72, 128.46, 128.22, 127.83, 127.57, 127.42, 127.17, 114.98, 91.43 (d, $^2J_{CP}$ = 13.2 Hz), 87.61 (d, $^2J_{CP}$ = 8.9 Hz), 81.51 (d, $^3J_{CP}$ = 2.2 Hz), 81.34 (d, $^3J_{CP}$ = 2.2 Hz), 68.30 (d, $^1J_{CP}$ = 169.4 Hz), 67.08, 28.13, 27.32; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.02; **HRMS (ESI)** calculated for $C_{46}H_{43}N_2O_7P$ $[M^+H]^+$: 767.2886 found 767.2891.

4-chloro-N'-(((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)(phenyl)methyl)benzohydrazide (244h)



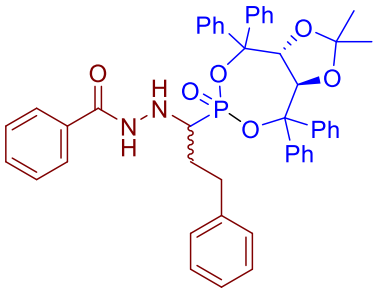
White solid; 46mg, 59% yield, dr 90:10 (single diastereomer after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 5.8 Hz, 1H),7.69 – 7.60 (m, 10H), 7.51 – 7.33 (m, 17H), 6.48 (d, *J* = 7.4 Hz, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 5.21 – 5.16 (m, 1H), 4.85 (d, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 13.7 Hz, 1H), 0.77 (s, 3H), 0.51 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 164.58, 149.89, 147.74, 143.29, 138.99, 137.55, 133.38, 130.46, 130.04, 129.51, 128.72, 128.50, 128.30, 128.21, 127.97, 127.91, 127.79, 127.33, 127.12, 126.92, 126.55, 126.14, 113.53, 91.01 (d, $^2J_{CP}$ = 13.1 Hz), 86.37 (d, $^2J_{CP}$ = 8.6 Hz), 78.94 (d, $^3J_{CP}$ = 2.2 Hz), 78.79 (d, $^3J_{CP}$ = 2.3 Hz), 66.92 (d, $^1J_{CP}$ = 168.23 Hz), 26.79, 25.46; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.92; **HRMS (ESI)** calculated for $C_{45}H_{40}ClN_2O_6P$ $[M^+H]^+$: 771.2391 found 771.2385.

N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-3-methylbutyl)benzohydrazide (244i)



White solid; 62mg, 86% yield, dr 30:70 (18:82 dr after column chromatography); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 6.1 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.42 (m, 8H)$^{+}$, 7.40 – 7.11 (m, 21)$^{+}$, 5.55 (d, *J* = 7.6 Hz), 5.26 (d, *J* = 7.9 Hz, 1H) 5.18 (d, *J* = 7.9 Hz, 1H)*, 5.05 (d, *J* = 17.4 Hz), 3.36 – 3.22 (m, 2H)$^{+}$, 2.12-1.94 (m, 4H)$^{+}$, 0.96 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.75 (s, 4H)$^{+}$, 0.59 (s, 3H) 0.54 (s, 1H)*; **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 166.37*, 165.88, 150.28, 144.39, 143.87, 137.97, 132.53, 131.78, 130.03, 129.79, 129.14, 128.66, 128.54, 128.42, 128.32, 127.90, 127.48, 127.36, 127.28, 127.13, 126.60, 125.40, 114.23*, 114.09, 91.22 (d, $^{2}J_{CP}$ = 13.7 Hz), 86.76 (d, $^{2}J_{CP}$ = 9.0 Hz)*, 86.49 (d, $^{2}J_{CP}$ = 8.9 Hz), 79.72 (d, $^{3}J_{CP}$ = 2.8 Hz), 79.59 (d, $^{3}J_{CP}$ = 2.7 Hz)*, 79.21 (d, $^{3}J_{CP}$ = 2.4 Hz), 79.07 (d, $^{3}J_{CP}$ = 2.5 Hz)*, 58.62 (d, $^{1}J_{CP}$ = 169.7 Hz)*, 58.50 (d, $^{1}J_{CP}$ = 174.0 Hz), 28.07, 26.93, 26.65, 23. 52*, 23.44, 22.58, 22,54* 21.57; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.19*,20.88; **HRMS (ESI)** calculated for $C_{43}H_{45}N_2O_6P$ [$M^{+}H^{+}$]: 717.3093 found 717.3092.

N'-(1-((3aR,8aR)-2,2-dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-3-phenylpropyl)benzohydrazide (244j)



White solid; 60mg, 79% yield, dr 35:65 (29:71 dr after column chromatography); 8.76 (d, *J* = 4.2 Hz, 1H), 8.1 (d, *J* = 8.4 Hz, 1H)*, 7.95 (d, *J* = 8.2 Hz, 2H)$^{+}$, 7.79 (d, *J* = 7.3 Hz, 2H), 7.68-7.39 (m, 32H)$^{+}$, 5.60 (d, *J* = 7.9 Hz 1H)*, 5.56 (d, *J* = 7.9 Hz, 1H), 5.28 (d, *J* = 7.9 Hz, 1H)*, 5.22 (d, *J* = 7.9 Hz, 1H), 3.67 – 3.55 (m, 1H)$^{+}$, 3.39-3.25 (m, 3H)$^{+}$, 3.16 – 3.07 (m, 3H)$^{+}$, 0.76 (s, 1H)*, 0.73 (s, 3H), 0.60 (s, 1H)*, 0.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 166.56, 166.01*, 150.26, 144.34, 143.76, 140.55, 137.97, 129.96, 129.71, 129.14, 128.70, 128.66, 128.55, 128.43, 128.33, 127.90, 127.50, 127.37, 127.17, 127.13, 12 6.62, 126.20, 126.14, 125.41, 122.97, 118.74, 114.26, 114.13*,91.29 (d, $^{2}J_{CP}$ = 11.9 Hz)*, 90.89 (d, $^{2}J_{CP}$ = 13.3 Hz), 87.72 (d, $^{2}J_{CP}$ = 9.1 Hz)*, 87.51 (d, $^{2}J_{CP}$ = 8.9 Hz), 79.78 (d, $^{3}J_{CP}$ = 2.1 Hz), 79.58 (d, $^{3}J_{CP}$ = 2.4 Hz)*, 79.29 (d, $^{3}J_{CP}$ = 2.4 Hz), 79.09 (d, $^{3}J_{CP}$ = 2.4 Hz)*, 59.52 (d, $^{1}J_{CP}$ = 169.7 Hz)*, 58.96 (d, $^{1}J_{CP}$ = 170.4 Hz), 32.27*, 32.13, 29.75*, 29.52, 27.96*, 27.89, 26.65, 26.59*; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 21.32*, 20.98; **HRMS (ESI)** calculated for $C_{47}H_{45}N_2O_6P$ [$M^{+}H$]$^{+}$: 765.3093 found 765.310.

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