NEW METHODOLOGIES FOR THE SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS

by

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LIST OF ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonate
AHP	Anilinium hypophosphite
AIBN	2,2′-Azobis(2-methylpropionitrile)
Alk	Alkyl
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
BDPP	2,4-Bis(diphenylphosphino)pentane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
BTSP	Bis(trimethylsiloxy)phosphine
Bu	Butyl
BuLi	Butyllithium
Bz	Benzoyl
b.p.	Boiling point
cat.	Catalytic
Cbz	Benzyloxycarbonyl

cod	Cylooctadienyl
conc.	Concentrated
CNS	Central nervous system
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxidel
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
eq	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
GABA	γ-Aminobutyric acid
GC	Gas chromatography
Hex	Hexyl
HMDS	Hexamethyldisilazane
HPLC	High Performance Liquid Chromatography
i-Pr	Isopropyl
L	Ligand

LDA	Lithium diisopropylamide
LAH	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
m.p.	Melting point
Me	Methyl
MS	Mass spectroscopy
MW	Microwaves
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
Oct	Octyl
PCC	Pyridinium chlorochromate
Pent	Pentyl
Ph	Phenyl
Piv	Pivaloyl
Pr	Propyl
Pyr	Pyridine
rt	Room temperature
TBDMS	tert-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

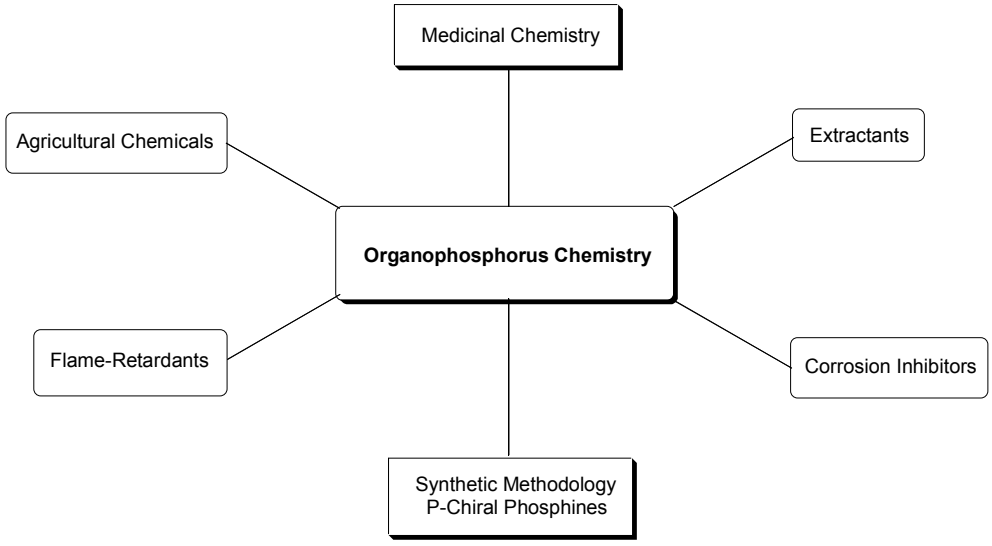
Ts	Tosylate
xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

Chapter I: Background: Organophosphorus Chemistry.

1.1 Introduction

Phosphorus is a ubiquitous element and its chemistry is of great importance. Until about 60 years ago, almost the entire field of phosphorus chemistry was dominated by inorganic phosphorus chemistry and the extent of known organophosphorus compounds was very limited.[1] However, since that time, organophosphorus chemistry has become a very broad and exciting field, with many possibilities for research and applications development (Figure 1.1). Organophosphorus compounds found their use in synthetic organic chemistry (olefination reagents, and ligands for catalysis) and medicinal chemistry (anticancer, antiviral, antibacterial agents, treatment of bone diseases).[2] They are also extensively employed as agricultural chemicals (insecticides, herbicides, and plant growth regulators), flame-retardants for fabrics and plastics, corrosion inhibitors, additives in the petroleum products field, and selective extractants of metal salts from ores, especially those from uranium.[2]

Figure 1.1 Applications of organophosphorus compounds



The use of the terms "inorganic phosphorus compound" and "organophosphorus compound" is traditional and very deep-rooted. Although no longer strictly desirable, because phosphorus chemistry now stands in its own right, these convenient terms still exist. Phosphorus chemistry can be defined as any transformation or structure involving phosphorus. Eight major classes of phosphorus compounds can be recognized:[1]

(1) Oxyphosphorus compounds, which contain covalent P-O linkages.

(2) Carbophosphorus (organophosphorus) compounds which contain P-C linkages.

(3) Azaphosphorus compounds which contain P-N linkages.

(4) Metallophosphorus compounds which contain P-metal linkages.

(5) Boraphosphorus compounds which contain P-B linkages.

(6) Silaphosphorus compounds which contain P-Si linkages.

(7) Thiaphosphorus compounds which contain P-S linkages.

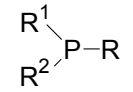
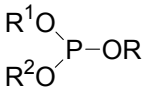
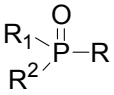
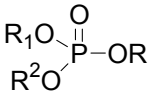
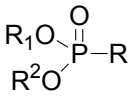
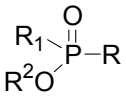
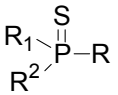
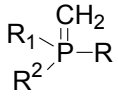
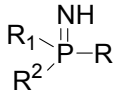
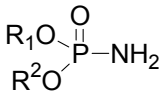
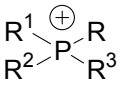
(8) Halophosphorus compounds which contain P-Halogen linkages.

Some compounds inevitably belong simultaneously to more than one of the above groups (1)-(8) and their classification is somewhat arbitrary.

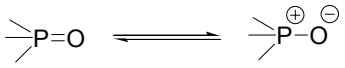
Organophosphorus compounds include any molecules containing direct or indirect phosphorus-carbon linkage (Figure 1.2, R = organic group). The most common organophosphorus compounds are trivalent (pyramidal) $\lambda^3\sigma^3$ and pentavalent (tetrahedral) $\lambda^5\sigma^4$ compounds, where the coordination number is designated by the σ with a superscript and λ is used to describe the total number of bonds including "π-bonds" and thus represents the valence of phosphorus.[2b] For example: pyramidal $\lambda^3\sigma^3$ compounds include phosphines (**1a**) and phosphites (1**b**) and tetrahedral $\lambda^5\sigma^4$ compounds include phosphine oxides (**1c**), phosphates (**1d**), phosphonates (**1e**), phosphinates (**1f**), phosphine

sulphides, (**1g**), alkylene phosphoranes (**1h**), iminophosphines (**1i**), amidophosphonates (**1j**). Another important group of organophosphorus compounds is phosphonium ions $\lambda^4\sigma^4$ (**1k**), which is derived from the tetrahedral PH_4^+ phosphonium cation.

Figure 1.2 Examples and nomenclature of some major organophosphorus compounds**.**

	**1a**	Phosphines	$\lambda^3\sigma^3$
	**1b**	Phosphites	$\lambda^3\sigma^3$
	**1c**	Phosphine oxides	$\lambda^5\sigma^4$
	**1d**	Phosphates	$\lambda^5\sigma^4$
	**1e**	Phosphonates	$\lambda^5\sigma^4$
	**1f**	Phosphinates	$\lambda^5\sigma^4$
	**1g**	Phosphine Sulphides	$\lambda^5\sigma^4$
	**1h**	Alkylene Phosphoranes	$\lambda^5\sigma^4$
	**1i**	Iminophosphines	$\lambda^5\sigma^4$
	**1j**	Amidophosphonate	$\lambda^5\sigma^4$
	**1k**	Phosphonium	$\lambda^4\sigma^4$

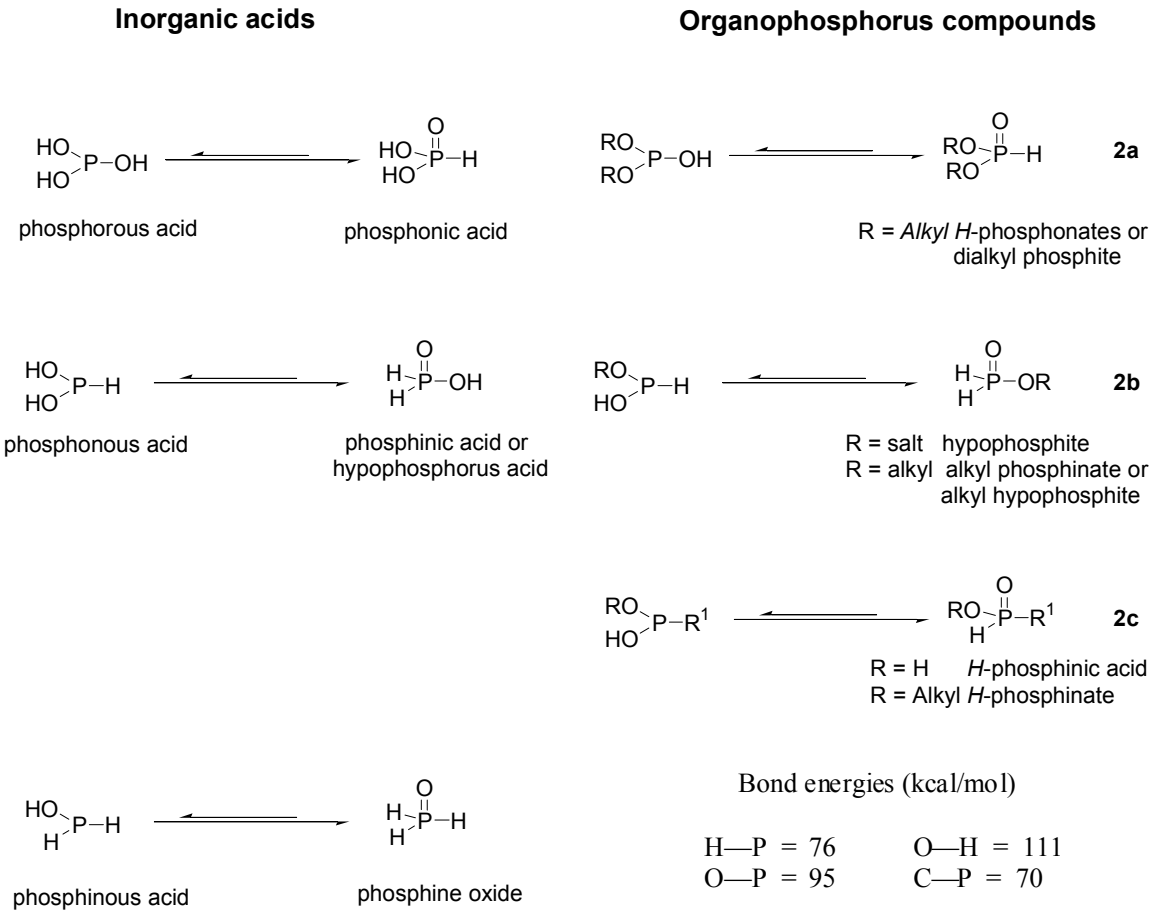
The resonance form with charge separation (Eq 1.1) is the better representation of the actual chemical state for compounds **1c-j**.



Eq. 1.1

Interestingly, pyramidal compounds containing P(OH) group undergo tautomeric changes to form more stable tetrahedral ($\lambda^5\sigma^4$) compounds P(O)H (Scheme 1.1, **2a, 2b, 2c**). The presence of a phosphinylidene [P(O)H] moiety works as a bridge between the P(V) and P(III) forms.[1]

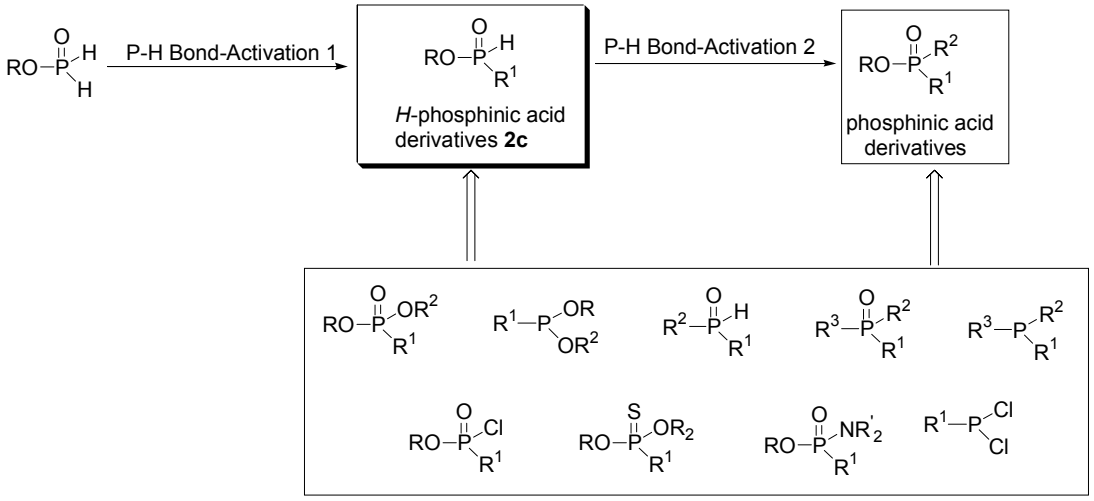
Scheme 1.1 Phosphorus compounds containing phosphinylidene moiety (P(=O)H)



1.2 *H*-Phosphinic Acid Derivatives, Useful Synthons of Organophosphorus Compounds

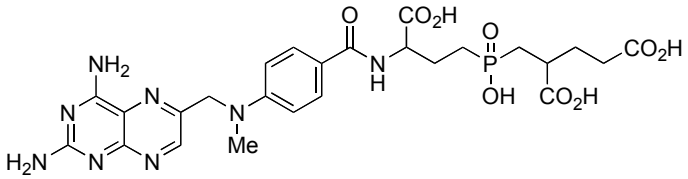
Since *H*-phosphinic acids and their esters ($R_1P(O)(OR)(H)$) **2c** (Scheme 1.1 and 1.2), are in an oxidation state intermediate between that of phosphonic acids and phosphines, they are flexible intermediates in the preparation of virtually any organophosphorus compounds (Scheme 1.2),[2b,3] including phosphonates, phosphinates,

Scheme 1.2 Transformations of *H*-phosphinic acid derivatives



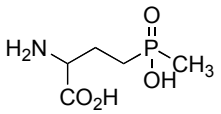
primary phosphines and secondary phosphine oxides. Particularly, they are useful intermediates in the synthesis of disubstituted phosphinic acids, which can mimic tetrahedral transition states in enzyme-catalyzed reactions and have been extensively studied to achieve pharmaceutical activity through the potent inhibition of these enzymes.[4] Representative examples of biologically active phosphinic acids are shown in Figure 1.3.

Figure 1.3 Examples of biologically-active phosphinic acids



Pseudopeptide Prodrug

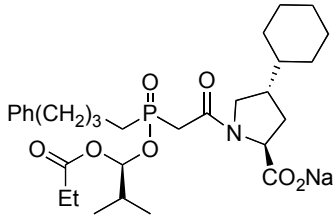
Potent Inhibitor of Folypoly-γ-glutamate Synthetase



Phosphinothricin

Glutamine Synthetase Inhibitor

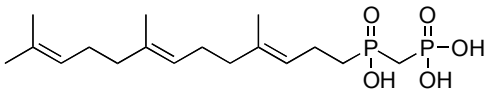
α-Aminobutyric Acid-Based Herbicide



Monopril

Inhibitor of angiotensin-converting enzyme

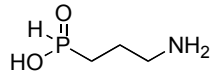
High blood pressure, heart failure



Analogs of Farnesyl Pyrophosphate

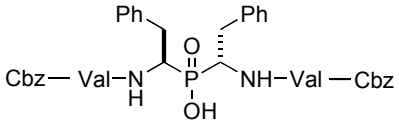
Farnesyltransferase and

Squalene Synthase Inhibitor



CNS Agent

Potent GABA-B Agonist



HIV-1 Protease Inhibitor

Additionally, phosphinic acids are used to replace labile phosphate groups with a non-hydrolyzable equivalent,[5] and to probe deprotonation states in enzyme and receptors.[6] However, these applications of phosphinic acids have only been exploited recently due to the lack of methodologies to prepare highly functionalized phosphinic acids. Furthermore, the phosphinic acid moiety also resembles a naturally occurring carboxylic acid and the replacement of carboxylate moieties in biological compounds by phosphinic acids can lead to an improved activity or selectivity for a particular receptor.[7]

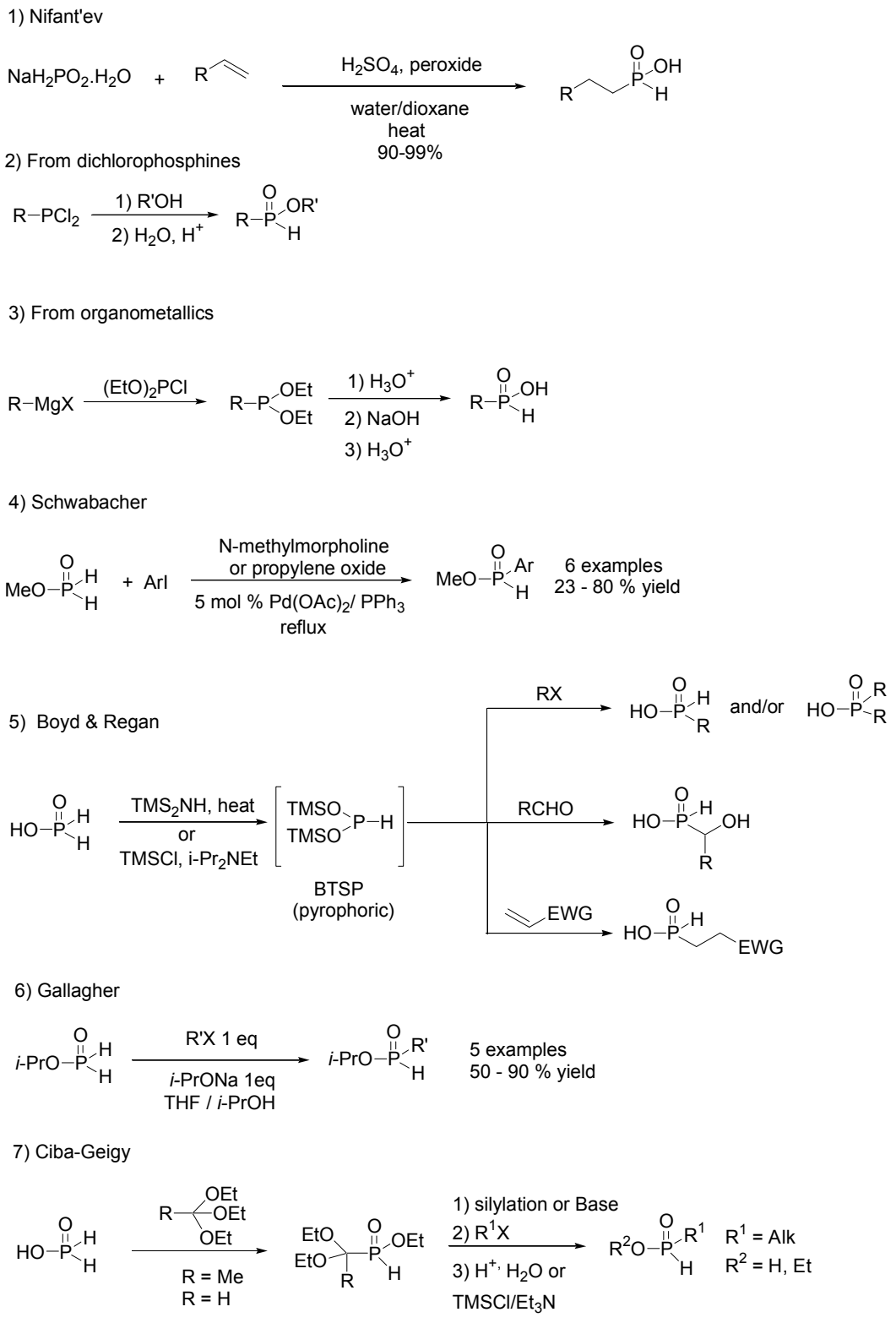
Phosphinic acid peptides where one peptide bond is substituted by a non-hydrolyzable phosphinate moiety represent a very convenient mimic of a substrate in the transition

state for Zn-metalloproteinases and aspartic acid proteinases.[8] Finally, *H*-phosphinic acids can also function as pro-drugs of biologically-active phosphonates (i.e. bisphosphonates),[9] through *in vivo* oxidation,[4a] or as synthetic precursors *via* chemical oxidation.[10]

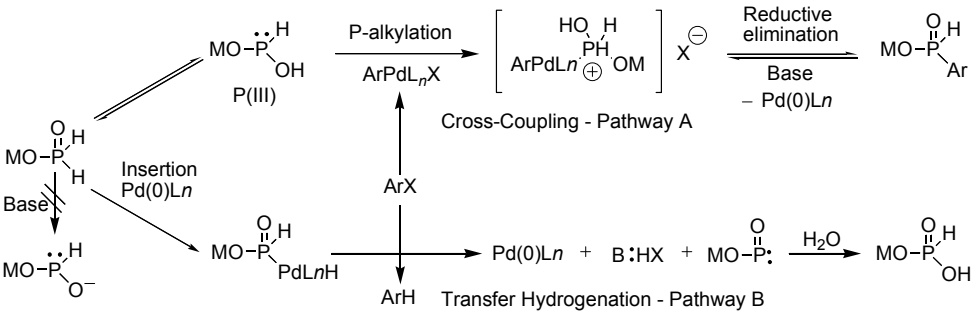
1.2.1 Preparation of *H*-phosphinic acid derivatives

The most commonly employed methods to prepare *H*–phosphinates are summarized in Scheme 1.3. Each of these methods suffers from limitations in scope. The radical reaction originally introduced by Nifant'ev *et al*.[11] and subsequently developed by Karanewsky *et al*.[12] suffers from the strongly acidic medium, thus limiting the scope of substrates that can be employed. Hydrolysis or alcoholysis of dichlorophosphines is limited by the availability of the starting materials. The reaction of a Grignard reagent (and other organometallics) with $(RO)_2PCl$[13] implies stability of the precursor toward Grignard formation. The scope of *H*-phosphinates prepared *via* cross-coupling reaction has been also limited. Holt reported a single example of the cross-coupling between triethylammonium hypophosphite with a steroid-derived dienyl triflate, but the generality of the reaction was not established.[14a] A few years later, Schwabacher developed a palladium-catalyzed cross-coupling of aryl iodides with methyl- or *tert*-butyl-phosphinates prepared *in situ*, using Fitch's orthoformate method (Chapter II Eq.).[14b,c] However, this reaction requires strict anaerobic and anhydrous conditions, and is limited to the use of very reactive aryl iodides due to the competing transfer hydrogenation (Pathway B, Scheme 1.4), as well as to the rapid thermal decomposition of the

Scheme 1.3 Methods for the preparation of *H*-phosphinates



Scheme 1.4 Cross-coupling vs. transfer hydrogenation competing pathways[18a]



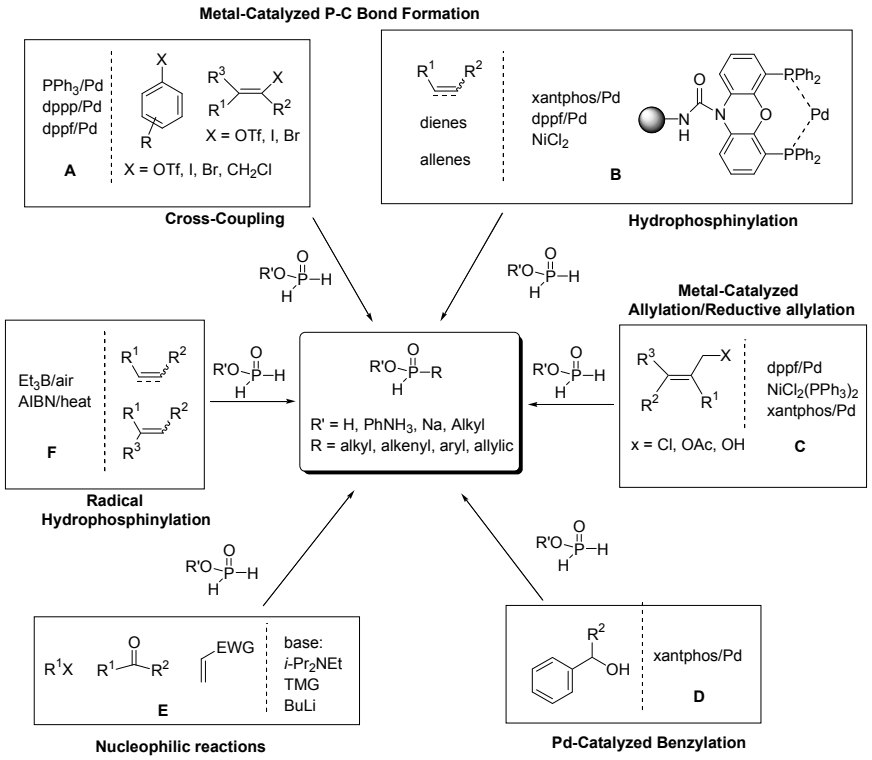
alkylphosphinates prepared by this method. The use of $(TMSO)_2PH$ is inconvenient and often requires a large excess of the reagent to avoid formation of symmetrically disubstituted phosphinates.[15] Decomposition and disproportionation also complicate handling and isolation. Only the most reactive alkyl halides produce a reasonable yield of product.[15] The limitation of the Gallagher method[16] and the Ciba–Geigy reagent[17] in the preparation *H*-phosphinates will be discussed in Chapter V, Section 5.1.

Much progress in the development of new methods for the P-C bond formation based on hypophosphorous compounds $ROP(O)H_2$ as the starting materials has been made by Montchamp (Scheme 1.5). Over the past several years he has reported several approaches for the synthesis of *H*-phosphinic acid derivatives *via* cross-coupling reactions[18] (method A, C and D) metal-catalyzed hydrophosphinylation (method B),[19,20] free radical reactions (method F),[21,22] and nucleophilic reactions of hypophosphorous compounds (method E).[23] His initial contribution dealt with Pd-catalyzed cross-coupling reactions of hypophosphite salts with aryl halides, alkenyl bromides and triflates (method A).[18a,b]

Then, he extended the cross-coupling reaction to alkyl phosphinates with a wide variety of aryl, heteroaryl, alkenyl, and allylic electrophiles.[18c] He also established that the

appropriate selection of ligands around the Pd promotes cross-coupling reaction over the competing reduction pathway (Scheme 1.4). With $Pd(OAc)_2$/dppp (2 mol% or less) as the catalyst, the competing reduction was highly decreased and even the coupling of one activated aryl chloride was reported for the first time.[18a] In the case of alkenyl electrophiles, steric hindrance due to *Z*-substitution required a ligand switch from dppp to dppf.[18b] More recently he also reported the cross-coupling of hypophosphorous compounds with allylic (method C)[18d] and benzylic alcohols (method D).[18e] Montchamp's metal catalyzed hydrophosphinylation (method B) and radical hydrophosphinylation (method F) will be discussed in Chapter II. The formation of P-C bond *via* nucleophilic reactions developed in his laboratory (method E) will be discussed in Chapter V.

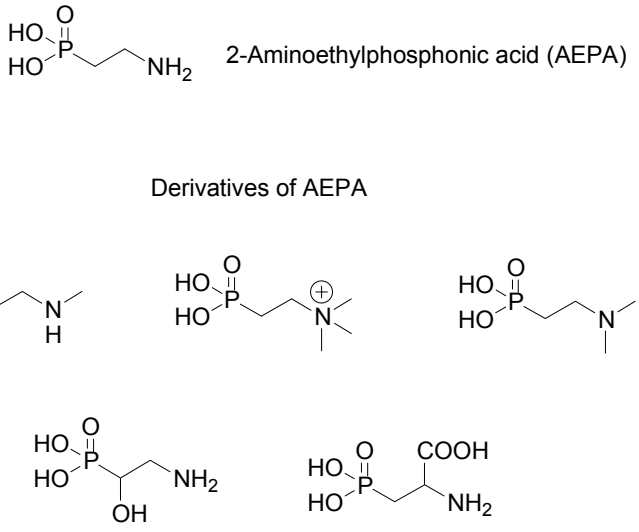
Scheme 1.5 Montchamp's methods for the synthesis of *H*-phosphinates



1.3 Phosphonic Acid Derivatives.

In contrast to the *H*-phosphinic and phosphinic acids derivatives, a large body of literature is available for the synthesis of phosphonic acids derivatives and consequently their biological applications are more developed. The first member of this family: 2-aminoethylphosphonic acid (AEPA) was isolated by Horiguchi and Kandatsu in 1959 from single cell organisms in sheep rumen.[24] Since then, several derivatives of AEPA were isolated from living organisms (Figure 1.4).

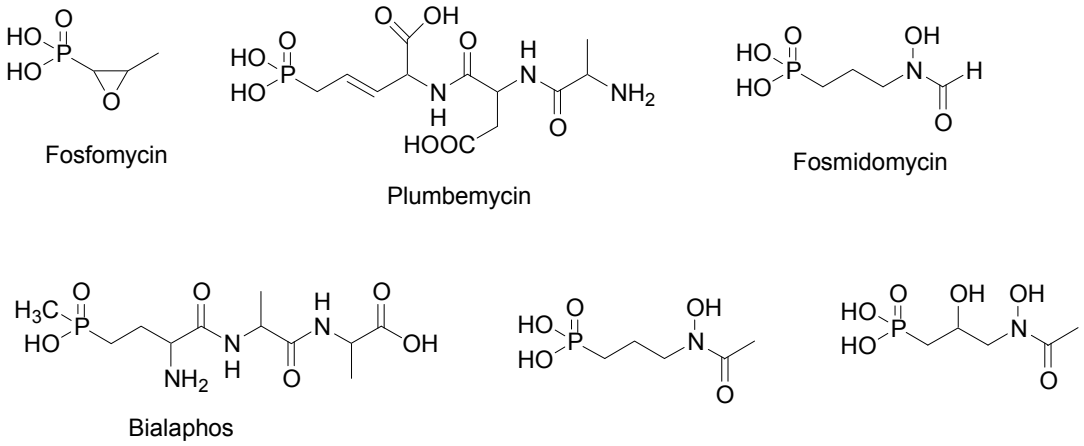
Figure 1.4 2-Aminoethylphosphonic acid (AEPA) and its derivatives



In 1969, the first phosphonic acid with the properties of an antibacterial antibiotic, Fosfomycin (Figure 1.5),[25] was found as a product in a fermentation broth of the bacterium *Streptomyces fradiae*. The discovery of Fosfomycin was an important event in phosphorus chemistry, since it brought fresh attention to applications of organophosphorus chemistry in medicine. Several novel phosphonic acids, as well as phosphinic and even *H*-phosphinic acids, were soon discovered in fermentation broths of

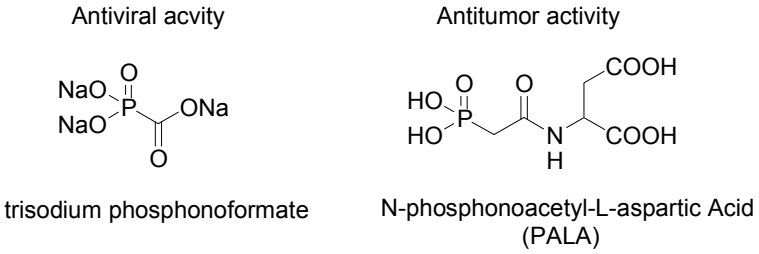
other *Streptomyces* forms, as well as other bacteria. Most of the characterized compounds are aminophosphonic or aminophosphinic acids with substantial antibiotic activity.[2b]

Figure 1.5 Examples of organophosphorus compounds with antibiotics activity



Apart from their antibiotic properties, phosphonic acids derivatives have also antitumor[2b] and antiviral activity[26] (Figure 1.6).

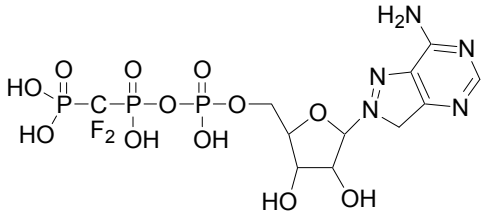
Figure 1.6 Examples of phosphonic acids with antitumor and antiviral activity



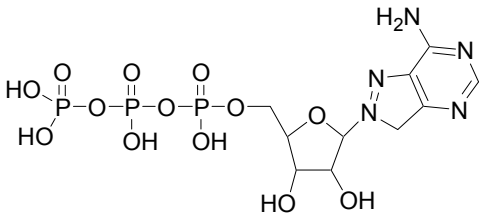
Similarly to phosphinic acids, phosphonic acids derivatives are used to replace labile phosphate groups with a non-hydrolyzable equivalent.[2b] An exact phosphonate replica of known biologically active phosphate could inhibit the process in which the phosphate is

involved. Since the CH_2 group attached to P is isosteric with O atom of a phosphate, a phosphonate and corresponding phosphate molecule are virtually superimposable. The high stability of the P-C bond would block any natural hydrolysis process of the phosphate ester group. The acidity difference between a phosphonic acid (slightly weaker) and a phosphate is not important in the case of the first ionization, since both acids are fully ionized at physiological pH. An adjustment in the phosphonic acid acidity, without creating a steric problem, can be accomplished by placing fluorine atoms on the α carbon. This modification will produce the phosphonic acid, which is isopolar with the natural substance (Figure 1.7).[2b]

Figure 1.7 Isosteric and isopolar ATP analog



Isosteric and isopolar ATP analog

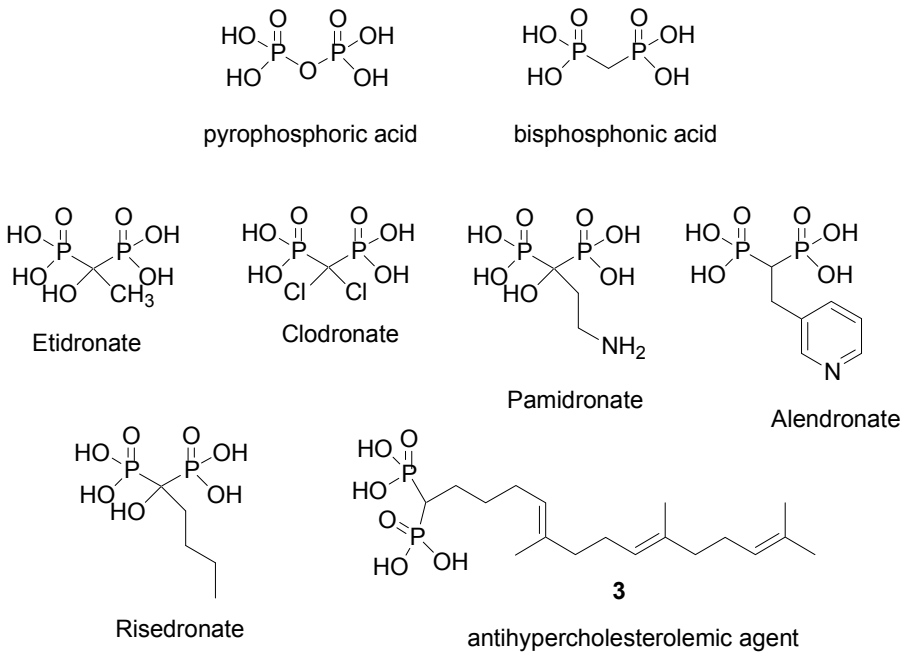


ATP adenylribosyl triphosphate

On the other hand phosphonic acids resemble naturally occurring carboxylic acids. Until now, phosphonic acid analogs of all the natural aminoacids have been synthesized.[2a] Finally, phosphonic acids similarly to phosphinic acids can mimic tetrahedral transition states in enzyme-catalysed reactions and act as inhibitors of hydrolytic enzymes.[2b,27] PALA (Figure 1.6) is a bisubstrate mimic of the transformation catalyzed by aspartate transcarbamylase, involved in pyrimidine biosynthesis and, as mentioned, is a potent anticancer drug. The idea of replacing O with CH_2 to create new bioactive phosphorus

agents has resulted in a major breakthrough in the treatment of bone diseases such as osteoporosis and Paget's disease.[2b,28,29] It has been found that pyrophosphate inhibits the formation and dissolution of hydroxyapatite in bone. The dissolution leads to medical problems. Hydrolytically stable bisphosphonic acid isosteric with pyrophosphoric acid might block the dissolution process. Many bisphosphonic acid derivatives, with substituent on the methylene carbon, have been found to exhibit the desired effect on bone, and several are in clinical use for the treatment of bone diseases (Figure 1.8).[2a] Activity against bone disease is not the only medical application for bisphosphonates. Compound **3** (Figure 1.8) found its use as antihypercholesterolemic agent.[2b]

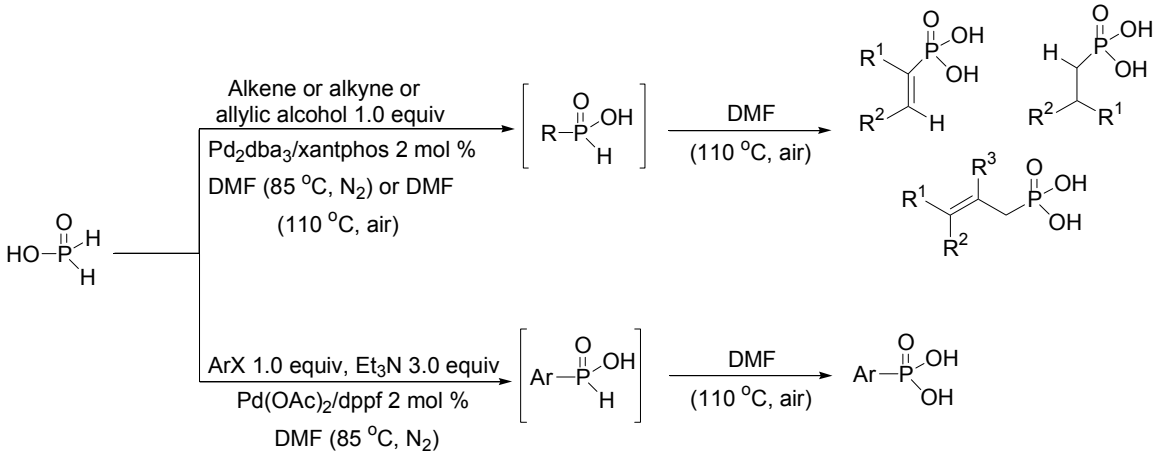
Figure 1.8 Biologically active analogs of pyrophosphate



1.3.1 Synthesis of phosphonic acid derivatives

As mentioned before, a large body of literature is available for the synthesis of phosphonic acids derivatives. The easiest approach for the synthesis of these compounds seems to be the oxidation reaction of *H*-phosphinic acids derivatives. However, only recently Montchamp developed an easy and efficient oxidation process of *H*-phosphinic acids.[30] He demonstrated that *H*-phosphinic acids can be converted into the corresponding phosphonic acids under the influence of oxygen, a Pd catalyst and heating. Since the conversion of hypophosphorous acid into *H*-phosphinic acids *via* his Pd-catalyzed P-C bond forming reactions (hydrophosphinylation and cross-coupling) proceeds often in quantitative yield,[18,19] he was able to develop the tandem process: P-C bond formation followed by oxidation in one pot without isolation of *H*-phosphinic acids intermediates (Scheme 1.6). His method delivers a variety of phosphonic acids from hypohosphorous acid in very good or even quantitative yields.

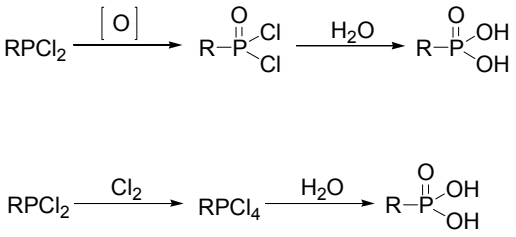
Scheme 1.6 Montchamp's tandem reaction for the preparation of phosphonic acids



The major disadvantages of other oxidations methods are associated with the harsh oxidative conditions such as H_2O_2 (30%, 80-90°C);[31] Br_2, I_2 or Cl_2 in H_2O/DMSO or in conc. HI/HCl (20-75°C);[32,33] $HgCl_2$ or HgO in H_2O (90-95°C);[32,34] $KMnO_4$/KOH in H_2O (50-250°C);[35] H_2SO_4/HNO_3 (100-110°C);[36] $CCl_4/Et_3N/H_2O$ (35°C);[31c,36] pyridinium chlorochromate/TsOH in DMSO;[37] or $NaIO_4$ (50°C).[38]

However, only recently has remarkable progress been made regarding the preparation of *H*-phosphinic acids derivatives. Before only few effective methods were available for the synthesis of these compounds. Therefore the formation of phosphonic acids *via* oxidation reactions of *H*-phosphinic acids has his far not occupied a large role, and other methods by-passing *H*-phosphinates were extensively used. Dichlorophosphines can be oxidized to give phosphonic dichloride and then easily hydrolyzed to the phosphonic acid (Scheme 1.7).[2b] Another method is to form a $RPCl_4$ species from the addition of chlorine to dichlorophosphines followed by hydrolysis.[2b]

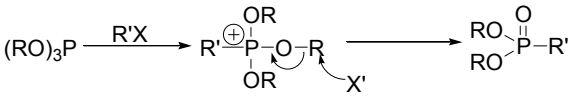
Scheme 1.7 Phosphonic acids from chlorophosphines



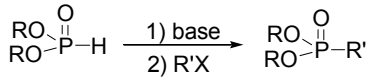
Several methods exist for the synthesis of phosphonic acid derivatives *via* the direct P-C bond forming reactions. Among these is the highly versatile and widely used Michaelis-Arbuzov method (Scheme1.8). The scope of the reaction is very wide and well described, and it has been used to make countless phosphonates and phosphonic acids.[39,40,41] Also

other organophosphorus compounds - phosphinates, bisphosphinates and phosphine oxides - can be obtained from Arbuzov-related processes.[2a]

Scheme 1.8 Mechanism of Michaelis-Arbuzov reaction



The dialkyl esters of phosphorus acids, having *H*-phosphonate structure, are also widely used in phosphonate synthesis. This is accomplished by removing the proton on phosphorus with active metals (most commonly sodium) or strong bases (NaOEt, NaH, $NaNH_2$, BuLi) to create an anion that acts as the nucleophile in alkylation reaction. With alkyl halides (primary are preferred), the attack is virtually exclusively on phosphorus (soft). The process is known as the Michaelis-Becker reaction (Eq. 1.2) and it is well described in the various reviews on phosphonic acids.[42]

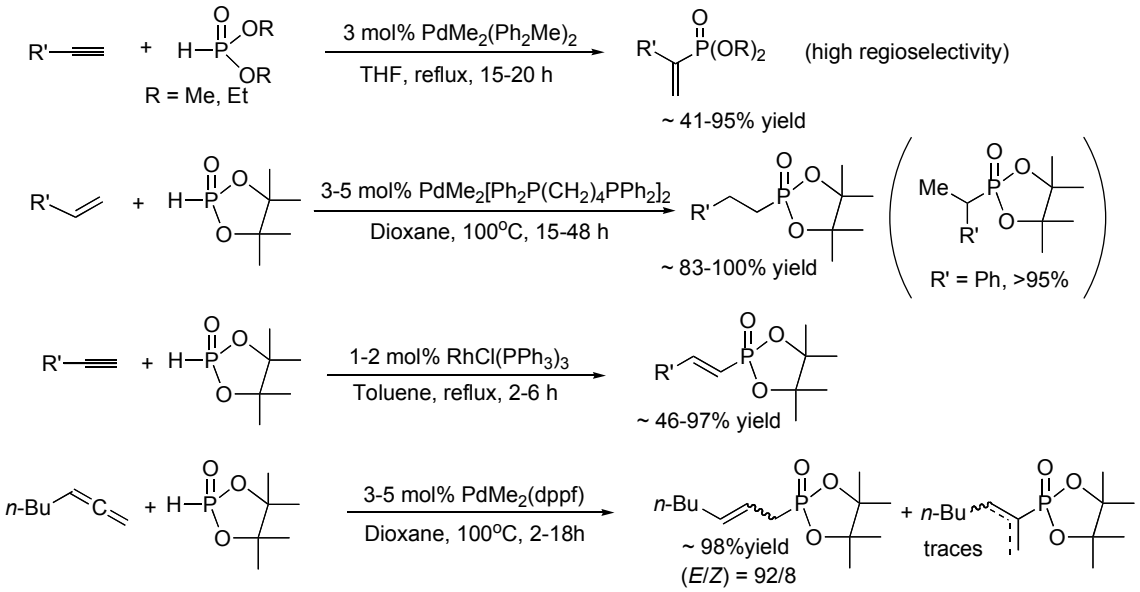


Eq. 1.2

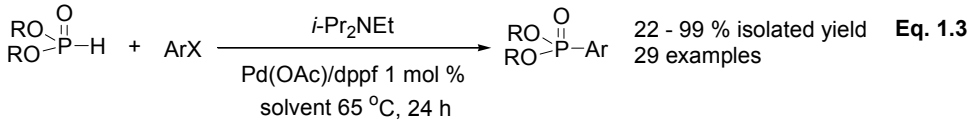
H-Phosphonate anions can also be used in conjugate addition reactions with an α, β-unsaturated system, including the usual functions such as ketone, esters, nitrile and amides. *H*-Phosphonates also add to carbonyl groups (and to C=N as well) in saturated compounds, giving rise to α-hydroxyphosphonates.[2b] Another useful synthesis starting with *H*-phosphonate is based on their free radical reaction with alkenes.[43] The abstraction of H from P is usually accomplished by peroxides, azo compounds, or by irradiation. More recently, *H*-phosphonates were employed in metal catalyzed P-C bond formation.

Tanaka has reported Pd and Rh catalyzed hydrophosphonylation of alkynes and alkenes leading to alkenyl- and alkylphosphonates (Scheme 1.9).[44]

Scheme 1.9 Hydrophosphonylation of alkenes, alkynes and allenes



The cross-coupling reaction of *H*-phosphonates, originally developed by Hirao[45] and recently improved by Montchamp[46] produces various arylphosphonates in good yields (Eq. 1.3).[46]

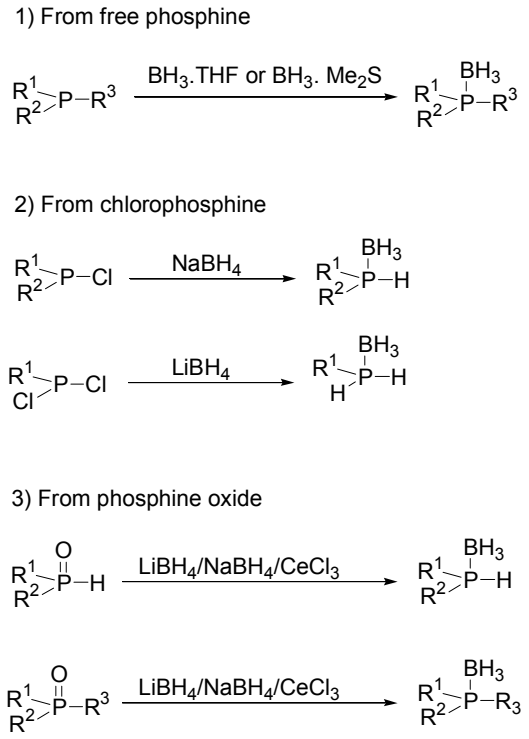


Other methods known from the literature for the synthesis of phosphonic acid derivatives including α and β functionalized phosphonates will be disclosed in Chapter IV along with the synthesis of organophosphorus compounds *via* organoboranes, developed in our laboratory.[47]

1.4 Phosphine-Borane Complexes

The last class of organophosphorus compounds relevant to this thesis, which will be briefly discussed, is adducts of phosphine and borane: phosphine-borane complexes. The unexpected stability of these complexes has been the focus of a great number of investigations which have revealed the interesting chemical properties of such compounds as well as the inherent P-B bond nature.[48]

Scheme 1.10 Methods for the synthesis of phosphine-borane complexes

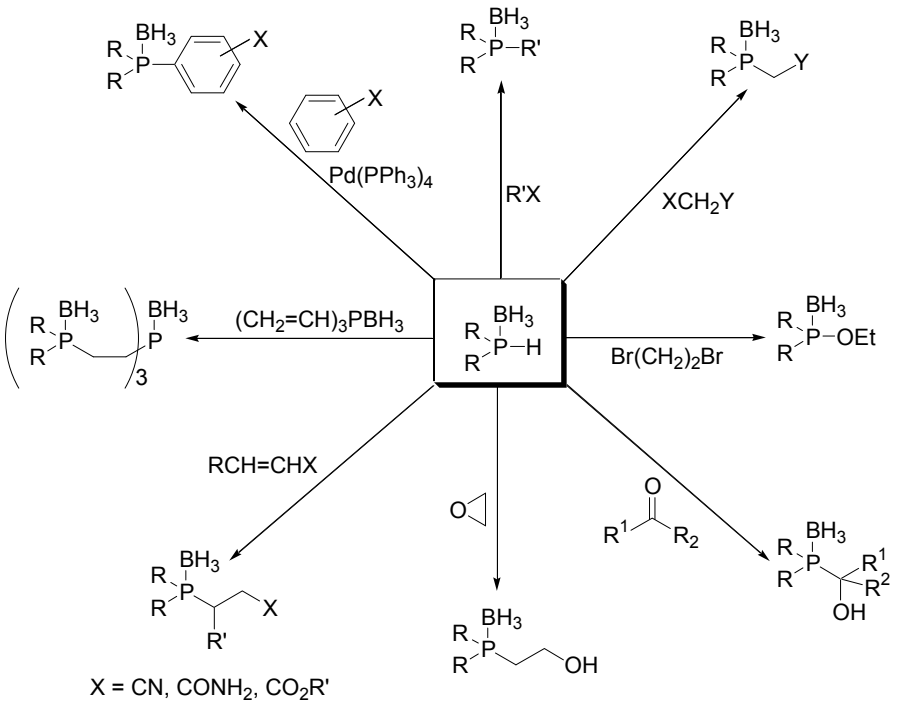


The most common approaches for the synthesis of phosphine-borane complexes are shown in Scheme 1.10. If a phosphine is available, the corresponding borane complex can be obtained simply *via* complexation reaction with BH_3.[48] In another extensively used method, borane complexes can be prepared by the reduction of chlorophosphines

with sodium or lithium borohydride.[49] The secondary and tertiary phosphine-borane complexes were also obtained *via* reduction of the corresponding secondary and tertiary phosphine oxides followed by complexation without isolation of intermediate phosphine.[50]

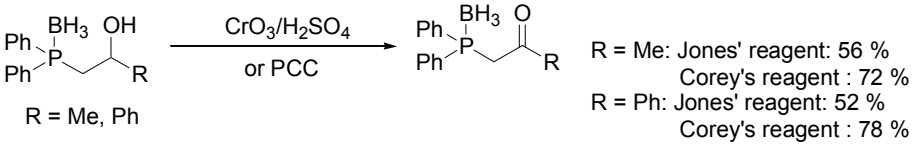
Moreover, the reaction of *H*-phosphine-borane complexes with various eleophiles under mild conditions provided a new variety of organophosphorus-borane complexes (Scheme 1.11).[48]

Scheme 1.11 Reactivity of secondary phosphine-borane complexes



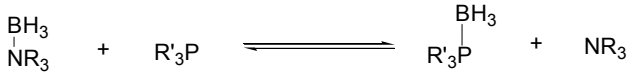
Since phosphines are very sensitive to oxidizing agents, the synthesis of functionalized phosphines cannot include an oxidation step. In contrast, phosphine-borane complexes

appear to be insensitive to the usual oxidizing reagents (Eq. 1.4) [48,51] and can be converted into other complexes in a variety of ways (Scheme 1.13).



Eq. 1.4

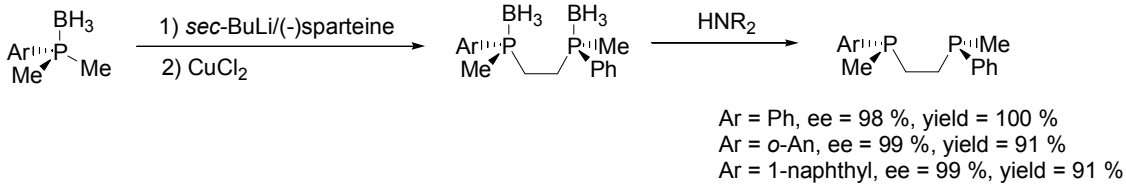
The further removal of borane from these complexes will lead to functionalized tricoordinated phosphines. The decomplexation process usually is accomplished with amines (Et_2NH, morpholine, DABCO, TMEDA). The reaction of a phosphine-borane adduct with an amine is an equilibrium (Eq 1.5) and the distribution of this equilibrium depends on the relative pK_a and amount of the amine and the phosphine.[48]



Eq. 1.5

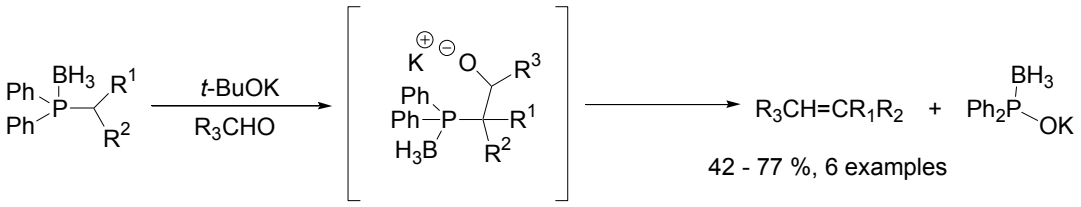
The efficient role of borane as a protecting group is well illustrated in the enantioselective synthesis of P-chiral bisphosphines (Scheme 1.12).[52]

Scheme 1.12 Borane as a protecting group in the enantioselective synthesis of bisphosphines



Phosphine-borane complexes are becoming not only an important tool for the preparation of functionalized chiral phosphines, but they are also used in the olefination reactions (Scheme 1.13).[53]

Scheme 1.13 Olefination reaction using phosphine-borane complexes



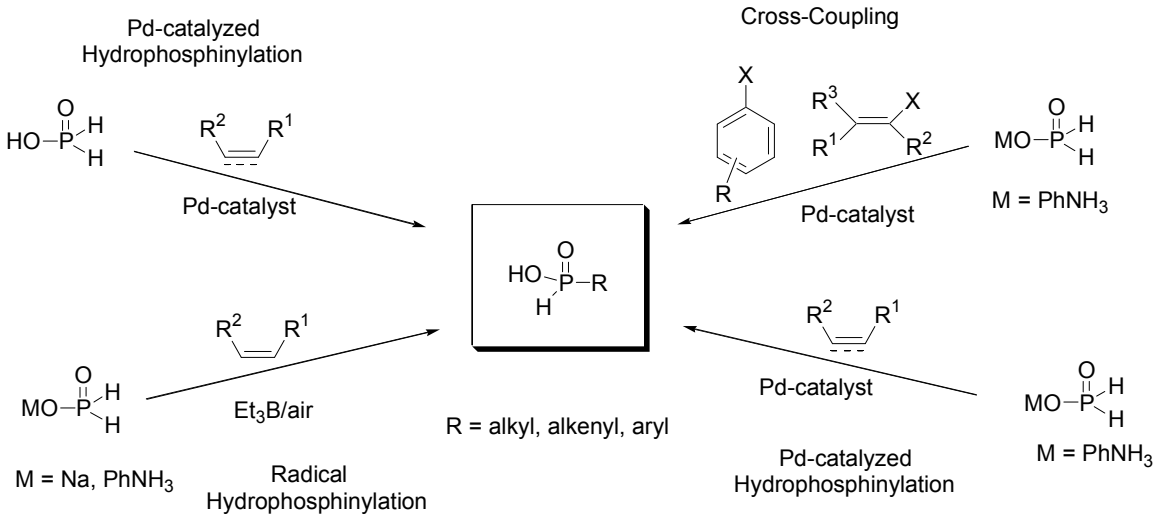
The preparation and the reactivity of novel dialkoxyphosphine-borane complexes, as the precursors of *H*-phosphinates and phosphinates corresponds to the work discussed in Chapter IV and V of this dissertation.

Chapter II: Hydrophosphinylation of Alkenes and Alkynes Using Alkyl Phosphinates

2.1 Introduction

Over the past several years Montchamp has reported several approaches to the synthesis of *H*-phosphinic acid derivatives.[54] His initial contribution in this area dealt with the preparation of *H*-phosphinic acids *via* cross-coupling reactions,[18a] Pd-catalyzed hydrophosphinylation,[19] and free radical reactions[21] (Scheme 2.1).

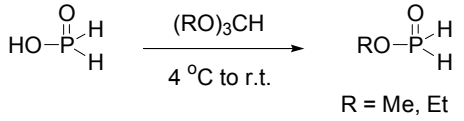
Scheme 2.1 Montchamp's methods for the preparations of *H*-phosphinic acids



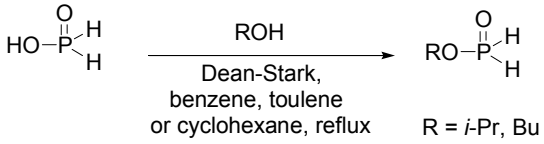
However, the access to *H*-phosphinate esters has been limited, since alkyl phosphinates ($ROP(O)H_2$) are highly sensitive to moisture, air, or heat, and have a propensity for disproportionation and decomposition. Methyl and ethyl hypophosphites ($MeOP(O)H_2$, $EtOP(O)H_2$) were first prepared by Kabachnik in 1960, by the esterification of hypophosphorous acid with diazoalkanes.[55] A few years later, Fitch reported the

esterification of crystalline hypophosphorous acid with orthoformates and related compounds (Scheme 2.2, Eq. 1)[56] and Nifant'ev described the direct esterification of hypophosphorous acid with alcohols under azeotropic water removal (Dean–Stark trap) (Scheme 2.2, Eq. 2).[57] At that time, the latter two methods were the most commonly employed, due in part to their relative experimental simplicity, and suitability for large scale reactions.

Scheme 2.2 Literature preparation of alkyl phosphinates $ROP(O)H_2$



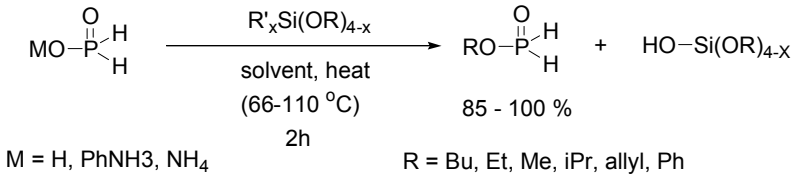
Eq. 1



Eq. 2

In terms of synthetic applications, Montchamp showed that methyl and butyl hypophosphites can successfully react with alkenes in the presence of Et_3B.[21] However, the mild and neutral conditions were critical to the use of alkyl phosphinates since they are thermally unstable. This property precludes alkyl phosphinates' use in AIBN-initiated reactions; for example, methyl hypophosphite decomposes completely in about an hour at 80 °C. Schwabacher showed that $MeOP(O)H_2$ can also successfully react with aryl iodides, but the scope was limited by transfer hydrogenation as well as the rapid thermal decomposition of methyl phosphinate.[14c] To fully explore reactivity of alkyl phosphinates, Montchamp developed novel methods to prepare these compounds in high yield, from inexpensive and easily handled reagents, and under conditions compatible

with a wide array of subsequent reactions. The reaction of hypophosphorous acid and its anilinium or ammonium salts with alkoxysilanes proceeds in excellent yields, in several solvents, and unlike in other preparative methods, the resulting solution of alkyl phosphinates have good thermal stability (Eq. 2.1).[58] When methyl phosphinate was prepared by esterification with alkoxysilanes, it only decomposed slightly after 20 h of heating at 80 °C; whereas the same compound, prepared by the Fitch method (using orthoformates), as mentioned before, decomposed totally after 1 h at the same temperature. In addition, stock solutions of alkylphosphinates can be safely stored at rt under N_2 for over a month, with less than 10% decomposition.



Eq. 2.1

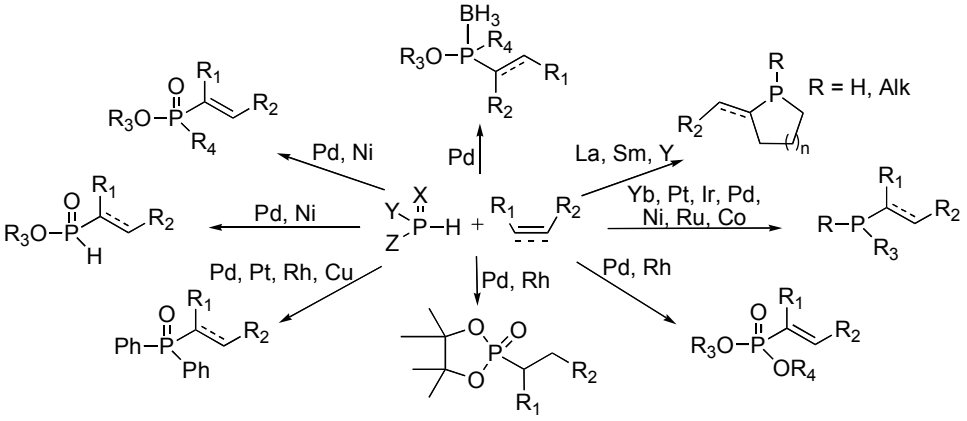
The remarkable thermal stability of the hypophosphite esters, prepared by the alkoxysilane method allowed Montchamp to develop novel methodology for the synthesis of *H*-phosphinate esters. He found that alkyl phosphinates couple successfully with aryl- and heteroaryl iodides, bromides, triflates, benzylic chlorides, and alkenyl halides.[18c] He also employed alkyl phosphinates in metal (Pd and Ni)[19a,20] catalyzed hydrophosphinylation and AIBN-initiated radical hydrophosphinylation[22] to produce a variety of *H*-phosphinate esters, which were not accessible before.

2.2 Nickel - Catalyzed Hydrophosphinylation

The formation of carbon-phosphorus bonds *via* metal-catalyzed reactions remains an important synthetic objective for the synthesis of organophosphorus compounds. Few catalytic methods have been reported for the addition of phosphorus-hydrogen bonds

across unsaturated substrates. In this area, the formation of carbon-phosphorus bonds by addition of P(III) reagents (hydrophosphination) and P(V) reagents (hydrophosphinylation and hydrophosphorylation) to various unsaturated substrates has been investigated as a possible route to obtain phosphines,[59,60,61] tertiary phosphine boranes,[62] phosphonates,[44,63,64] tertiary phosphine oxides,[65] phosphinates,[66,67] and *H*-phosphinates[19,20] (Scheme 2.3).

Scheme 2.3 Metal-catalyzed additions of phosphorus to unsaturated substrates

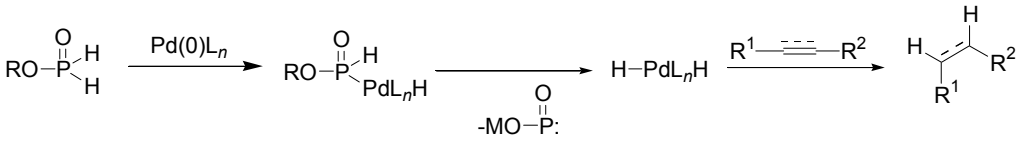


With the exception of PH_3,[60] the compounds usually employed in transition-metal-catalyzed reactions do not contain more than one P-H bond. For example, Beletskaya has reported the Pd- and Ni-catalytic addition of secondary phosphines to styrenes and terminal alkynes.[61k-p] Marks developed the hydrophosphination of unsaturated compounds using lanthanide catalysts.[61a-e] Recently, Dixneuf (ruthenium) and Oshima (cobalt) reported the addition of diphenylphosphine to alkynes[61q] and propargyl alcohols,[61s] respectively. The Pd-catalyzed addition of secondary phosphine-borane complexes to alkynes has also been developed and its asymmetric version provided low enantiomeric excesses of tertiary phosphines (up to 42%).[62] Tanaka developed the

catalytic addition reactions of *H*-phosphonates and secondary phosphine oxides using rhodium or palladium catalysts.[44,64] Han and co-workers recently described the nickel catalyzed addition of dimethyl phosphite, diphenyl phosphine oxide, and ethyl *H*-phenylphosphinate to alkyne.[67]

However, catalytic P-C bond formations using hypophosphorous acid or its derivatives (compounds containing two P-H bonds) as starting materials have been overlooked. Hypophosphorous derivatives are particularly strong reducing agents. In fact, the preparatively useful transfer hydrogenation of alkenes, alkynes, aldehydes, ketones, and aryl halides is well documented to take place with H_3PO_2 or its sodium and amine salts, in the presence of almost all transition-metals.[68] This process is believed to occur *via* insertion of the metal into a P-H bond with subsequent formation of a metal hydride, which is the catalytically active reducing agent (Scheme 2.4) and suggests that P-C bond formation would be difficult.

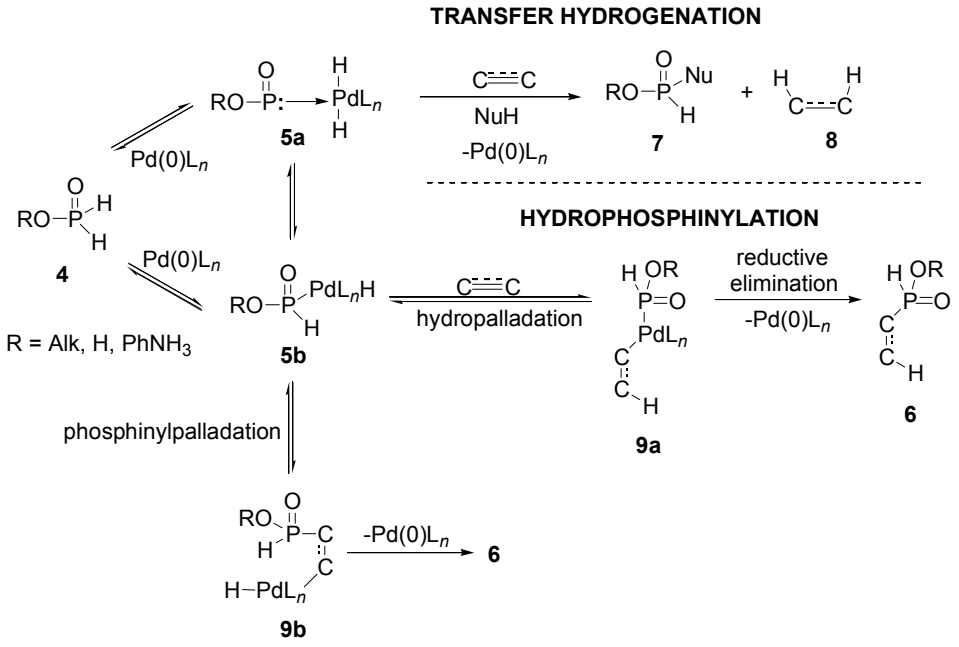
Scheme 2.4 Transfer hydrogenation



However, Montchamp and co-workers discovered that the transfer hydrogenation reaction (Scheme 2.5, pathway 1) could be minimized or even suppressed and P-C bond formation occurred.[19] They demonstrated that the appropriate selection of ligands around the Pd harnesses the reactivity of the postulated phosphinyl palladium intermediate (intermediate **5b**, Scheme 2.5) before the decomposition of complex **5a** to a palladium

dihydride species, leading the reaction towards addition instead of transfer hydrogenation (Scheme 2.5).

Scheme 2.5 Postulated mechanistic pathways in the Pd-catalyzed hydrophosphinylation reaction

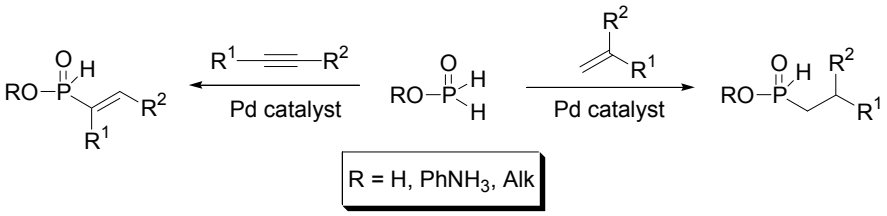


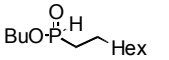
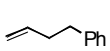
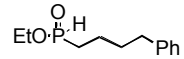
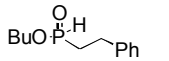
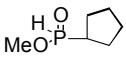
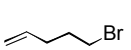
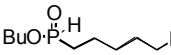
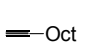
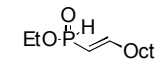
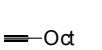
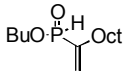
Consequently they developed a remarkably general Pd-catalyzed addition of H_3PO_2, anilinium hypophosphite (AHP) and alkyl phosphinates to alkenes and alkynes under homogeneous catalytic conditions. Pd_2dba_3/xantphos appeared as the most useful catalytic system, where loadings as low as 0.02 mol% Pd still provided good conversions.[19]

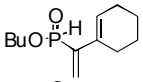
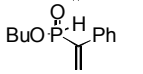
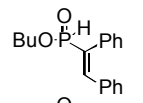
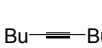
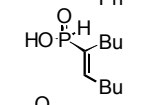
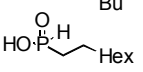
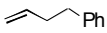
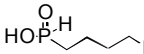
Montchamp's hydrophosphinylation yields *H*-phosphinic acid derivatives in high yields (Table 2.1) and does not require strict anhydrous conditions.[19a] An environmentally friendly variant of this process was later developed using a water-tolerant, recyclable

polymer-supported catalyst [19b] The ligand can even be employed with Pd/C to furnish a doubly-heterogeneous reusable catalyst.

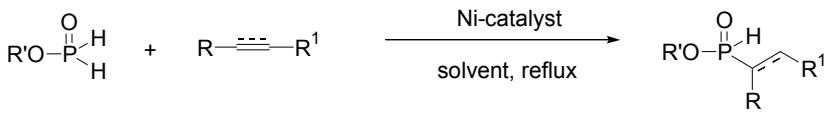
Table 2.1 Palladium-catalyzed hydrophosphinylation of alkenes and alkynes



Substrate	Product	^{31}P NMR (isol.)yield %	catalyst
		89 (76)	Pd_2dba_3 xantphos
		100 (84)	Pd_2dba_3 xantphos
		100 (69)	Pd_2dba_3 xantphos
		13	Pd_2dba_3 xantphos
		100 (61)	Pd_2dba_3 xantphos
		75 (70)	Pd_2dba_3 xantphos
		70	$Cl_2Pd(PPh_3)_2$ 2 MeLi

Substrate	Product	^{31}P NMR (isol.)yield %	catalyst
		90	$Cl_2Pd(PPh_3)_2$ 2 MeLi
		85 (50)	$Cl_2Pd(PPh_3)_2$ 2 MeLi
		56	$Cl_2Pd(PPh_3)_2$ 2 MeLi
		100 (88)	Pd_2dba_3 xantphos
		100 (67)	Pd_2dba_3 xantphos
		81 (75)	Pd_2dba_3 xantphos

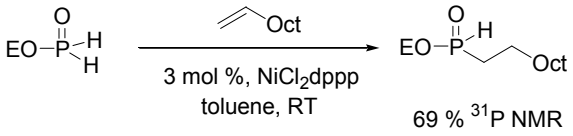
Although palladium-catalyzed hydrophosphinylation has a broad scope and proceeds with low catalyst loadings or can be conducted with a reusable catalyst, we were interested in exploring still cheaper and, more importantly, possibly more reactive nickel-based catalysts. Herein, we investigated a simple and inexpensive nickel chloride catalyzed hydrophosphinylation (Eq. 2.2).[20]



Eq. 2.2

2.2.1 $NiCl_2$-catalyzed addition of alkyl phosphinates to alkynes

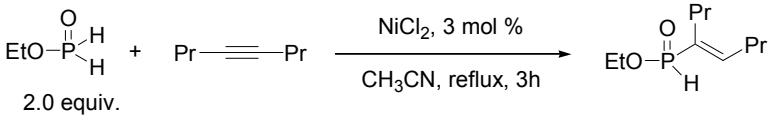
During the development of palladium hydrophosphinylation,[19] Montchamp observed that nickel is a poor catalyst compared to palladium for the addition of alkyl phosphinates to alkenes. In the best cases, he obtained product in 69 % ^{31}P NMR yield (Eq. 2.3) and this result was not sufficiently good to compete with the palladium-catalyzed reaction (Table 2.1).



Eq. 2.3

However, the situation was very different when alkynes were used. With palladium, internal alkynes are poor substrates with alkyl phosphinates (Table 2.1), even if H_3PO_2 and $PhNH_3OP(O)H_2$ do react in good yield, whereas with nickel both terminal and internal alkynes are excellent substrates. Furthermore, even 0.5 mole % $NiCl_2$ afforded a quantitative yield of alkenyl-*H*-phosphinate in 12 h in refluxing acetonitrile. Other nickel sources also gave good results (Table 2.2). There was no significant difference between various nickel halide precatalysts (Table 2.2, entries 1-6). The reaction is not air and moisture sensitive (Entry 13-15) and even nickel chloride hydrate could be used to catalyze the addition in excellent yield (Entry 2). The fact that $Ni(cod)_2$ is not necessary is significant since this complex is highly air-sensitive and requires careful handling. Moreover, the reaction does not require the addition of any ligand, alkyl phosphinate $ROP(O)H_2$ serves not only as the reducing agent to form a catalytically active Ni(0) species form Ni(II), but also the excess alkyl phosphinate present in the reaction mixture could presumably act as a ligand complexed to Ni(0).

Table 2.2 Reactivity of various Ni-catalysts in the addition of ethyl phosphinate to 4-octyne

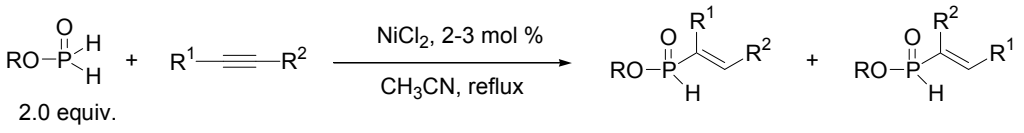


Entry	Catalyst	Additive	NMR yield, %[a]
1	$NiCl_2$	None	100
2	$NiCl_2.6H_2O$	None	99
3	$NiBr_2$	None	97
4	NiI_2	None	99
5	$NiCl_2(PPh_3)_2$	None	100
6	$NiBr_2(PPh_3)_2$	None	100
7	$Ni(acac)_2$	None	94
8	$Ni(OAc)_2.H_2O$	None	47
9	$NiCp_2$	None	15
10	Ni powder	None	11
11	Ni on SiO_2/Al_2O_3[b]	None	8
12	$PdCl_2$	None	11
13	$NiCl_2$	H_2O (1 eq.)	100
14	$NiCl_2$	EtOH (3 eq.)	100
15	$NiCl_2$	O_2[c]	100

[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra. [b] 65 wt.% Ni. [c] Open to air with a drierite trap.

While alkyl phosphinates ($ROP(O)H_2$, R = Me, Et, Bu, *i*-Pr), prepared by the silicate-based methodology (alkoxysilanes or aminosilicates salts, Eq 2.1),[58] react in high yield, both H_3PO_2 or its anilinium salt (AHP) fail to undergo the nickel-catalyzed reaction (less than 20 %). We have found that several variations of our silicate-based esterification producing alkyl phosphinates could be successfully employed in nickel-catalyzed hydrophosphinylation. The stock solutions of alkyl phosphinates or alkyl phosphinate formed in situ in a single reaction step (Table 2.3, entry 1d) are equally successful. The use of the trifluoroacetate salt of an aminosilicate is also possible, the hydrophosphinylation still taking place in high yield (Table 2.3, Entries 2b, 6b, 7b, 11, 12) and allows removal of the silicate byproducts by extraction and therefore simplifies

Table 2.3. Scope of the $NiCl_2$-catalyzed hydrophosphinylation of alkynes



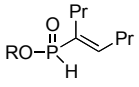
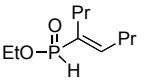
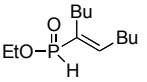
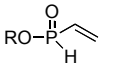
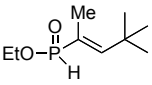
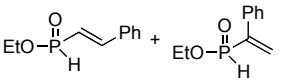
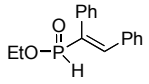
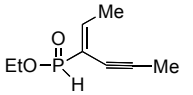
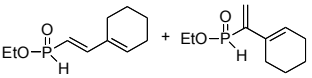
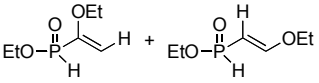
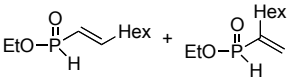
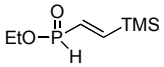
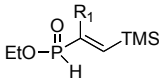
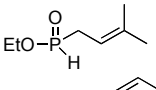
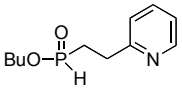
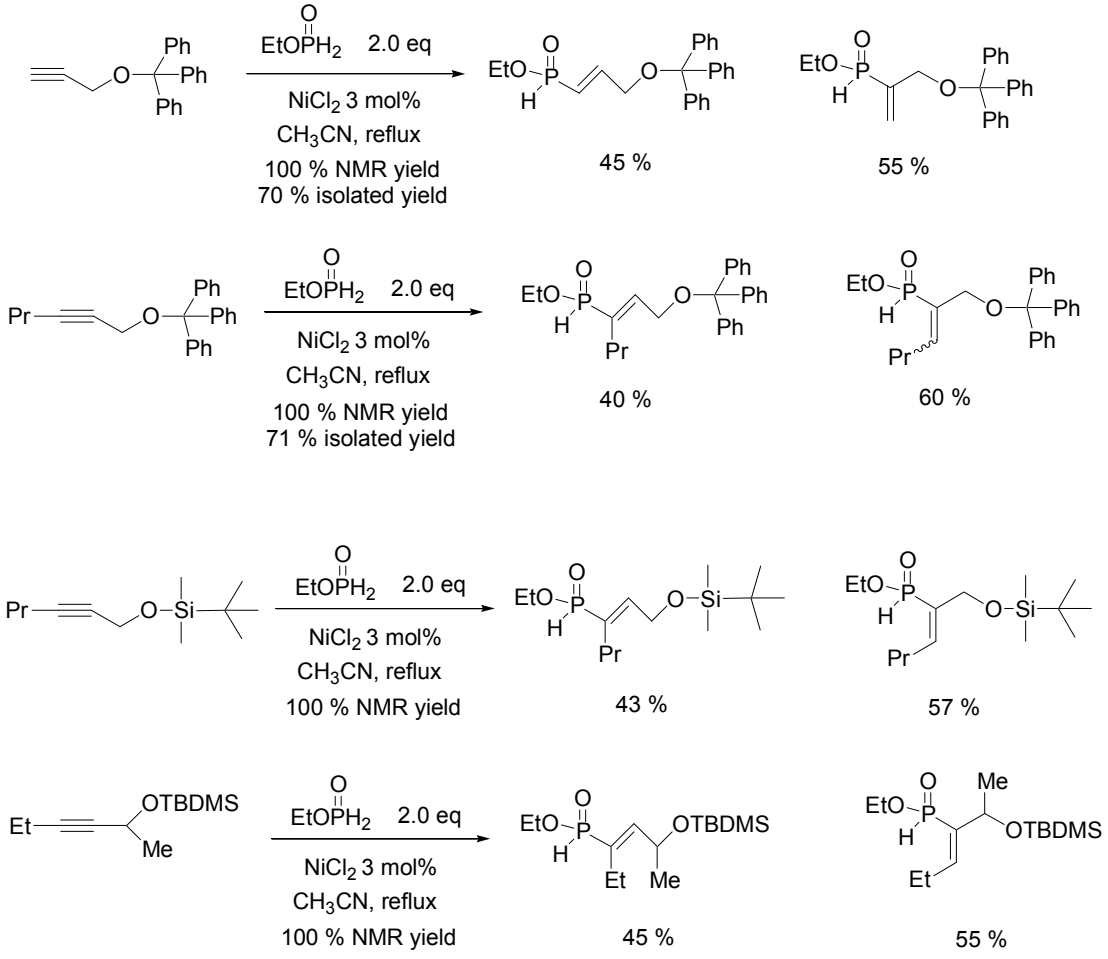
Entry	R^1	R^2	R	Time (h)	Reagent for $ROP(O)H_2$ formation	Product(s)	Yield %[a]
1a	Pr	Pr	Me	38	$(MeO)_4Si$		90
1b			*i*-Pr	13	$(i\text{-}PrO)_4Si$		96
1c			Bu	2.5	$(BuO)_4Si$		100
1d			Bu	16[b]	$(BuO)_4Si$[b]		90[b]
2a	Pr	Pr	Et	7	$Me_2Si(OEt)_2$		75
2b				13	$(EtO)_3Si(CH_2)_3NH_2$		100
3	Bu	Bu	Et	12	$Me_2Si(OEt)_2$		76[c]
4a	H	H	Et	1	$(EtO)_3Si(CH_2)_3NH_2$		[d]
4b			Et_2CHCH_2		$(Et_2CHCH_2O)_4Si$		[e]
5	*t*-Bu	Me	Et	12	$Me_2Si(OEt)_2$		77
6a	Ph	H	Et	6	$Me_2Si(OEt)_2$		40
6b			Et	5	$(EtO)_3Si(CH_2)_3NH_2$		100 (1:1)
7a	Ph	Ph	Et	4.5	$Me_2Si(OEt)_2$		85
7b				1.5	$(EtO)_3Si(CH_2)_3NH_2$		93
8	MeC≡C	Me	Et	3	$Me_2Si(OEt)_2$		57
9	1-cyclo hexenyl	H	Et	12	$Me_2Si(OEt)_2$		63 (1.5:1)
10	EtO	H	Et	18	$Me_2Si(OEt)_2$		42/0 (3:1)
11	Hex	H	Et	13	$(EtO)_3Si(CH_2)_3NH_2$		100 (3:1)
12	TMS	H	Et	2.5	$(EtO)_3Si(CH_2)_3NH_2$		75
13a	Bu	TMS	Et	13	$Me_2Si(OEt)_2$		64
13b	Pr			20			46
14	Me_2CCl	H	Et	3	$Me_2Si(OEt)_2$		55[f]
15	2-Pyr	H	Bu	24	$(BuO)_4Si$		32

Table 2.11. Scope of the $NiCl_2$-catalyzed hydrophosphinylation of alkynes: [a] All yields are isolated. Ratios in parentheses indicate regioselectivity determined on the crude reaction mixture. All reactions were conducted in refluxing reagent grade CH_3CN. Details can be found in the Experimental Section. [b] One-pot process, where esterification and hydrophosphinylation take place simultaneously (see text). [c] Conducted on a 50 mmol scale. [d] ^{31}P NMR yield = 43%, conducted at rt with heat activation (see Experimental Section). [e] ^{31}P NMR yield = 31%, conducted at rt with heat activation. [f] ~85% pure.

the workup. Table 2.3 illustrates that the scope of nickel-catalyzed alkyne hydrophosphinylation is very broad. The alkynes react in general and stereospecifically to form *E*-product, as a result of a *syn* addition, in high yields. However, poor regiocontrol is usually observed with unsymmetrical alkynes (1:1 - 3:1). The regioselectivity could be improved when significant steric or electronic biases are present. For example, alkynes with a terminal *tert*-butyl or trimethylsilyl group react regioselectively to afford the *β*-substituted *H*-phosphinate (Entries 5, 12, and 13). In the case of 2,4-hexadiyne, high regioselectivity is also observed (entry 8). Terminal alkynes give the linear product as the major isomer (Entry 11), but inductively electron withdrawing substituents (phenyl, alkene, or ethoxy group) increase the amount of the branched isomer (entries 6, 9, 10). Also Scheme 2.6 demonstrates the electronic effect of substituents on regiocontrol. When sterically demanding substituents are also electron withdrawing substituents, they are not able to direct the addition of alkyl phosphinate to alkynes to form selectively the less hindered regioisomer. In all the cases, we obtained ~1:1 ratio (Scheme 2.6).

Although, palladium-catalyzed hydrophosphinylation of terminal alkynes is superior in terms of regioselectivity, since it is more selective for linear products with Pd_2dba_3/xantphos and highly selective for the branched isomer with $Cl_2Pd(PPh_3)_2$/MeLi (Table 2.1), palladium is a poor catalyst compared to nickel for the hydrophosphinylation of internal alkynes with alkyl phosphinates. Alternatively, alkenyl-*H*-phosphinates could also be prepared stereo- and regiospecifically through cross-coupling of alkenyl halides. Nonetheless, the direct addition to an alkynes is often more convenient because the starting material is more generally available than the corresponding alkenyl halide.

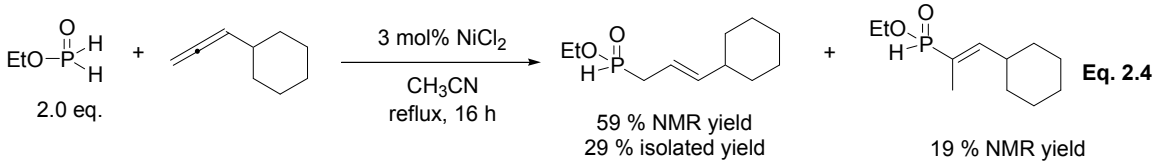
Scheme 2.6 Ni-catalyzed hydrophosphinylation of alkenes with sterically demanding and electron withdrawing substituents



The ratio of regioisomers was determined by ^{31}P NMR

Table 2.3 illustrates that a variety of alkynes react in satisfactory yields. With a propargylic chloride (Entry 14), an allylic product was obtained as the major product, apparently through the allene intermediate. Interestingly, in the case of 2-ethynylpyridine, the saturated product is obtained cleanly (Entry 15). At this time, the mechanistic details of this reaction remain unclear. Also acetylene gas can be employed as the substrate (Entry 4), but we were unable to isolate the product in good purity due to the fact that low

molecular weight vinyl-*H*-phosphinates are highly water soluble and sensitive to hydrolysis.

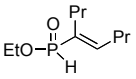
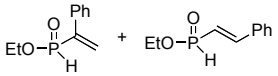
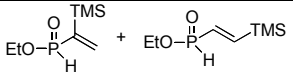
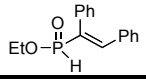


Eq. 2.4

Another particularly interesting substrate is cyclohexylallene (Eq. 2.4). The reaction provides the corresponding allylic-*H*-phosphinate in 59 % NMR yield, but the isolated yield was low (29 %).

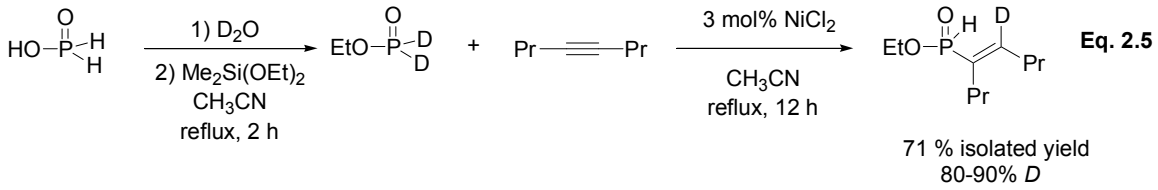
We also investigated the nickel-catalyzed hydrophosphinylation in a microwave reactor. Excellent yields were obtained in minutes under microwave irradiation, but no improvement in the regioselectivity with terminal alkynes was observed.

Table 2.4 Ni-Catalyzed hydrophosphinylation of alkynes with microwave heating

R_1	R_2	Catalyst	Time (min)	Temp (°C)	Power (W)	P (bars)	Product(s)	NMR yield, % [isomeric ratio] (Isolated yield, %)
Pr	Pr	$NiCl_2.6H_2O$	5	100	20	0		100 (73)
Pr	Pr	$NiCl_2$	5	100	25-30	1		100 (81)
Pr	Pr	$NiCl_2$	5	125	25	2		96
Pr	Pr	$NiCl_2$	1	125	25	2		93
Pr	Pr	$NiCl_2$	10	125	30	2		92
Pr	Pr	$NiCl_2$	1	150	40	5		85
Pr	Pr	$NiCl_2$	10	80	15	0		43
Ph	H	$NiCl_2$	5	80	15	0		91 [2.8/1] (41)
Ph	H	$NiCl_2$	1	100	20	0		97 [2.5/1]
Ph	H	$NiCl_2$	2.5	80	15	0		96 [3.2/1]
Ph	H	$NiCl_2$	2.5	60	0	0		91 [2.8/1]
TMS	H	$NiCl_2$	10	80	15	0		72 [0/1] (41)
TMS	H	$NiCl_2$	5	100	40	0.5		65 [1.7/1]
Ph	Ph	$NiCl_2$	5	100	25	0		100 (83)

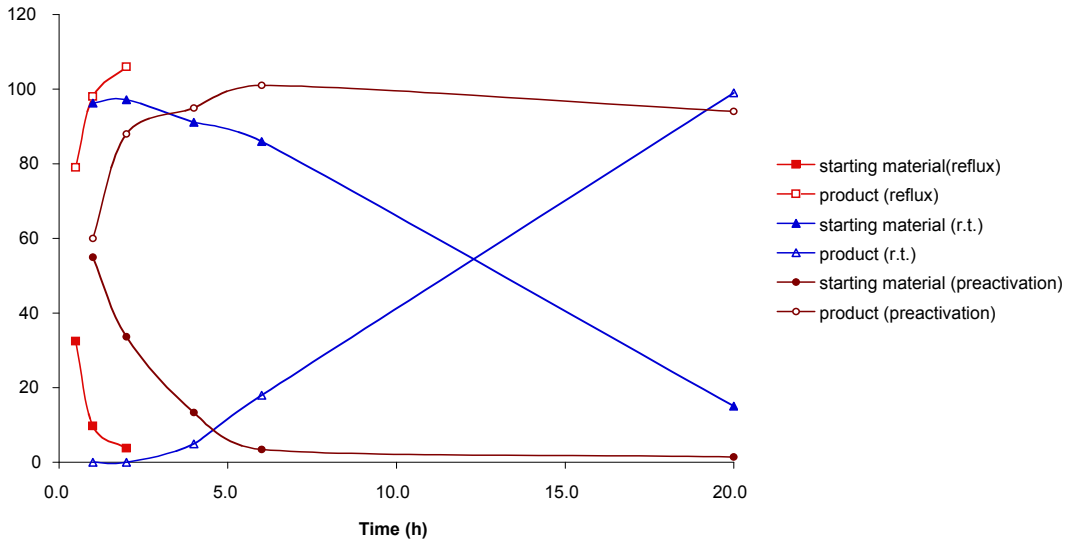
2.2.2 Mechanistic considerations

Although, the mechanism of nickel-catalyzed hydrophosphinylation was not studied in detail, it is likely to proceed through hydrometallation followed by reductive elimination, similarly to the palladium-catalyzed hydrophosphinylation (Scheme 2.5).[19] To confirm this thesis, we conducted the hydrophosphinylation of an internal alkyne with $EtOP(O)D_2$. As expected, the deuterium was incorporated *via* a *syn* addition in 80 - 90% isotopic purity (Eq. 2.5).



Eq. 2.5

Figure 2.1 Hydrophosphinylation of 4-octene with $EtOP(O)H_2$



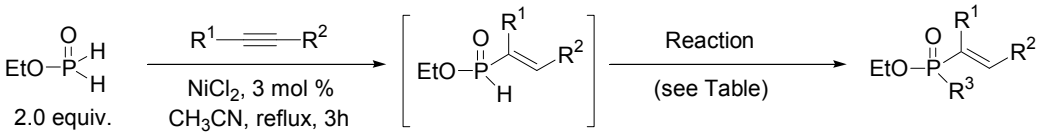
In the next stage, we studied the influence of the temperature on the formation of the catalytically active Ni(0) species by reduction of the precatalyst $NiCl_2$ with the alkyl phosphinate (Figure 2.1). The various runs were followed by both ^{31}P NMR (product formation) and GC chromatography (alkyne disappearance). While the reaction of 4-

octyne and ethyl phosphinate under reflux was completed within a few hours, this same reaction at rt reached completion in about 20 h, after an induction period (Figure 2.1). We assumed that lower temperature slows down the formation of catalytically active Ni(0), and thus affects the reaction time. Therefore, we conducted a preactivation process. A mixture of ethyl phosphinate and nickel chloride in acetonitrile was heated for 15 min to promote the formation of catalytically active Ni(0). Next, the solution was cooled down to rt for 15 min before alkyne addition. The reaction proceeded much faster, reaching completion within 6 h. This room-temperature protocol was also the one employed with acetylene gas (Table 2.3, entry 4). In addition, we obtained a good match between the data obtained from GC and from ^{31}P NMR, which also validates the NMR yield measurements.

2.2.3 Tandem one-pot alkyne hydrophosphinylation-functionalization

Since the *H*-phosphinates products of the nickel-catalyzed hydrophosphinylation are well-known to undergo various transformations to produce a variety of organophosphorus compounds, we turned our attention to synthetic applications of our reaction. The conversion of alkyl phosphinate into alkenyl-*H*-phosphinate, as it was demonstrated before, proceeds in very high yield (100 % ^{31}P NMR yield) under the influence of a nickel catalyst. Therefore, the transformation of the alkyl phosphinate into various functionalized organophosphorus compounds, without purification of the alkenyl-*H*-phosphinate intermediate, seems to be feasible.

Table 2.5 Tandem one-pot alkyne hydrophosphinylation-functionalization

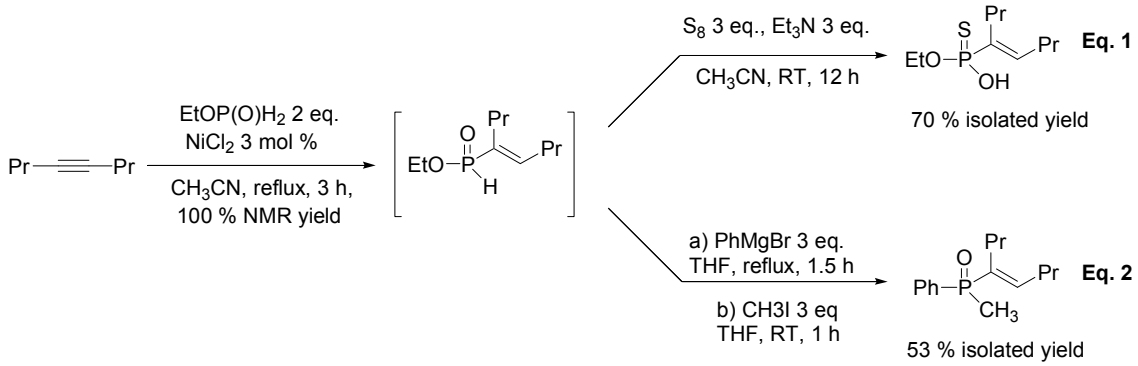


Entry	R_1	R_2	R_3	Reaction a	Isolated yield %
1	Pr	Pr	OEt	A	48
2	Pr	Pr	Ph	B	58
3	Pr	Pr	CH_2CH_2CN	C	63
4	Pr	Pr	allyl	D	76
5	Pr	Pr	Me	E	62
6	C≡CMe	Me	$CH_2CH_2CO_2Bn$	F	32
7	Me	*t*-Bu	OEt	G	57

[a] Reactions: (A) EtOH (55 equiv), CCl_4 (33 equiv), Et_3N (10 equiv), rt, 12 h. (B) PhI (3 equiv), Et3N (6 equiv), 2mol % $Cl_2Pd(PPh_3)_2$, reflux, 12 h. (C) acrylonitrile (3 equiv), DBU (3 equiv), rt, 6 h. (D) allyl chloride (3 equiv), BSA (6 equiv), reflux, 3 h. (E) Me_2SO_4 (2 equiv), BSA (6 equiv), rt, 3 h. (F) benzyl acrylate (3 equiv), DBU (3 equiv), rt, 6 h.

Indeed, some examples of tandem reactions are shown in Table 2.5. As expected, the oxidative esterification gave alkenylphosphonate diesters (Table 2.5, entries 1 and 7). Also tandem cross-coupling (Table 2.5, entry 2), conjugate addition (Table 2.5, entries 3 and 6), and alkylation (Table 2.5, entries 4 and 5) provided acceptable yields (generally 50 - 60%) of unsymmetrically disubstituted phosphinate esters. Even three phosphorus-carbon bonds could be formed in a single pot (Scheme 2.7). After hydrophosphinylation, a Grignard reagent displaces the ester group, and the resulting secondary phosphine oxide anion can be trapped with an electrophile in 53 % overall isolated yield. Another interesting example is the oxidation with elemental sulfur to prepare phosphonothioic acids (Scheme 2.7). The resolution of phosphonothioic acids with chiral amines has been reported in the literature as a way to access P-chiral compounds. Therefore, the developed nickel-catalyzed hydrophosphinylation could ultimately become useful for the preparation of P-chiral ligands.

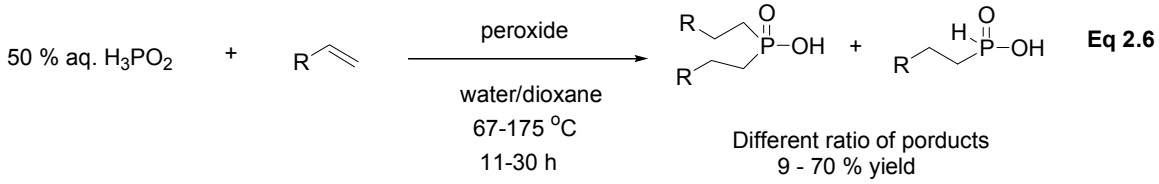
Scheme 2.7 Phosphonothioate and tertiary phosphine oxide via tandem reactions



In conclusion, we have developed a novel nickel-catalyzed phosphorus-carbon bond-forming reaction. The catalytic amount of inexpensive $NiCl_2$ makes this reaction particularly useful. The high yield of our hydrophosphinylation opens the possibility of the transformation of alkyl phosphinate into various functionalized organophosphorus compounds, without purification of the alkenyl-*H*-phosphinates intermediate. Taken with previously reported palladium-catalyzed hydrophosphinylation, radical-based hydrophosphinylation, and palladium cross-coupling of aryl and alkenyl halides, this methodology further expands the scope of *H*-phosphinic acid derivatives that can be obtained.

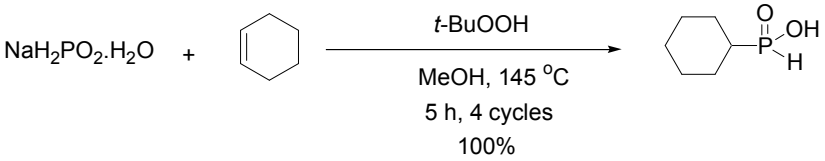
2.3 Radical Hydrophosphinylation. AIBN-i nitiated Radical Reactions of Alkyl Phosphinates.

The addition of phosphorus-centered radicals to olefins has been known for several decades.[69] In 1955, Williams and Hamilton developed the addition of aqueous H_3PO_2 to alkenes initiated by organic peroxides, at high temperatures (Eq. 2.6),[70] the reaction yields could be improved by using hazardous crystalline H_3PO_2.[71]

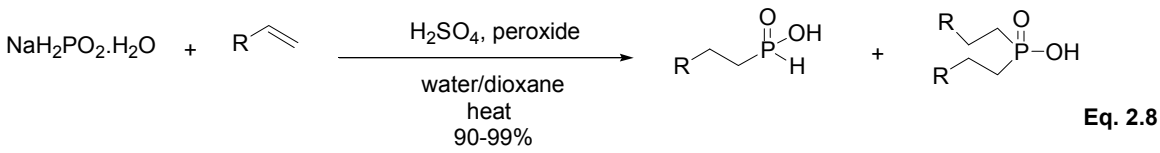


Eq 2.6

However, Nifant'ev and co-workers were mostly responsible for the synthetic development of this reaction, which has become one of the most convenient methods for the preparation of phosphinic acids (Eq. 2.7 and Eq. 2.8).[11,72] First, they studied the radical reaction of sodium hypophosphite in the presence of peroxides and found that *H*-phosphinic acids could be obtained in good yields (Eq. 2.7).[72a] Unfortunately, the reaction requires very high temperatures (130-150 °C), an autoclave, since sodium hypophosphite is soluble only in water or low-boiling alcohols (methanol, ethanol), and multiple additions of a peroxide initiator, thereby significantly complicating the reaction in practice. To avoid solubility problems of sodium hypophosphite, they generated hypophosphorous acid in situ, by treating sodium hypophosphite with sulfuric acid (Eq. 2.8)[11]. The acidic conditions of the reaction mixture catalyze the breakdown of the peroxide initiators, allowing for lower reaction temperatures and more efficient radical formation.

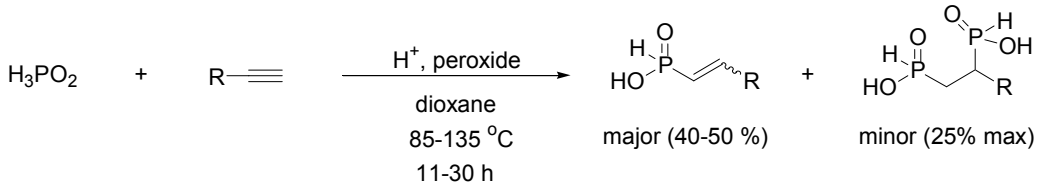


Eq. 2.7



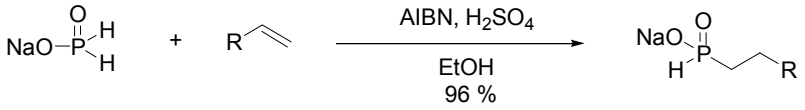
Eq. 2.8

Nifant'ev and co-workers also investigated the thermal, peroxide-initiated radical reaction of hypophosphorous acid with alkynes.[73] They obtained several products, depending on the employed conditions (Eq 2.9). A mixture of *trans*- and *cis*-alkenyl-*H*-phosphinic acids was produced as the major component, along with minor amounts of disubstituted 1,2-bis-*H*-phosphinic acids.



Eq. 2.9

In 1988 Karanewsky introduced AIBN as radical initiator for the hydrophosphinylation reaction, providing a major practical breakthrough (Eq. 2.10).[12] However, the conditions remained strongly acidic and incompatible with acid-sensitive functionalities.



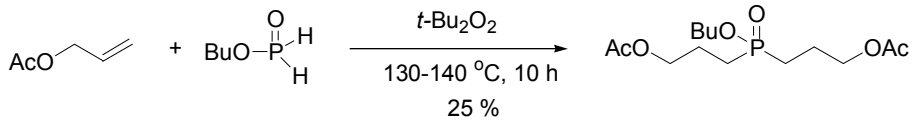
Eq. 2.10

Recently, Montchamp reported a more efficient method for the radical hydrophosphinylation at rt (Eq. 2.11 and Eq. 2.12).[21] H_3PO_2, its salts (sodium, anilinium and ammonium Eq. 2.11), or even alkyl phosphinates (Eq. 2.12) add to alkenes in the presence Et_3B /O_2 as initiator to produce *H*-phosphinic acid derivatives in good yields.

Eq. 2.11

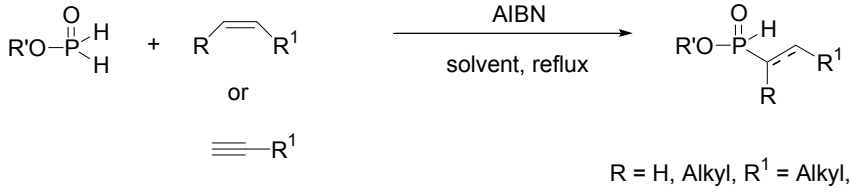
Eq. 2.12

The mild conditions (rt) of Montchamp's radical hydrophosphinylation are critical when alkyl phosphinates are used as starting materials (Eq. 2.12). Alkyl phosphinates were originally prepared by Nifant'ev method ($BuOP(O)H_2$, Scheme 2.2, Eq. 2)[57] or Fitch method ($MeOP(O)H_2$, Scheme 2.2, Eq. 1)[56] and they were air, moisture sensitive and thermally unstable. Only one example of an alkyl phosphinate in a thermally-initiated radical reaction had ever been reported. Aleksandrova reacted butyl phosphinate with allyl acetate in the presence of di-*tert*-butyl peroxide (130-140 ^{o}C, 10 h, sealed tube) and obtained bis-(3-acetoxypropyl)-phosphinate in 25% yield (Eq. 2.13).[74] Interestingly, the symmetrically disubstituted phosphinate was obtained, probably due to the harsh forcing conditions.



Eq. 2.13

Since, the alkoxysilane-based esterification (Eq. 2.1)[58] developed in our laboratory, provides alkyl phosphinate solutions which have exceptional thermal stability in various solvents, we were able to investigate the thermal, AIBN-initiated, radical reaction of alkyl phosphinate (prepared from H_3PO_2 and $Me_2Si(OEt)_2$) with alkenes and alkynes (Eq. 2.14).[22]



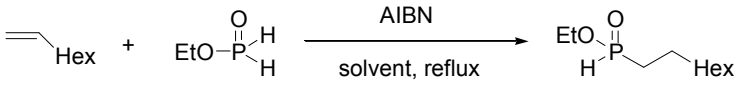
Eq. 2.14

R = H, Alkyl, R^1 = Alkyl, R' = Et, Bu

2.3.1 Reaction of alkyl phosphinates with alkenes

To test the possibility of the reaction depicted in Eq. 2.14, the reaction of 1-octene and ethyl phosphinate (2.0 and 2.5 equiv.) in the presence of AIBN in refluxing solvent (acetonitrile, THF) was investigated. The addition of 1-octene to ethyl phosphinate in the presence of 0.1 equiv. of AIBN during 6 h of reflux did not give satisfactory results. We obtained ethyl octyl-*H*-phosphinate in 50 % and 25 % ^{31}P NMR yield in acetonitrile and THF respectively, when 2.5 equiv. of ethyl phosphinate was used (Table 2.6, Entry 2 and 6). Therefore, we improved the reaction's yield by adding another 0.1 equiv. of AIBN and refluxing reaction mixture during an additional 10 h (Table 2.6, Entry 4 and 8). Thus, 0.2 equiv. of AIBN (0.1 + 0.1 equiv.) and 2.5 equiv. of ethyl phosphinate in acetonitrile resulted in 72 % of isolated yield of ethyl octyl-*H*-phosphinate (Table 2.7, Entry 1).

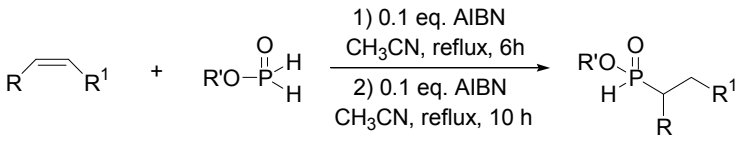
Table 2.6 Reaction of ethyl phosphinate with 1-octene

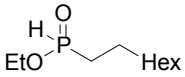
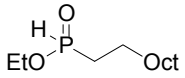
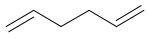
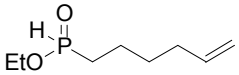
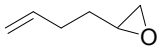
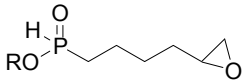
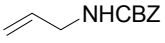
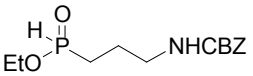
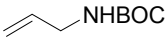
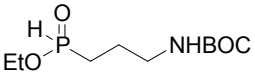
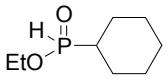
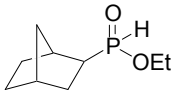
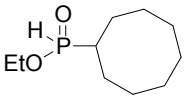
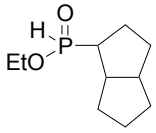


Entry	Solvent	Equiv. of AIBN	Equiv. of $EtOP(O)H_2$	^{31}P NMR yield %
1	CH_3CN	0.1	2.0	30
2	CH_3CN	0.1	2.5	50
3	CH_3CN	0.1 + 0.1	2.0	70
4	CH_3CN	0.1 + 0.1	2.5	100
5	THF	0.1	2.0	20
6	THF	0.1	2.5	25
7	THF	0.1 + 0.1	2.0	30
8	THF	0.1 + 0.1	2.5	40

Additionally, the diethyl phosphite by-product does not add to the olefin under the reaction conditions, and disubstitution from over-reaction of the *H*-phosphinate product is still not observed. Although the radical reaction of *H*-phosphinate esters with unsaturated

Table 2.7 Reaction of alkyl phosphinate with alkenes

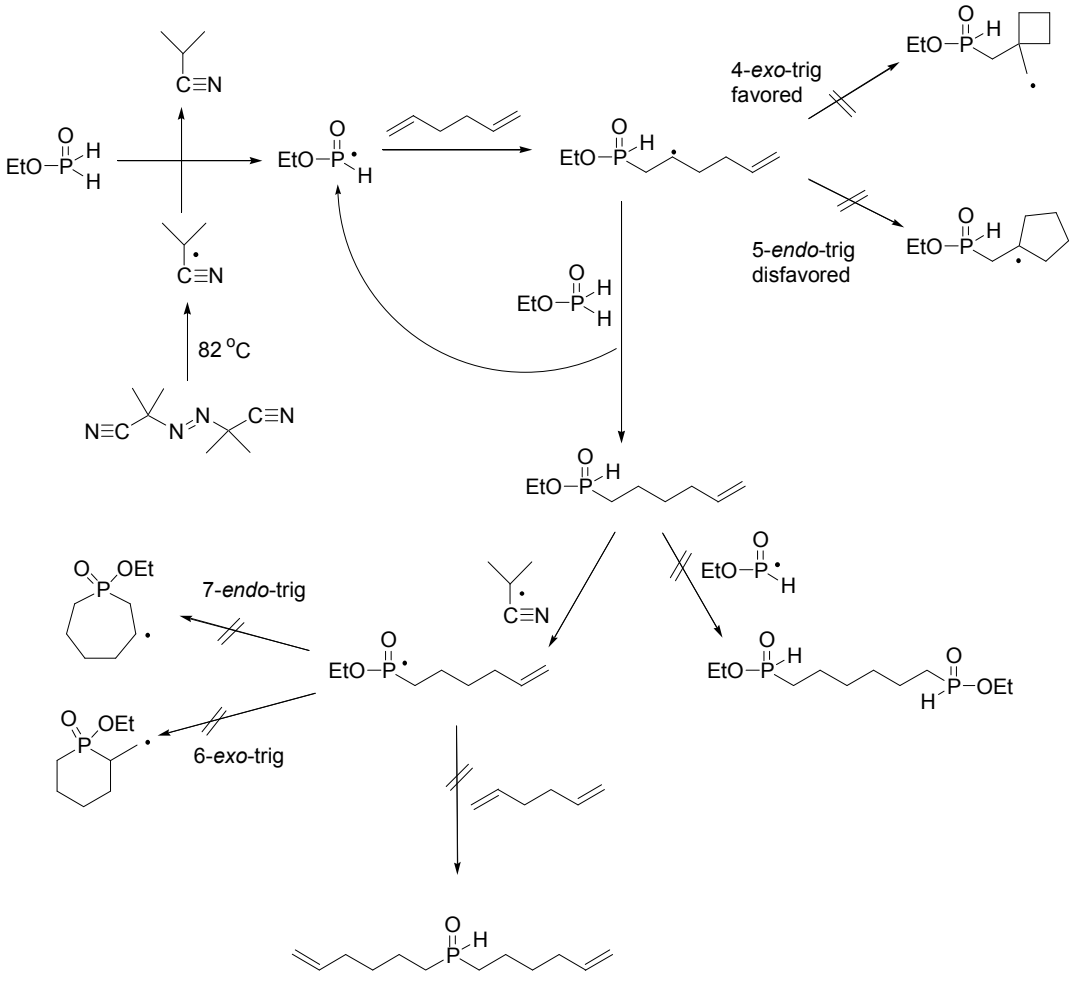


Entry	Alkene	Product	Isolated Yield (%)
1			72
2			68
3			76
4a 4b			R = Et, 61 R = Bu, 58
5			80
6			75
7			40
8			75
9			68
10			63

compounds is well-known in the literature[75] to produce disubstituted phosphinates, the chain process is inefficient and yields are generally low. The reaction is also dependent upon the structure of the *H*-phosphinate ester: for example, Montchamp showed that PhP(O)(OBu)H reacts in acceptable yields under Et_3B/air initiation, while other starting materials did not give the disubstituted phosphinic product.[21] Therefore, it is not

unexpected that the AIBN-initiated reaction provides only *H*-phosphinate esters, and the formation of disubstituted products was not observed.

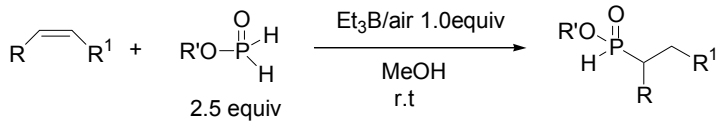
Scheme 2.8 Reaction of ethyl phosphinate with 1,5-Hexadiene in the presence of AIBN

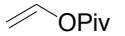
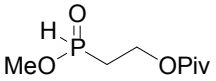
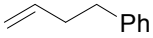
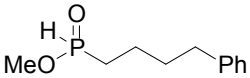
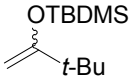
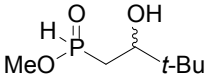
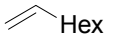
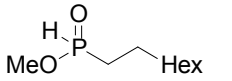
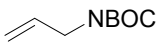
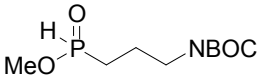
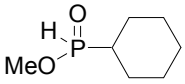
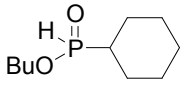
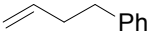
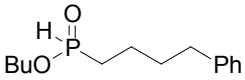
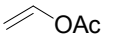
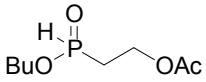
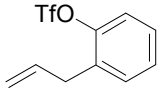
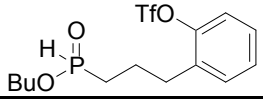


Results obtained with other unsaturated substrates are shown in Table 2.7. For the most part isolated yields were in the 60 - 80% range. As expected, there was virtually no difference between 1-octene and 1-decene (Entries 1 & 2, respectively). 1,5-Hexadiene also reacted uneventfully to produce the mono-hydrophosphinylated product: ethyl hexenyl-*H*-phosphinate in 76 % isolated yield (Entry 3). Radical cyclization to form four

membered ring (4-*exo*-trig) or P-heterocycle did not take place under the reaction conditions. Also the formation of bis substituted product did not occur (Scheme 2.8).

Table 2.8 Reaction of alkyl phosphinate with alkenes in the presence of Et_3B



Entry	Alkene	Product	Isolated Yield (%)
1			40
2			45
3			55
4			96
5			37
6			60
7			60
8			65
9			52
10			59

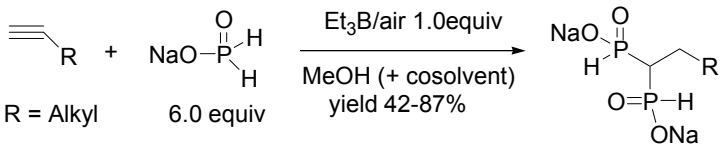
Functional groups, such as epoxide (Entry 4, Table 2.7), BOC (Entry 5, Table 2.7), and CBZ (Entry 6, Table 2.7) were also tolerated since the reaction takes place under neutral conditions. Cyclic alkenes could also be used. Although the isolated yield of ethyl cyclohexyl-*H*-phosphinate is only moderate (the reaction was conducted in a sealed tube,

since b.p. of cyclohexyl is 50 ^{o}C; Entry 7, Table 2.7), other substrates worked well (Entries 8-10, Table 2.7). Since the phosphorus atom is a chiral center, equal amounts of diastereomeric products are obtained in entries 8 and 10.

As mentioned before, alkyl phosphinates (methyl and butyl) react with alkenes in the presence of Et_3B/O_2 to produce alkyl-*H*-phosphinate (Eq. 2.12)[21]. This method, previously developed in our laboratory, gives comparable yields of alkyl-*H*-phosphinate (Table 2.8) to the AIBN method. Since there is almost no difference in yields, both methods can be used. However, AIBN initiated hydrophosphinylation is more economical, since 0.2 equiv. of AIBN is cheaper than 1.0 equiv. of Et_3B.

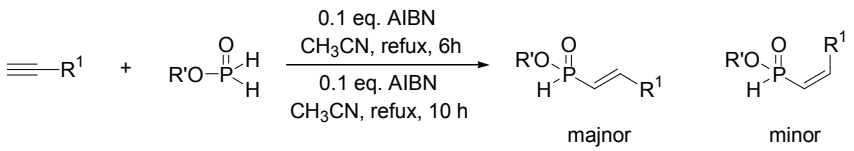
2.3.2 Reaction of alkyl phosphinates with alkynes

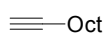
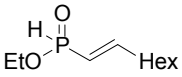
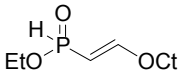
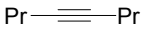
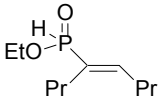
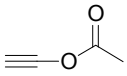
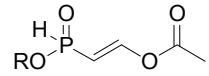
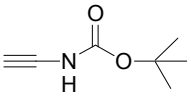
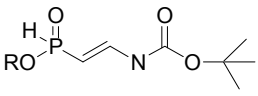
The reaction of terminal alkynes with alkyl phosphinates in the presence of AIBN is particularly interesting. We are aware of only one report of the synthesis of alkenyl-*H*-phosphinic acids *via* radical reaction (Eq. 2.9). Nifant'ev obtained a mixture of *trans*- and *cis*-alkenyl-*H*-phosphinic acids as the major component, along with minor amounts of disubstituted 1,2-bis-*H*-phosphinic acids.[73] Also our reaction of sodium hypophosphite with alkynes in the presents of Et_3B did not give satisfactory results. A mixture of alkenyl-*H*-phosphinic acids and 1-alkyl-1,1-bis-*H*-phosphinates was obtained. In the latter case, the reaction conditions were optimized to obtain 1-alkyl-1,1-bis-*H*-phosphinates in good yield (Eq. 2.15).[10]



Eq. 2.15

Table 2.9 Reaction of alkyl phosphinate with alkenes

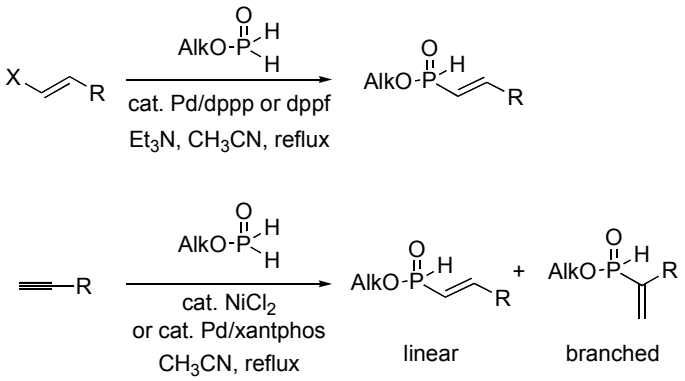


Entry	Alkyne	Product	Isolated Yield
1			68
2			59 trans/cis 2.5:1
3			18
4a 4b			R = Et, 54 R = Bu, 51
5a 5b			R = Et, 63 R = Bu, 65

Hence, we were interested in investigating the reaction of alkyl phosphinates with alkynes in the presence of AIBN to obtain alkenyl-*H*-phosphinates. To test the possibility of this reaction, the reaction of 1-octyne and 2.5 equiv. of ethyl phosphinate in the presence of AIBN in refluxing acetonitrile was performed (Table 2.9, Entry 1). The addition takes place smoothly delivering ethyl octenyl-*H*-phosphinate in 80 % ^{31}P NMR yield and 3.5:1.0 *trans/cis* ratio. After purification, the *trans* product was obtained exclusively in 68% isolated yield possibly due to the loss of *cis* isomer during the purification step or isomerization of *cis* product into *trans* product on silica gel. Also reaction with 1-decyne gave good *trans* selectivity 3.0:1.0 *trans/cis* ratio in the reaction mixture, and after purification the product was obtained in 2.5:1.0 ratio and 59% isolated yield (Table 2.9, Entry 2). However, reaction with internal alkynes did not give satisfactory results (Table 2.9, Entry 3) and we obtained the product in only 18% isolated yield. These compounds (Table 2.9, Entry 1, 2 and 3) can also be accessed (Scheme 2.9)

via cross-coupling of the corresponding alkenyl halides,[18c] or via palladium-,[19a] or nickel-catalyzed hydrophosphinylation[20] of alkynes. The former method requires alkenyl halides or triflates which are not always readily available, and the latter method gives mixtures of linear and branched isomers which are not readily separated. Thus, the present radical reaction fills a significant methodological gap. However, our $NiCl_2$-catalyzed hydrophosphinylation is far superior to the present method with internal alkynes.[20]

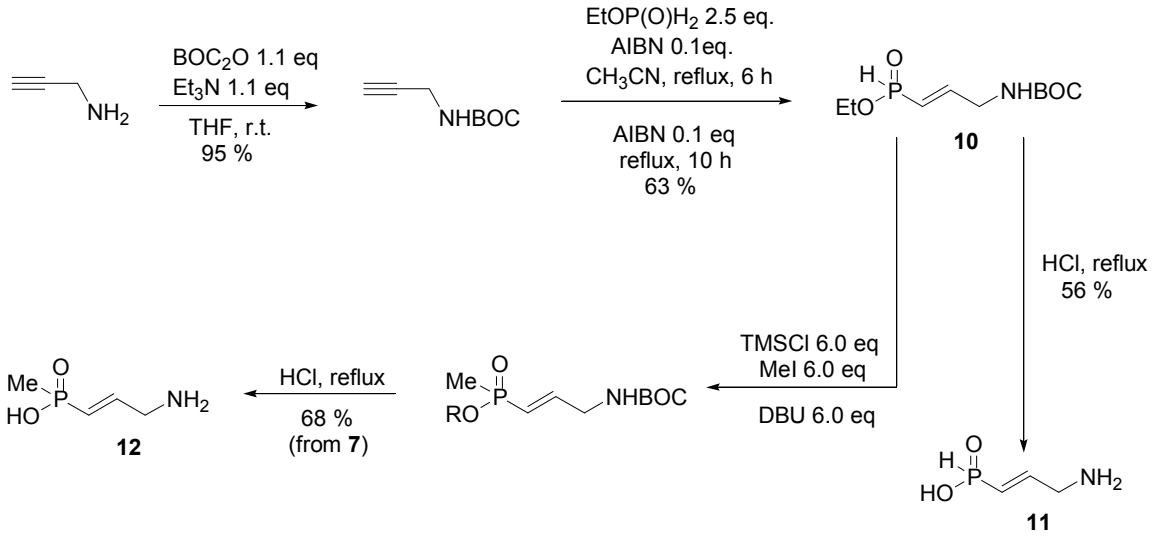
Scheme 2.9 Alkenyl-H-phosphinates alternate approaches



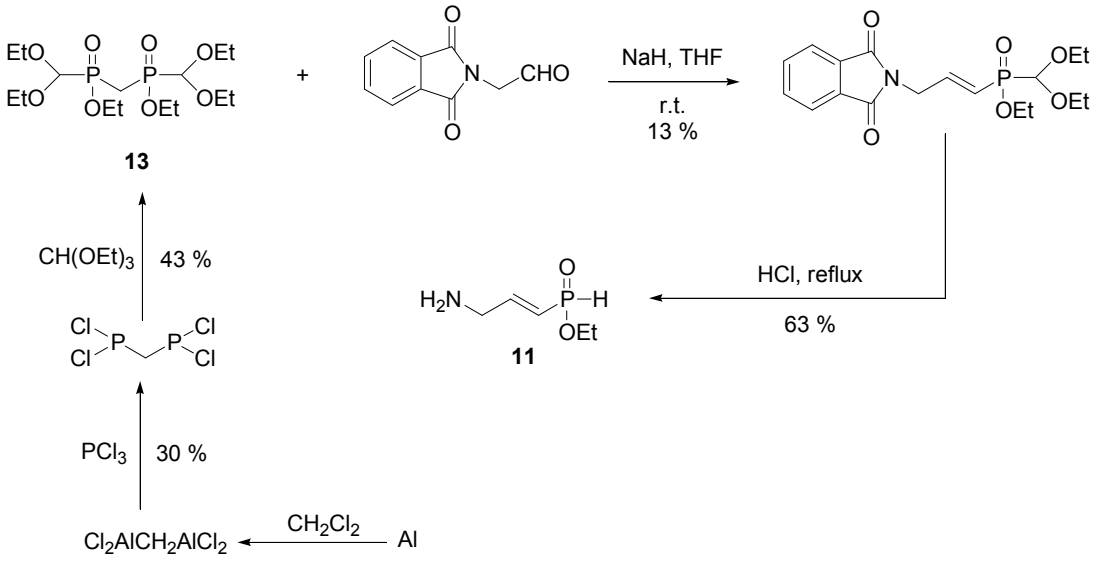
A synthetic application of our AIBN-initiated hydrophosphinylation is shown in Scheme 2.10. When BOC-protected propargyl amine reacted under the standard conditions, the *trans* isomer of (3-*tert*-butoxycarbonylaminopropen-1-yl)phosphinic acid ethyl ester **10** was obtained exclusively in 63% isolated yield. Deprotection with HCl afforded (*trans*-3-aminopropen-1-yl)phosphinic acid **11**. Compound **11** is a known GABA analog, which was previously synthesized in two steps from diethyl methylenebis(diethoxymethyl)phosphinate **13** (a reagent which itself requires

cumbersome multistep synthesis) and 2-phthalimidoacetaldehyde in only 8% yield (Scheme 2.11).[76]

Scheme 2.10 Synthesis of GABA analogs **11** and **12** from ((*trans*)-3-aminopropen-1-yl)phosphinic acid



Scheme 2.11 Literature synthesis of GABA analog **11**



Similarly, GABA analog **12** was prepared from **10** in 68% yield. During the alkylation step, both the ester and acid are obtained, but the mixture was directly converted into **12**. Propargyl acetate is another interesting substrate, as this alkyne fails with our other hydrophosphinylation methodologies. Both nickel- and palladium-catalyzed processes give mixtures of products due not only to poor regioselectivity, but also to π-allyl metal intermediates, and isolation of pure compounds was not possible. With the present thermal radical reaction ethyl *trans*-3-acetyl-propen-1-yl phosphinate was obtained in 53% isolated yield (Table 2.9, entry 4). The potential of this synthon in palladium-catalyzed allylations remains to be fully investigated.

Not surprisingly, butyl phosphinate ($BuOP(O)H_2$) reacted like ethyl phosphinate (Table 2.7, entry 4; Table 2.9, entries 4 and 5). Virtually identical yields were obtained with either phosphinate.

The present reaction offers a simple alternative to other methods. Some unsaturated substrates do not react in satisfactory yield, and in these cases other methods appear superior. However, with terminal alkynes, the corresponding *trans*-alkenyl-*H*-phosphinates are obtained in good yield, thus providing the best synthetic approach to these compounds. Straightforward application to the synthesis of biologically active GABA analogs **11** and **12** is also demonstrated. This thermal radical reaction provides yet another tool in the growing arsenal of phosphorus-carbon bond formations and further showcases our alkyl phosphinate preparation method.

2.4 Conclusion

The remarkable thermal stability of alkyl phosphinates, prepared by the alkoxysilane method allowed us to develop novel methodologies for the synthesis of *H*-phosphinate esters. We have demonstrated that AIBN-initiated hydrophosphinylation and nickel-catalyzed hydrophosphinylation fills a significant methodological gap. The nickel-catalyzed addition of alkyl phosphinates to internal alkynes generates products (alkenyl-*H*-phosphinate), which could be obtained directly only *via* cross coupling reaction of alkyl phosphinates with alkenyl halides. High yielding nickel-catalyzed conversion allowed functionalization of the alkyl phosphinates into various organophosphorus compounds, without purification of alkenyl-*H*-phosphinate intermediate. On the other hand AIBN-initiated hydrophosphinylation provides one of the best synthetic approaches for the preparation of *trans*-alkenyl-phosphinates. We demonstrated that *trans*- (3-*tert*-butoxycarbonylaminopropen-1-yl)phosphinic acid ethyl can be easily converted into biologically active GABA analogs. Furthermore, our radical addition is the only known possibility for the preparation of ethyl *trans*-3-acetyl-propen-1-yl phosphinate. Finally, the AIBN-initiated hydrophosphinylation and nickel-catalyzed hydrophosphinylation taken with the previously reported palladium-catalyzed hydrophosphinylation, Et_3B-initiated hydrophosphinylation, and palladium cross-coupling of aryl and alkenyl halides further expand the scope of *H*-phosphinic acid derivatives that can be obtained.

Chapter III: Synthesis of the GABA analogs

3.1 Introduction

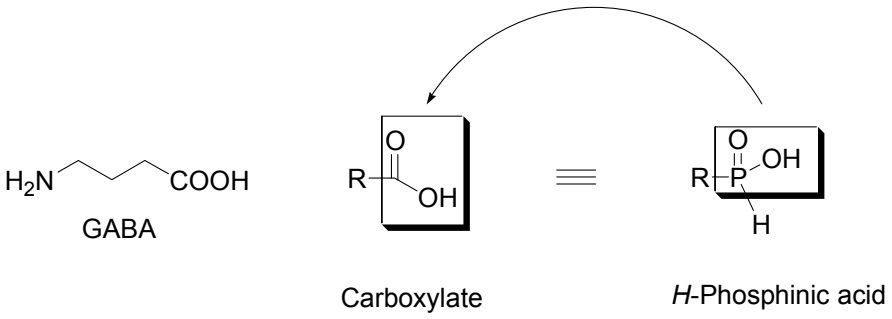
γ - Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS).[77] GABA and its receptors affect brain function and mediate a variety of neurological and physiological responses including those involved in several disorders and diseases. Analgesia, anxiety, epilepsy, schizophrenia, Alzheimer's disease and Huntington's disease are all, at least in part, linked to the GABA system. Three major types of GABA receptors (designated as $GABA_A$, $GABA_B$, and $GABA_C$) have been identified, and the elucidation of their specific roles continues to be the object of intense research efforts. A large body of literature is available on the first two receptors,[77,78] but $GABA_C$ receptors[79] have been comparatively less studied and their physiological role is currently not very well understood. $GABA_A$ receptors are ligand-gated chloride channels that mainly function as postsynaptic receptors and mediate fast synaptic inhibition.[78a,80] They contain multiple allosteric binding sites for benzodiazepines, picrotoxin, barbiturates, centrally active steroids, avermectin and propofol. $GABA_B$ receptors are metabotropic and are located mainly on nerve terminals, where they mediate slow synaptic inhibition. A major function of $GABA_B$ receptors is to modulate the release of several neurotransmitters, such as glutamate[81], dopamine[82], noradrenaline[82], serotonin[82], substance P[83], cholecystokinin[84] and somatostatin[85] *via* presynaptic $GABA_B$ binding sites. $GABA_C$ receptors are ligand-gated chloride ion channels and are only located in neurons of the retina, where they mediate slow and sustained responses.[78a,79,80] A fourth possible target for GABA analogs is the enzyme γ-

aminobutyric acid aminotransferase (GABA-AT) which degrades GABA (an inhibitory neurotransmitter) to produce glutamate (a stimulatory neurotransmitter). Inhibition of GABA-AT to maintain high levels of GABA is of interest, for example in the treatment of drug addiction, or to achieve anticonvulsant activity.[86] Compounds that influence the GABA receptors activity (agonists, partial agonists, and antagonists) have the potential to mediate various CNS diseases and provide scientists with a better understanding of the architecture and specific functioning of GABA receptors. The structural variety of these compounds is astonishing. It is difficult or even impossible to predict the biological activity of a molecule in a particular class of GABA receptors due to the tremendous complexity of neurochemistry. Therefore the preparation of new GABA analogs is very important both to study GABA receptors, and to achieve medicinal activity.

3.2 Phosphinic Acids as GABA Analogs

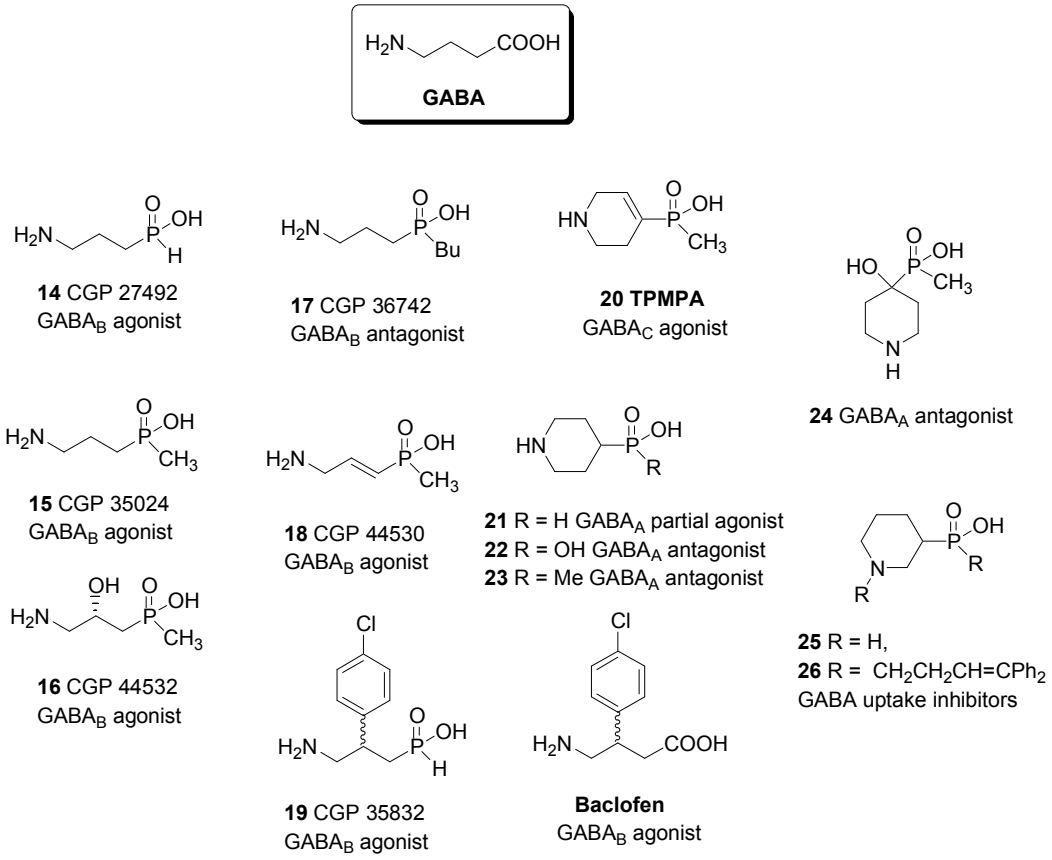
Phosphinic acids have become important targets in the search for biologically active GABA analogs, due to their ability to mimic the carboxylic acid functionality (Figure 3.1).

Figure 3.1 Isosteric carboxylate replacement



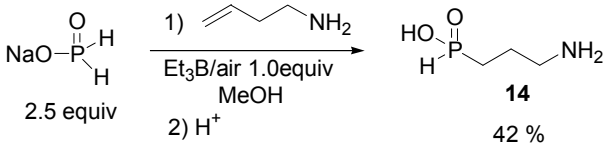
Since 1995, several compounds of this type have been reported (Figure 3.2). The majority of the work originates from the Froestl's group at Novartis (formerly Ciba Geigy).[87,88] A few other compounds have been prepared by Krogsgaard-Larsen,[89] Overman,[79] and Chebib.[90] As can be seen in Figure 3.2, a wide range of activities against the GABA receptors can be achieved. For example, compound **14** (CGP 27492) is the simplest *H*-phosphinic acid analog of GABA and the most potent $GABA_B$ agonist *in vitro*, but it is much less active *in vivo*, presumably because it is oxidized to the corresponding phosphonic acid, itself a weak $GABA_B$ antagonist.[88] In contrast TPMPA **20** is a potent and selective antagonist of $GABA_C$ receptors.[79]

Figure 3.2 Phosphinic acids as GABA analogs

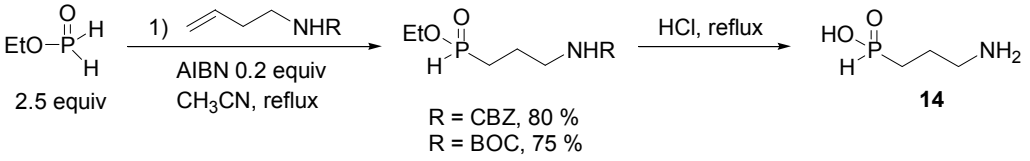


As demonstrated in Chapter II, several methodologies for the formation of phosphorus-carbon bond were developed in our laboratory over the past several years. Our methodologies often provide more-direct synthetic routes to known, biologically active organophosphorus compounds. For example, 3-aminopropylphosphinic acid **14** (Figure 3.2, CGP 27492) was prepared by Montchamp in a single step from allylamine and sodium hypophosphite *via* his Et_3B-initiated radical reaction (Scheme 3.1, Eq.1).[21] Although the isolated yield was only 42 %, it is already comparable to, or better than, the published multistep syntheses of **1**.[88,91] In another approach, using our AIBN-initiated radical hydrophosphinylation of BOC or CBZ protected allylamine with ethyl phosphinate, the corresponding ethyl *H*-phosphinates were obtained in 75 % and 80 % isolated yield (Chapter II, Table 2.6, Entry 6 and 5),[22] which could be easily converted into 3-aminopropylphosphinic acid **14** under acidic conditions (Scheme 3.1, Eq. 2).

Scheme 3.1 Synthesis of GABA analog **14** *via* radical reaction



Eq. 1

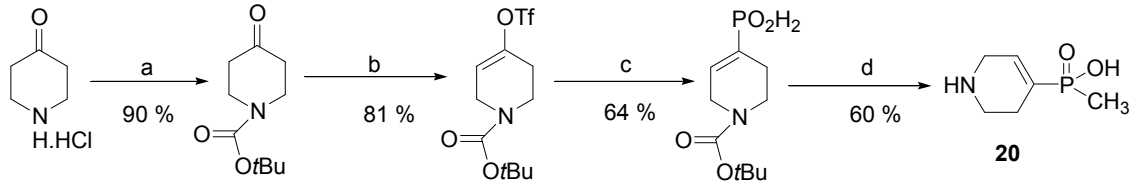


Eq. 2

Another example is the synthesis of (*trans*-3-aminopropen-1-yl)phosphinic acid (Chapter II, Scheme 2.10, compound **11)** and (*trans*-3-aminopropen-1-yl)-methyl-phosphinic acid (Chapter II, Scheme 2.10, compound **12)**. Our AIBN-initiated radical

hydrophosphinylation[22] is one the best synthetic approaches for the preparation of these active $GABA_B$ analogs. Montchamp also demonstrated that biologically active $GABA_C$ analog **20** can be obtained using his cross-coupling reaction (Scheme 3.2).[18b]

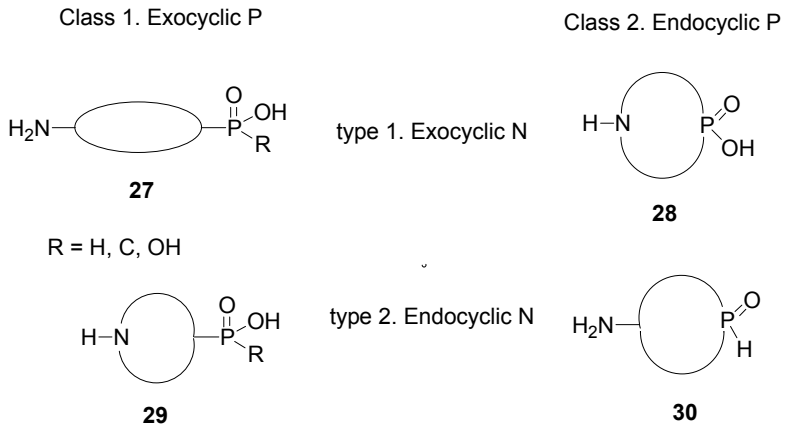
Scheme 3.2 Synthesis of GABA analog **20** *via* cross-coupling



(a) BOC_2O, Et_3N, DMF, rt. (b) (i) LDA, THF, -78°C, (ii) $PhNTf_2$, -78°C to 0°C. (c) $PhNH_3.H_2PO_2$, $Pd(OAc)_2$, dppp, Et_3N, THF, reflux. (d) (i) DBU, MeI, TMSCl, -78°C to rt, (ii) Dowex 50 H^+.

It is important to note that compound **20** is an example of GABA analogs, which is conformationally-restricted. Since the inhibitory neurotransmitter GABA is a conformationally flexible molecule and the receptors selectively bind specific conformers, the use of conformationally-restricted GABA analogs should increase binding affinity and selectivity.

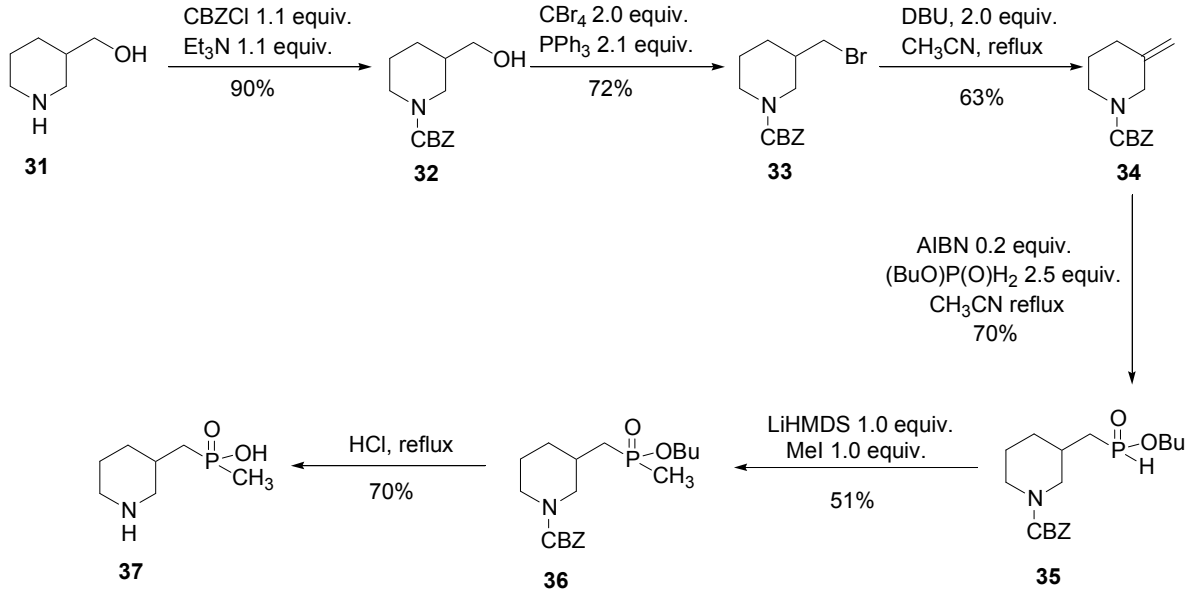
Figure 3.3 Structural classes and types of phosphinyl GABA analogs



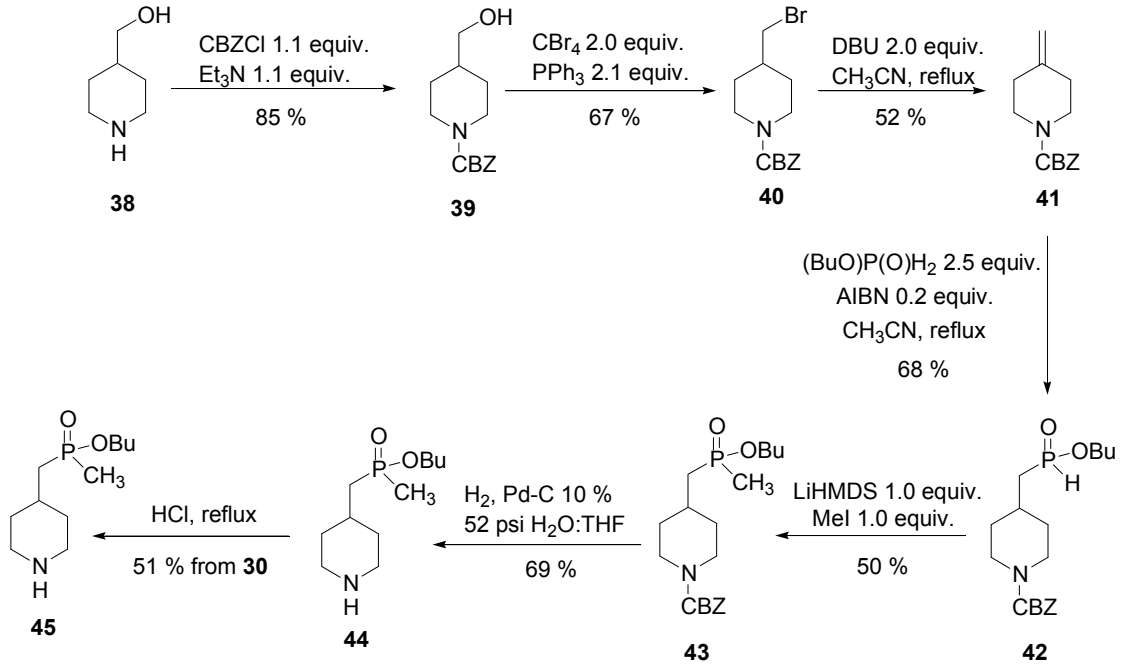
Therefore we decided to prepare and evaluate new conformationally-restricted phosphinyl GABA analogs. These analogs can be divided into two classes (Figure 3.3). Compounds **27** and **29** belong to the first class, where the phosphorus atom is exocyclic. Compounds **28** and **30** belong to the second class, where the phosphorus atom is endocyclic (phosphorus heterocycles).

The examples of new exocyclic phosphorus GABA analogs are compounds **37** (Scheme 3.3), **45** (Scheme 3.4), **47** (Scheme 3.5) and **49** (Scheme 3.5). GABA analogs **37** and **45** were synthesized from 3- and 4-piperidine methanol in respectively 6 and 7 steps with 11% and 5% overall yield. CBZ-protected 3- and 4-piperidine methanol obtained in 90% and 85% isolated yield from the commercially available amine were converted into bromides in the presence of bromoform and triphenylphosphine in respectively 72% and 67% isolated yield. Alkenes **34** and **41** were then produced *via* elimination reaction with DBU in 63% and 52% isolated yield. The first phosphorus-carbon bond formation was accomplished *via* AIBN-initiated hydrophosphinylation of **31** and **41** with butyl phosphinate in respectively 70% and 68% isolated yield. The second phosphorus-carbon bond formation *via* alkylation reaction in the presence of LiHMDS (this method also was developed in our laboratory)[23] was achieved in 51% and 50% isolated yield. The attempted hydrogenolysis of compounds **43** with hydrogen in the presence of palladium did not give satisfactory results (Scheme 3.5), therefore the deprotection reaction was accomplished with refluxing HCl to yield compound **37** and **45** in 70% and 51% isolated yield (Scheme 3.3 and 3.4).

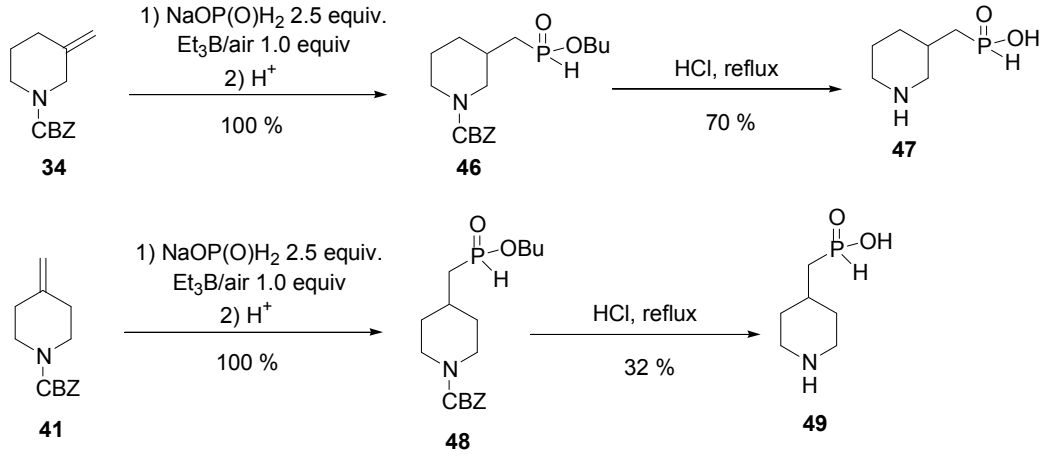
Scheme 3.3 Synthesis of methyl-piperidin-3-ylmethyl-phosphinic acid



Scheme 3.4 Synthesis of methyl-piperidin-4-ylmethyl-phosphinic acid



Scheme 3.5 Synthesis of piperidin-3 and -4-ylmethyl-phosphinic acid

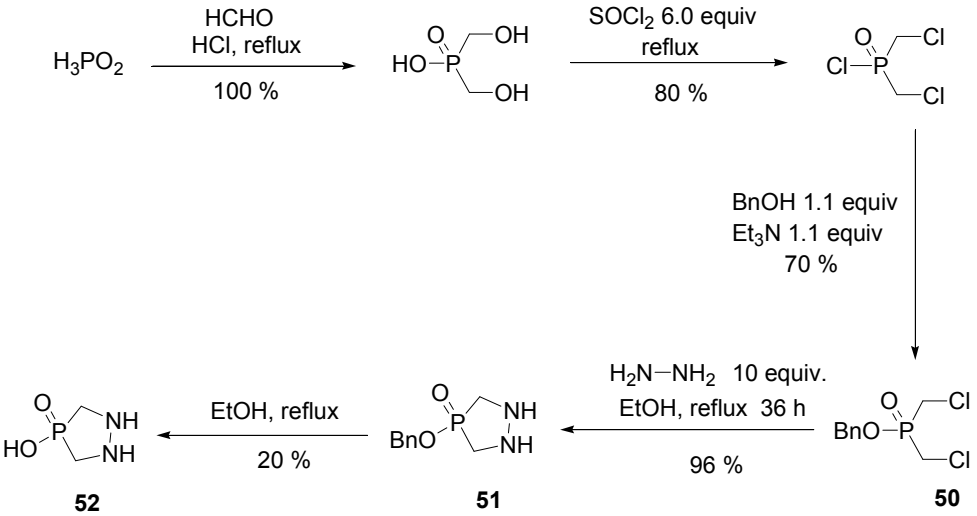


The precursors of the GABA analogs **47** and **49** were synthesized in 100 % isolated yield form alkenes **34** and **41** *via* Et_3B-initiated radical hydrophosphinylation with sodium hypophosphite (Scheme 3.5). The hydrogenolysis of compounds **46** and **48** with hydrogen in the presence of palladium did not result in the formation of products **47** and **49**. Fortunately, these compounds could be obtained from reaction with refluxing HCl, in 66 % and 32 % isolated yield. The overall yields of **47** and **49** after 5 steps, starting from 3- and 4-piperidine methanol were 27 % and 9 % respectively. Both compounds **34** and **41** were converted into corresponding *H*-phosphinic acids in 100 % ^{31}P NMR yield. The lower isolated yield of product **49** is possibly due to the loss of this compound during the workup.

An example of endocyclic GABA analogs is compound **52**, which was synthesized from benzyl [bis(chloromethyl)]phosphinate **50** and 10 equiv of hydrazine in 100 % ^{31}P NMR yield (Scheme 3.6). The solvent (EtOH) and an excess of the hydrazine was removed in vacuo to afford compound **51** as a thick oil in 96 % purity. We were not able to purify compound **51** *via* column chromatography, due to its poor solubility in organic solvents,

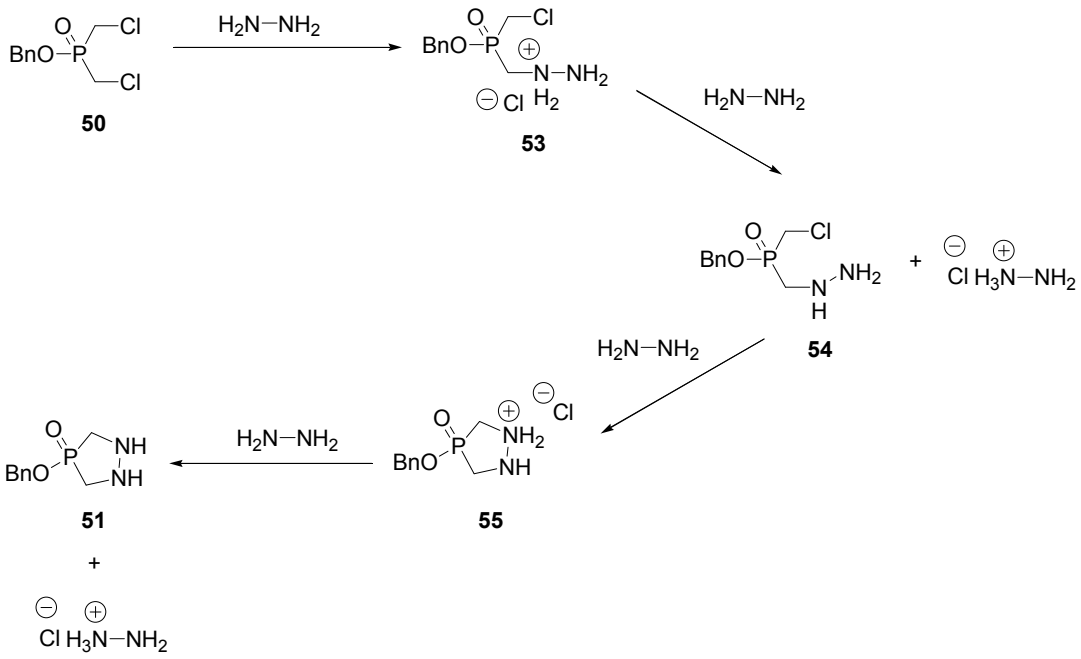
except EtOH or DMSO. Fortunately, attempted recrystallization in hot EtOH afforded compound **52** as colorless crystals in 20 % isolated yield and >99 % purity.

Scheme 3.6 Synthesis of 4-oxo-4λ^5-[1,2,4] diazaphospholidin-4-ol



Interestingly, the formation of compound **51** was conducted in refluxing EtOH during 36 h and the cleavage of benzyl group was not observed. However when this same compound was refluxed in EtOH for a few minutes in the absence of hydrazine and cooled down to 0 ^{o}C, the cleavage of benzyl group occurred in 20 % isolated yield. It is also interesting to note that the formation of product **51** requires a large excess of hydrazine (we used 10 equiv.), possibly due to the formation and then the deprotonation of intermediates **53** and **55** (Scheme 3.7). The use of 3.0 equiv. of hydrazine was not efficient enough to promote the cyclization process. Also the mixture of hydrazine and Et_3N did not yield product **51**.

Scheme 3.7 Mechanism of the formation of 4-oxo-4λ^5-[1,2,4] diazaphospholidin-4-ol



3.3 Biological Evaluation of GABA Analogs

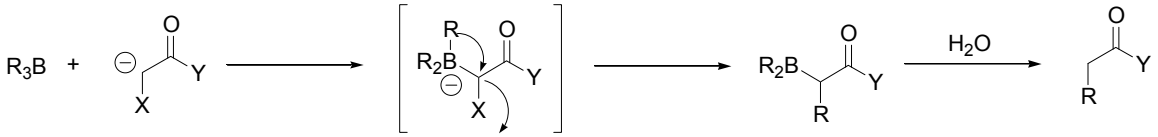
Compounds **47, 49** and **52** were submitted to Dr. Wolfgang Froestl at Novartis for testing their activity toward $GABA_B$ receptors. Unfortunately, none showed any activity.

Chapter IV: Synthesis of Fun ctionalized Organophosphorus Compounds via Organoboranes

4.1 Introduction

Organoboranes have become routine and ubiquitous reagents in organic synthesis. One important reason for this success is the variety of functional groups that can be obtained by transforming a carbon-boron bond.[92] A wide range of organoboranes reaction producing a new carbon-carbon bond proceed by a common mechanism involving an intermolecular anionotropic shift of an alkyl, alkenyl or alkynyl group from tetracoordinated boron atom of an "ate" complex to an adjacent electron-deficient carbon atom. The "ate" complex, which is the transient species, is usually generated by complexation of an organoborane (Lewis acid) with a nucleophile. Carbenoids derived from α-halocarbonyl compounds, α-halonitriles, α-bromosulfones, and sulfonates react with trialkylboranes to give organoborate intermediates rearranging to α-alkylated products (Scheme 4.1).[93]

Scheme 4.1 Alkylation of carbonyl compounds *via* trialkylboranes



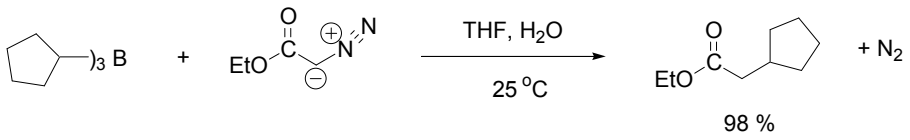
R = alkyl, alkenyl, aryl; X = halogen, OPh, Me_2S; Y = H, R, OR.

The anions are generated by sterically hindered bases, e. g., *tert*-butoxide or 2,6-di-tert-butylphenoxide for sensitive compounds. The use of B-alkyl-9-BBN derivatives instead

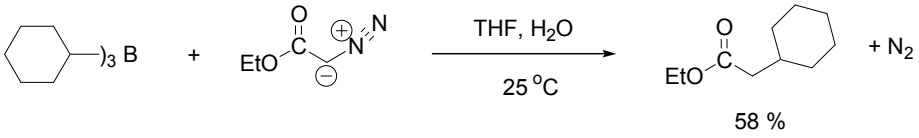
of trialkylboranes allows better utilization of the alkyl group. B-Alkyl-9-BBN derivatives undergo facile reaction with α-halocarbanions generated from ethyl bromoacetate, phenacyl bromide, and chloroacetonitrile in the presence of base, providing the desired product in good yield (Eq. 4.1).[94]

Eq. 4.1

The reaction of organoboranes with diazo derivatives provides another valuable means for forming carbon-carbon bonds under mild conditions. The reaction has been demonstrated for diazoacetaldehyde,[95] diazoacetone,[96] diazoacetonitrile,[97] and ethyldiazoacetate.[97] Consequently, the reaction appears to be general for these reactive reagents (Eq. 4.2 and 4.3).



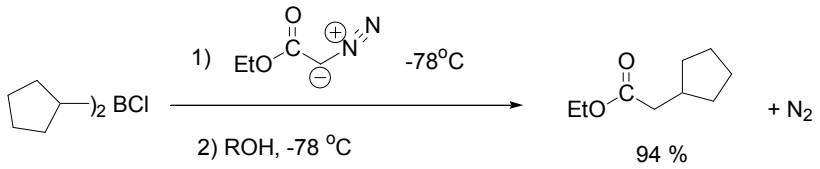
Eq. 4.2



Eq. 4.3

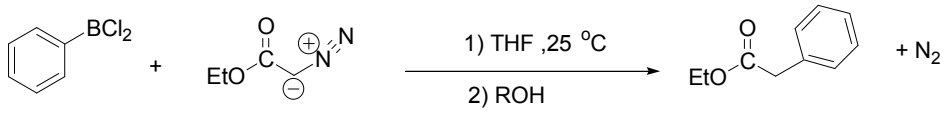
These reactions are highly promising. They have a major advantage in that they frequently take place very readily at 0 °C or 25 °C in the absence of added bases or acids. Therefore, they should be very useful for achieving the functionalization of labile groups. Unfortunately, in this original form the reaction suffers from certain disadvantages. First, the reaction generally uses only one of the three alkyl groups of the R_3B reactant. Second, the reaction becomes relatively sluggish with sharp decreases in yield with bulkier R groups. For example, the reaction of ethyl diazoacetate with tri(2-methyl-1-butyl)borane is slow, and the yield is only 40 %.[96] Unfortunately, the R-B-9-BBN

derivatives do not solve the problem in the present case. They react with ethyl diazoacetate with opening of the bicyclooctyl ring system instead of with transfer of the R-group.[94,98] However, the dialkychloroboranes do provide a considerable improvement. Prepared in ether solution, they react directly at -78 °C to liberate nitrogen and give intermediates, which subsequently treated with alcohol at -78 °C, to give the desired products in nearly quantitative yields (Eq. 4.4)[99]



Eq. 4.4

The far greater rate of reaction is undoubtly a reflection of the smaller steric requirement and higher Lewis acid strength of R_2BCl molecule as compared to R_3B. In this reaction one of the two R groups in R_2BCl is still not utilized. This suggested trying $RBCl_2$ derivatives. In the case of aryldichloroborane, this solution is ideal. Essentially quantitative yields were obtained for several aryl groups (Eq. 4.5).[100]



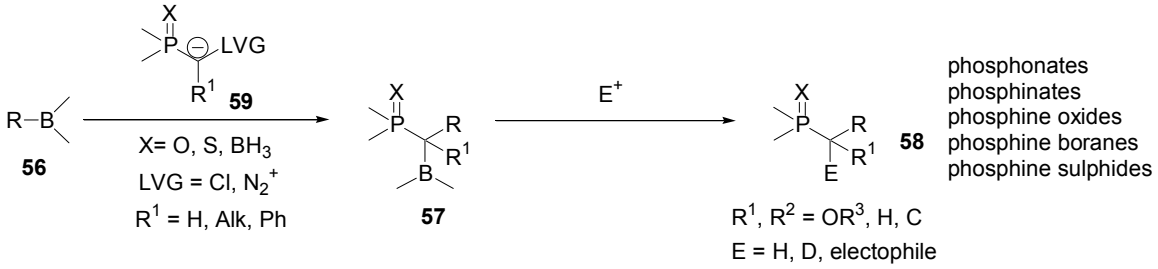
Eq. 4.5

The yields are poorer with monoalkyldichloroboranes, in a 57-71% range, so that for alkyl groups this procedure has little advantage over the more conveniently synthesized reagents, R_2BCl.

Based on these extensive precedents for reaction of organoboranes with halocarbonyl anions and diazocarbonyl compounds, the feasibility of the analogous reaction of phosphorus-containing reagents appeared reasonable. However, to the best of our knowledge, application of this general reactivity pattern has surprisingly not been implemented in organophosphorus chemistry. Herein, we investigated the formation of

phosphonates using the functionalization of a C-B bond into a C-C-P motif, and the corresponding extension to phosphinates, phosphine sulfide, oxides and phosphine borane (Scheme 4.2).

Scheme 4.2 Homologation of phosphorus carbenoids with organoboranes

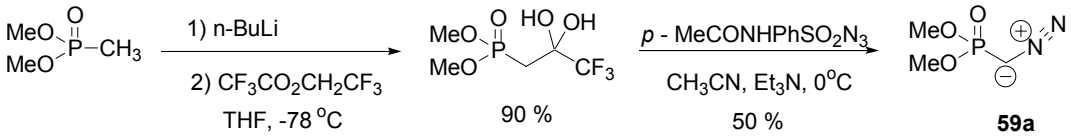


4.2 Reaction of Phosphorus-Containing Carbenoids with Organoboranes

4.2.1 Reactions with symmetrical trialkylboranes

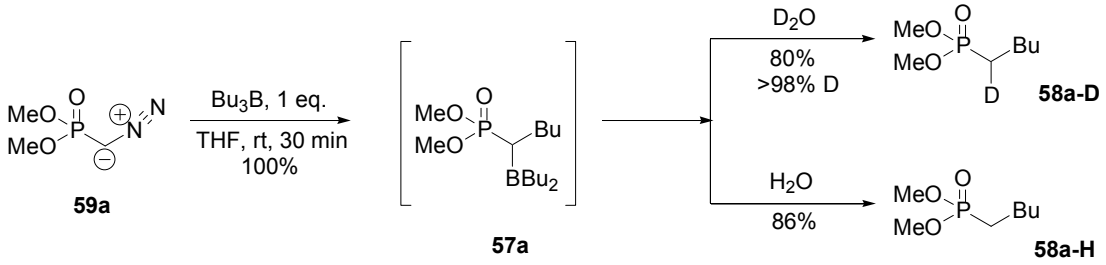
To test the possibility of the reaction depicted in Scheme 4.2, the reaction of dimethyl (diazomethyl)phosphonate (Seyferth/Gilbert reagent, **59a**) with tributylborane was investigated. (Diazomethyl)phosphonate **59a** was prepared from dimethyl methylphosphonate in two steps according to the literature procedure (Scheme 4.3).[101]

Scheme 4.3 Synthesis of dimethyl (diazomethyl)phosphonate **59a**



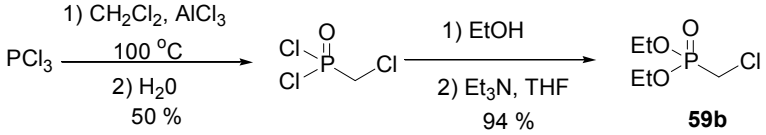
Treatment of **59a** with commercially available Bu_3B at rt in THF resulted in the instantaneous evolution of N_2 and formation of **57a**, which was hydrolyzed with water or D_2O to produce dimethyl pentylphosphonate **58a** (protio **58a-H**, or deuterio **58a-D**) in 86% and 80% isolated yields, respectively (Scheme 4.4). In the latter case, deuterium incorporation was higher than 98% as determined by ^{13}C NMR and HRMS

Scheme 4.4 Reaction of dimethyl (diazomethyl)phosphonate with tributylborane



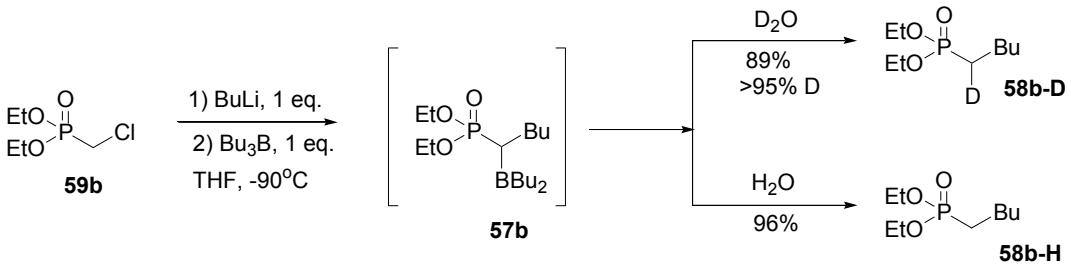
While the synthesis of **59a** is relatively straightforward, a large body of literature is available on the preparation and reactivity of diethyl (chloromethyl)phosphonate **59b** (Scheme 4.5). We thus turned our attention to this phosphonate carbenoid precursor, which was prepared from (chloromethyl)phosphonic dichloride and EtOH in the presence of Et_3N in 94 % isolated yield. (Chloromethyl)phosphonic dichloride was prepared form phosphorus trichloride, aluminium chloride and dichloromethane in 50 % isolated yield (Scheme 4.5)[102]

Scheme 4.5 Synthesis of diethyl (chloromethyl)phosphonate **59b**



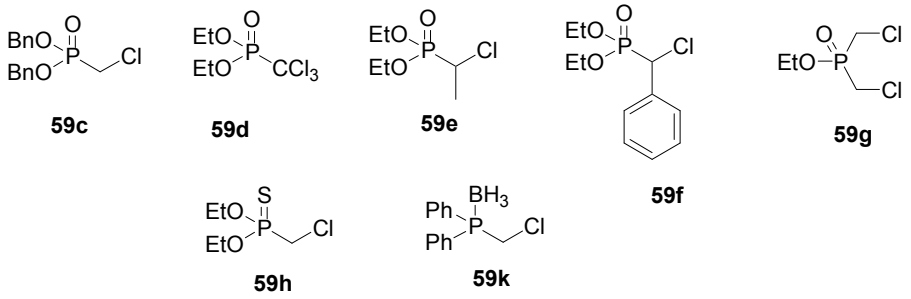
Initially, Bu_3B was selected as a model reagent to investigate the reactivity of the presumed intermediate **57**. Deprotonation of **59b** and reaction with Bu_3B at –90 ^oC gave excellent results upon simple hydrolysis (Scheme 4.6). Diethyl pentylphosphonate **58b-H** was obtained in 96% isolated yield, and deuterated **58b-D** was obtained in 89% (>95% D).

Scheme 4.6 Reaction of diethyl (chloromethyl)phosphonate with tributylborane



In the next stage, we studied other carbenoid precursors (Figure 4.1), and the synthesis of these compounds is depicted in Scheme 4.7.

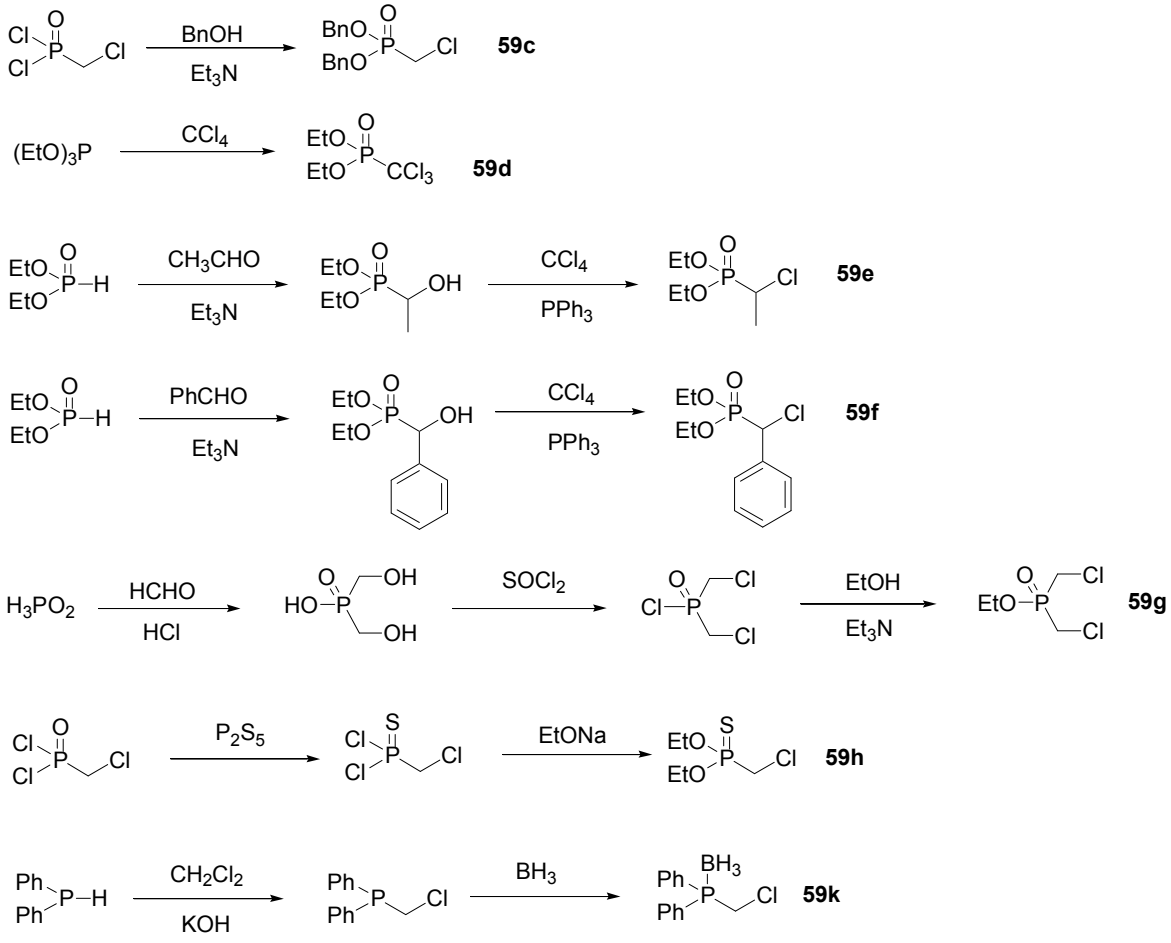
Figure 4.1 Organophosphorus compounds used in the reaction with organoboranes



Dibenzyl (chloromethyl)phosphonate **59c** was prepared from (chloromethyl)phosphonic dichloride and benzyl alcohol in the presence of Et_3N in 80 % isolated yield.[103] (Trichloromethyl)phosphonate **59d** was obtained from reaction of triethyl phosphite and

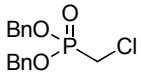
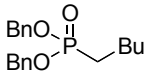
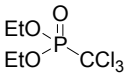
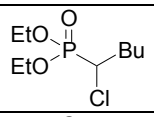
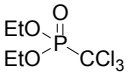
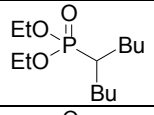
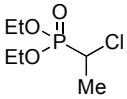
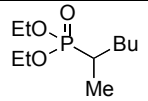
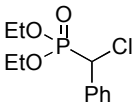
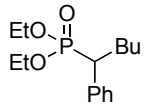
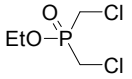
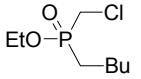
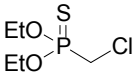
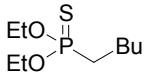
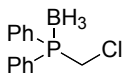
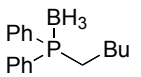
carbon tetrachloride.[104] Diethyl (1-chloroethyl)phosphonate **59e** and diethyl 1-chloro-benzylphosphonate **59f** were prepared in two steps from diethyl phosphite and the appropriate aldehyde (acetaldehyde and benzaldehyde) in the presence of Et_3N to yield diethyl (hydroxyethyl)phosphonate and 1-hydroxy-benzylphosphonate, and then reaction with carbon tetrachloride in the presence of triphenylphosphine produced diethyl (1-chloroethyl)phosphonate **59e** and diethyl 1-chloro-benzylphosphonate.[105]

Scheme 4.7 Synthesis of organophosphorus compounds used in the reaction with organoboranes



Ethyl [bis(chloromethyl)]phosphinate, **59g**, was prepared from bis(chloromethyl)phosphinic chloride, EtOH and Et_3N in 85 % yield.[106] Bis(chloromethyl)phosphinic was obtained by refluxing $SOCl_2$ and bis(hydroxymethyl)phosphinic acid, which was prepared form H_3PO_2, concentrated HCl and paraformaldehyde.[107] Diethyl (chloromethyl)phosphonothioate, **59h**, was prepared from (chloromethyl)phosphonic dichloride and sodium ethoxide in 80 % yield.[108] (Chloromethyl)diphenylphosphine-borane, **59k**, was obtained from reaction of diphenylphosphine with dichloromethane in the presence of KOH to yield (chloromethyl)diphenylphosphine[109], which was then protected with BH_3 (Scheme 4.7).

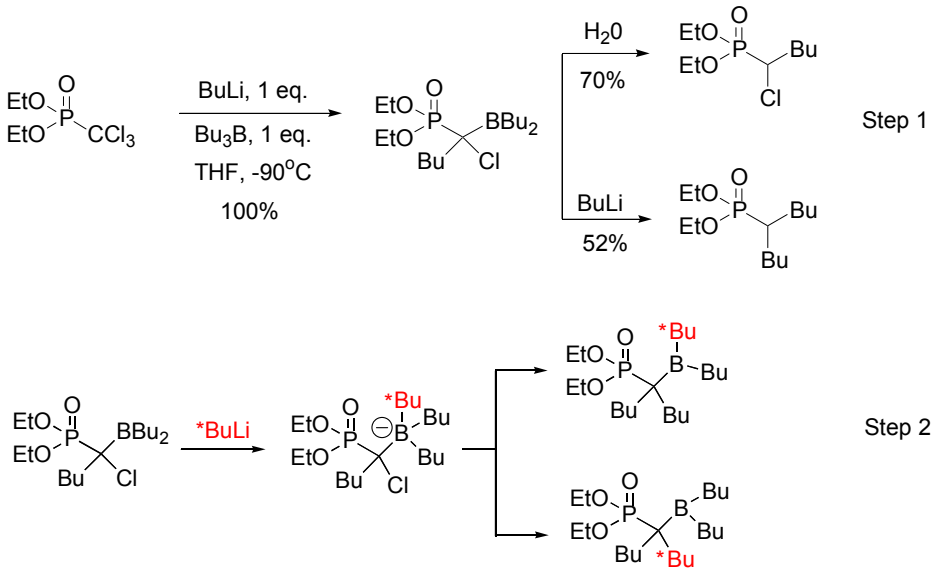
Table 4.1 Reaction of carbenoid precursors with Bu_3B, then H_2O

Entry	Starting material	Product	Isolated Yield (%)
1			85
2			70
3			52
4			63
5			60
6			78
7			90
8			62

All prepared compounds reacted successfully with Bu_3B (Table 4.1) in the presence of BuLi. Yields are good to acceptable, the lower yield being observed only when a second migration is involved (entry 3). In this case, a second equivalent of BuLi must be added prior to hydrolysis, to promote the second migration. It should be noted that the second butyl group in the product is then as likely to originate from the added butyl lithium (33% chance) as from the initial Bu_3B (Scheme 4.8). This might have been true with any combination of BuLi/Bu_3B, however, entry 8 shows that the butyl group came from the organoborane, and additional results below indicate that the BuLi used to generate the carbenoid is not incorporated into the product.

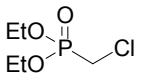
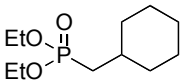
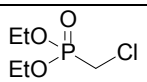
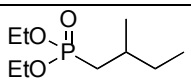
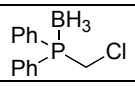
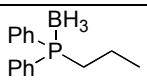
It is important to note that the direct alkylation of phosphonate anions is often inefficient, so that secondary phosphonates are not readily available.[110] Similarly, the classic Arbuzov reaction rarely works well to produce secondary phosphonates.[111]

Scheme 4.8 Butyl group scrambling in Table 4.1, Entry 3



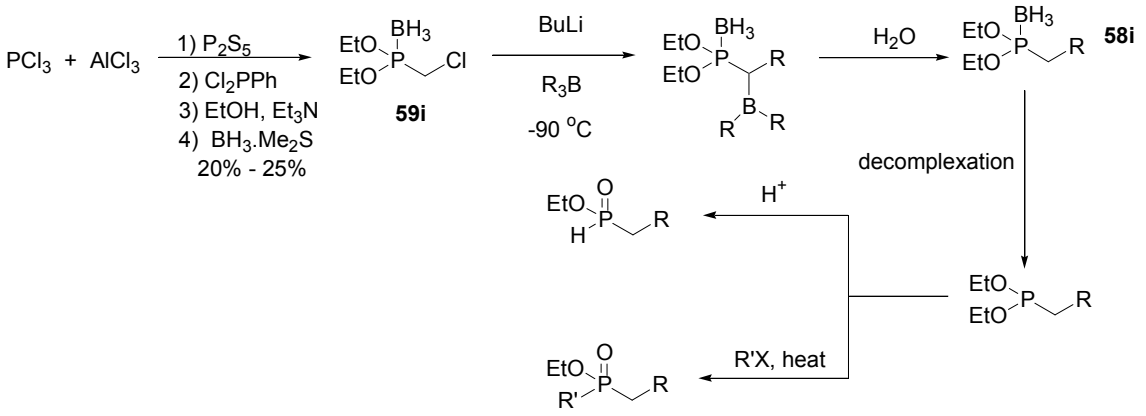
Aside from phosphonate derivatives (entries 1-5), phosphinate (entry 6), phosphonothioate (entry 7), and phosphine-borane complex (entry 8) could also be prepared (Table 4.1). The latter compound has obvious potential in the synthesis of ligands for transition metal-catalyzed reactions. Our approach therefore seemed promising and potentially important as a general route to produce various organophosphorus compounds. The next question was to determine the reactivity of other organoboron compounds. Table 4.2 shows that a secondary trialkylborane ((*sec*-Bu)$_3$B, entry 2) and a cyclic trialkylborane (Cy_3B, entry 1) can be also employed.

Table 4.2 Reaction with other organoboranes

Entry	Starting material	Organoboron Compound	Product	Isolated Yield (%)
1		Cy_3B		83
2		(*sec*-Bu)$_3$B		86
3		Et_3B		85

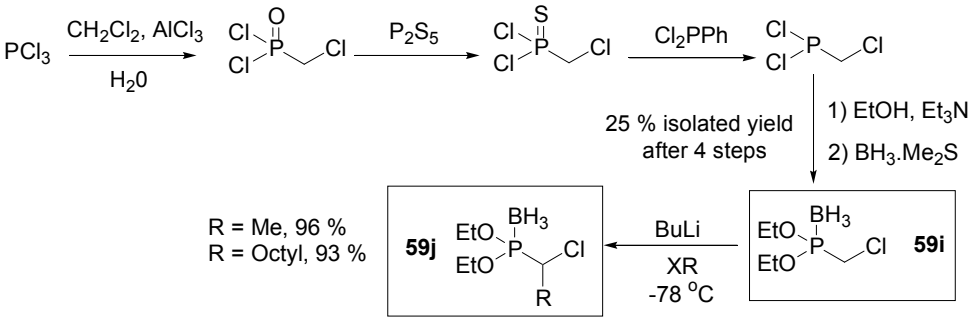
Although phosphonates, phosphonothioates, phosphinates, and phosphine-boranes are of tremendous interest in their own right, we were also interested in extending the methodology to *H*-phosphinate esters. Hence, we introduced the novel phosphonite-borane complex **59i**. Decomplexation of the borane complexes **58i**, after reaction with organoboranes, would provide the phosphonous esters $RCH_2P(OEt)_2$ which can be hydrolyzed to the *H*-phosphinate, or alkylated in situ to introduce a second P-C bond (Scheme 4.9).

Scheme 4.9 Reagent **59i** in the preparation of phosphinates



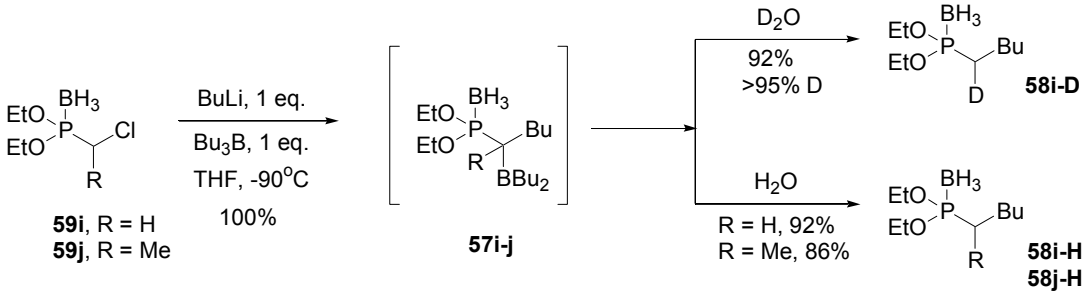
Diethoxy-(chloromethyl)phosphonite-borane **59i** was prepared in 5 steps from PCl_3 in 25 % overall yield (Scheme 4.10). Chloromethylphosphonic dichloride reacts with phosphorus pentasulfide to produce (chloromethyl)phosphonothioic dichloride in 68 % isolated yield. In the next step, reaction between chloromethylphosphonothioic dichloride and dichlorophenylphosphine yields dichloro (chloromethyl)phosphine (71%), which was converted into diethoxy-(chloromethyl)phosphonite-borane **59i** in the presence of EtOH and BH_3 in 95 % yield. Diethoxy (chloromethyl)phosphonite-borane can be alkylated with various electophiles to produce α-substituted diethoxy (chloromethyl)phosphonite-borane complexes in high yields.

Scheme 4.10 Synthesis of phosphonite-borane **59i** and **59j**

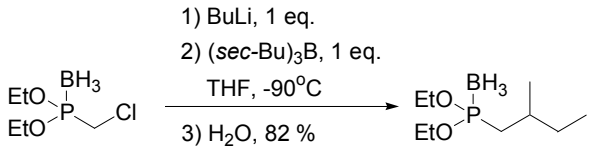


Deprotonation of **59i** and reaction with Bu_3B at - 90°C gave excellent results upon simple hydrolysis (Scheme 4.11). Diethoxy pentylphosphonite-borane **58i-H** was obtained in 92% isolated yield, and deuterated **58i-D** was obtained in 92% (>95% D).

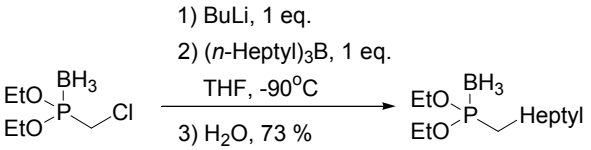
Scheme 4.11 Reaction of **59i** and **59j** with tributylborane



Also reactions with other organoboranes, (*sec*-Bu)$_3$B and (*n*-Heptyl)$_3$B, give products in good yields (Eq. 4.6 and 4.7)



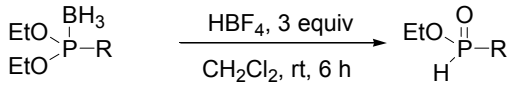
Eq. 4.6

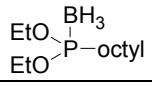
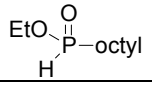
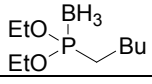
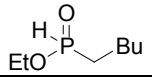
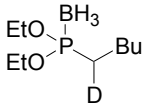
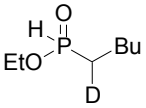
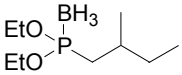
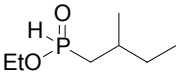
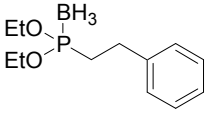
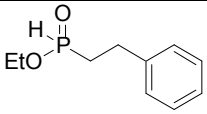
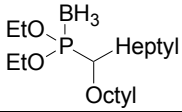
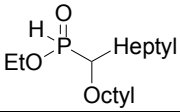
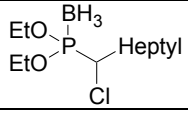
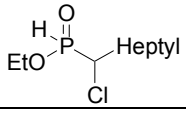


Eq. 4.7

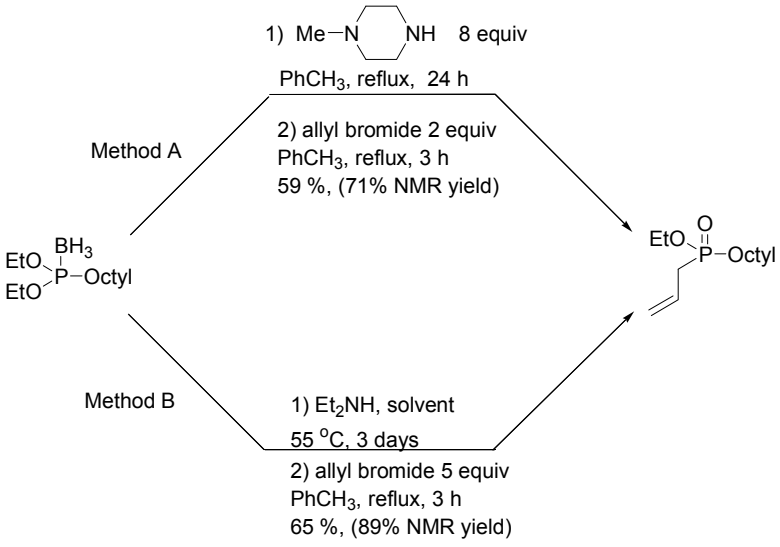
The successful reactions with phosphonite-borane **59i** provided a variety of novel phosphonite-borane complexes ("boranophosphonates") **58**. Conversion of these complexes to phosphinate derivatives could be achieved easily. Cleavage to ethyl *H*-phosphinate esters was readily accomplished with tetrafluoroboric acid (Table 4.3). Under these conditions, no further hydrolysis of the ester group was observed.

Table 4.3 Conversion of phosphonite-boranes into *H*-phosphinate esters



Entry	Starting material	Product	Isolated Yield (%)
1			96
2			95
3			95
4			95
5			98
6			93
7			92

Scheme 4.12 Conversion of phosphonite-boranes into phosphinate esters



Interestingly, decomplexation to the phosphonite derivative could also be conducted with amines, and subsequent treatment with allyl bromide, in "one-pot", led to an Arbuzov reaction with formation of a disubstituted phosphinate (Scheme 4.12). Although more work must be done to develop and optimize this tandem decomplexation-Arbuzov reaction, these results are promising for the preparation of complex phosphinic acid derivatives.

4.2.2 Selective migration with nonsymmetrical organoboranes

The next question was to determine the migratory selectivity with non-symmetrical organoboranes. First, we turned our attention to R-B-9-BBN compounds, since it was shown already that B-Alkyl-9-BBN derivatives undergo facile reaction with α-halocarbanions providing the desired product in good yield (Eq. 4.1). To test the possibility of the reaction depicted in Scheme 4.13, the reaction of diethyl (chloromethyl)phosphonate **59b,** diethyl 1-chloro-benzylphosphonate **59f**, diethoxy-(chloromethyl)phosphonite-borane **59i** and diethyl (diazomethyl)phosphonate **59a** with B-benzyl-9-BBN, B-octyl-9-BBN, Alpine borane and B-cyclohexyl-9-BBN was investigated (Table 4.4, Entry 1-7).

Scheme 4.13 Homologation of phosphorus carbenoids with R-B-9-BBN

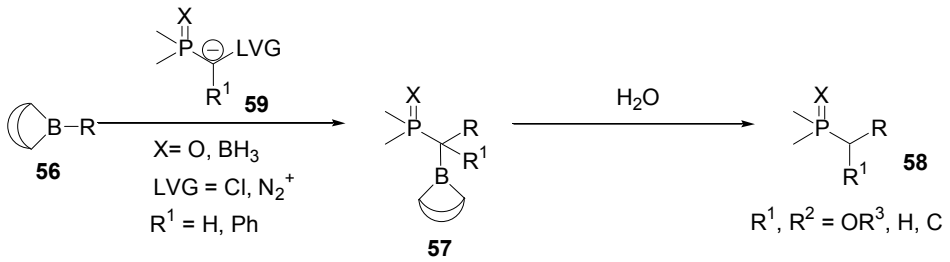
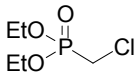
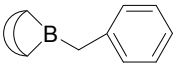
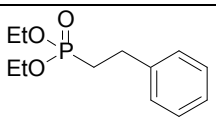
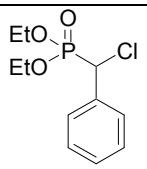
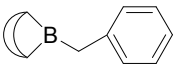
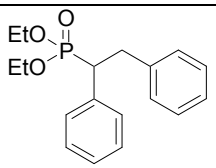
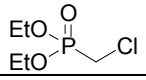
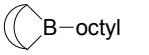
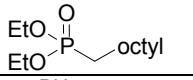
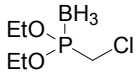
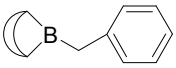
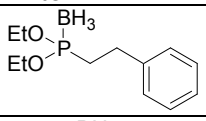
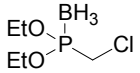
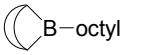
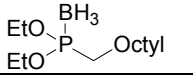
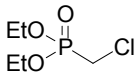
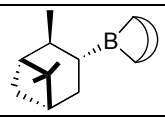
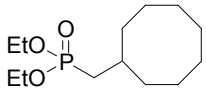
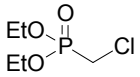
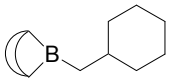
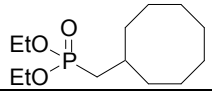
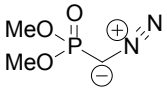
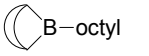
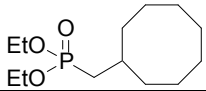
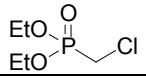
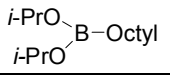
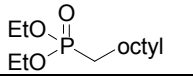
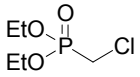
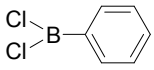
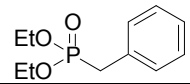
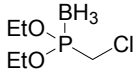
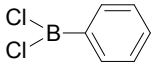
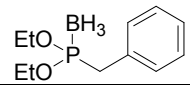
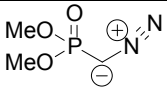
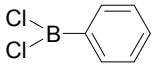
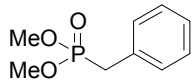
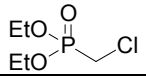
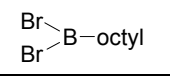
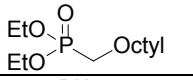
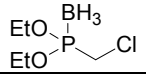


Table 4.4 Selective migration

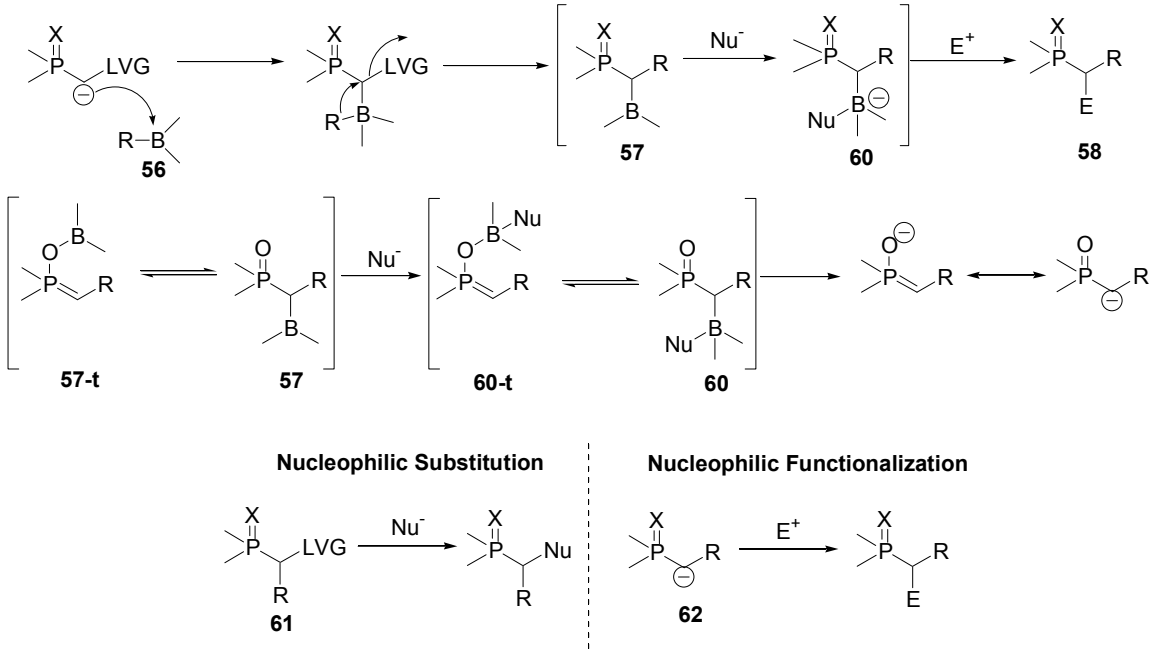
Entry	Starting material	Organoborane reagent	Product	Yield (%)
1				69
2				59
3				50
4				71
5				62
6				83
7				75
8				70
9				0
10				0
11				0
12				0
13				0
14				0
15				0
16				0

Selective transfer of benzyl and octyl groups was observed (Entries 1, 2, 3, 4, 5) when B-benzyl-9-BBN and B-octyl-9-BBN were used. However, B-cycloalkyl-9-BBN derivatives, Alpine borane (entry 6) and cyclohexyl-9-BBN (entry 7), react with carbenoids with opening of the bicyclooctyl ring and cyclooctyl group migrates selectively instead of the desired R group. Also, reaction of diethyl (diazomethyl)phosphonate with B-octyl-9-BBN similarly provides selective migration the cyclooctyl group (entry 8). However, the latter result was not unexpected since it is known from the literature that α-diazocarbonyl compounds react with B-alkyl-9-BBN with opening of the bicyclooctyl ring and cyclooctyl group migration.[98] In the next stage, we studied haloboranes reagents, RBX_2 (R = Alkyl, Ph, X = Cl, Br), known from the literature to react with α-diazocarbonyl compounds with selective migration of R (Eq. 4.4). Unfortunately, our reaction of dimethyl (diazomethyl)phosphonate **59a** or of the anions of diethyl (chloromethyl)phosphonate **59b** and diethoxy-(chloromethyl)phosphonite-borane **59i** failed with dichloro and dibromoborane (entry 8-16): no formation of desired product was observed. Also reaction with $(i\text{-PrO})_2BR$ did not provide the desired product (entry 9).

In conclusion, we have demonstrated a novel synthesis of organophosphorus compounds using organoboron reagents. In some cases, selective transfer of one group attached to the boron atom has been achieved. Reagent **59i** was introduced as a novel precursor of *H*-phosphinate derivatives. However, perhaps an even more important advantage of this methodology is that the intermediate organoborate **57** not only can decompose easily and under simple hydrolysis/deuterolysis, with migration of the R-group from boron to the α-position of phosphorus to form **58** (Scheme 4.2), but also

intermediate **57** can potentially undergo a variety of typical C-B to C-Y transformations (Y = O, N, C, X, etc.). In some cases, in situ formation of the ate-complex **60**, (Scheme 4.14) using butyllithium may be necessary to boost reactivity further. Because a tautomeric equilibrium (albeit unfavorable) can exist (**57-t**, **60-t**), the reactivity of **57** and **60** are expected to be between that of a typical organoborane and enolborane, or organoborate and phosphonate anion, respectively.

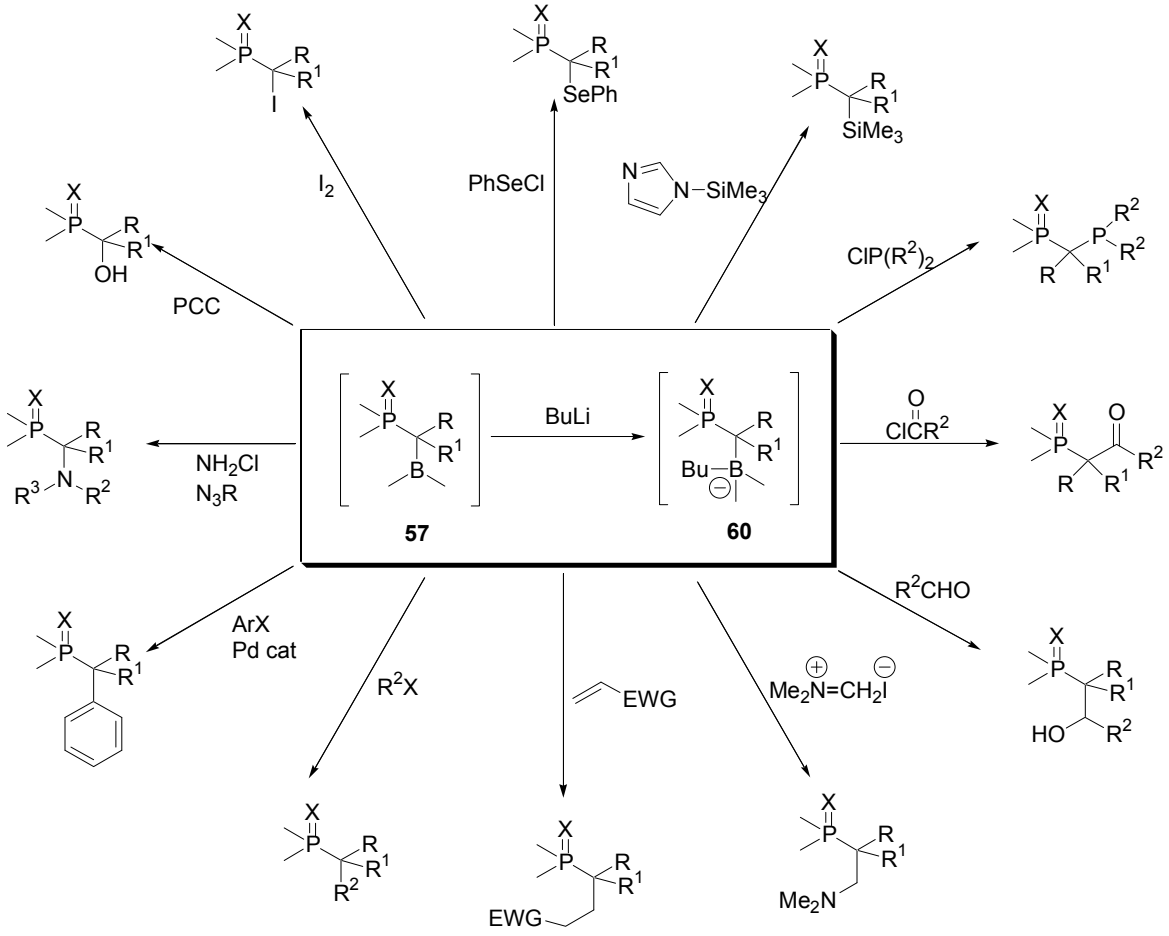
Scheme 4.14 Proposed mechanism



In contrast, nucleophilic displacement at the α-carbon of organophosphonates **61** is generally very difficult even when R = H. The approach where polarity is reversed is also problematic because phosphonate-stabilized carbanions **62** are hindered, relatively unreactive toward alkylation, and thermally unstable, and therefore conditions are sometimes incompatible with functionalized molecules. Furthermore, the classic

Arbuzov or Michaelis-Becker reactions are ill-suited to the synthesis of α-substituted functionalized phosphonates, including those containing secondary carbons. Additionally, intermediate organoboranes **57** provide a handle for numerous transformations, that are not available with any other methods. This provides added flexibility which could be exploited for the preparation of combinatorial libraries while minimizing

Scheme 4.15 Examples of boron intermediate **57** functionalizations, which will be discussed



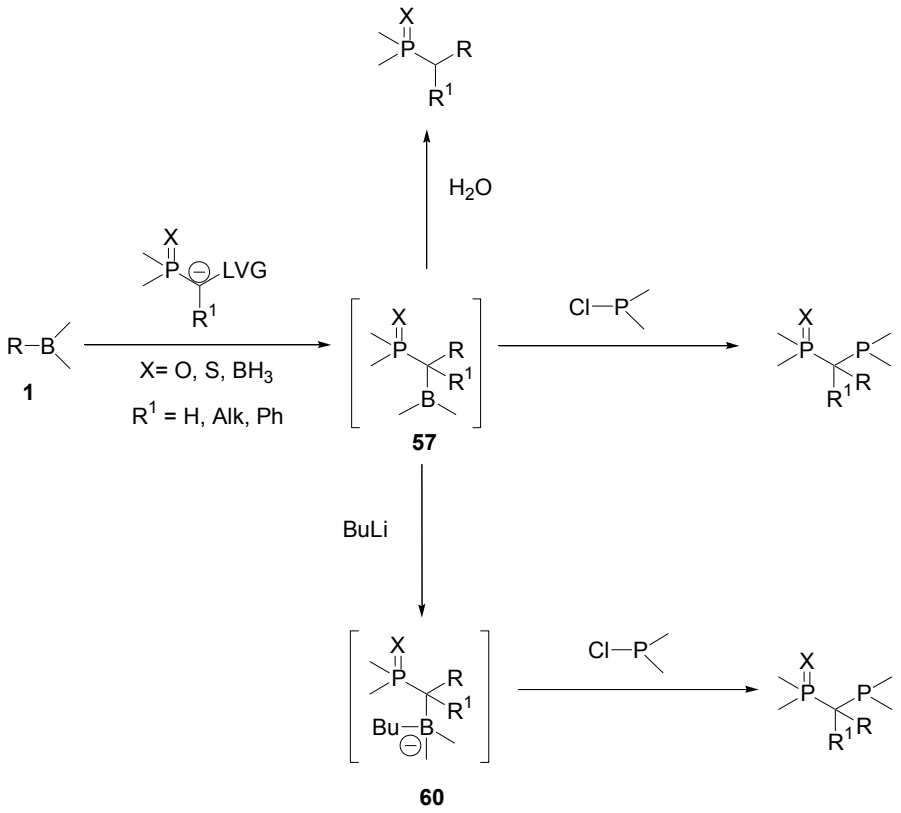
the number of manipulations required to achieve structural complexity. Therefore, in the next stage of our work, we focused on exploring possible conversions of the boron intermediate **57** into important functionalities *via* phosphorylation, acylation, aldol, conjugate addition, alkylation, oxidation, iodination, fluorination, amination, silylation, selenylation, reaction with iminium ions, radical reaction, and cross coupling. Scheme 4.15 summarizes some examples of boron intermediate **57** functionalizations, which will be discussed.

4.3 Transformation of α-Boranophosphorus Intermediates 57: C-B Elaboration

4.3.1 Synthesis of 1,1-bis-phosphorus compounds from organoboranes. Transformation P-C-B complex into P-C-P

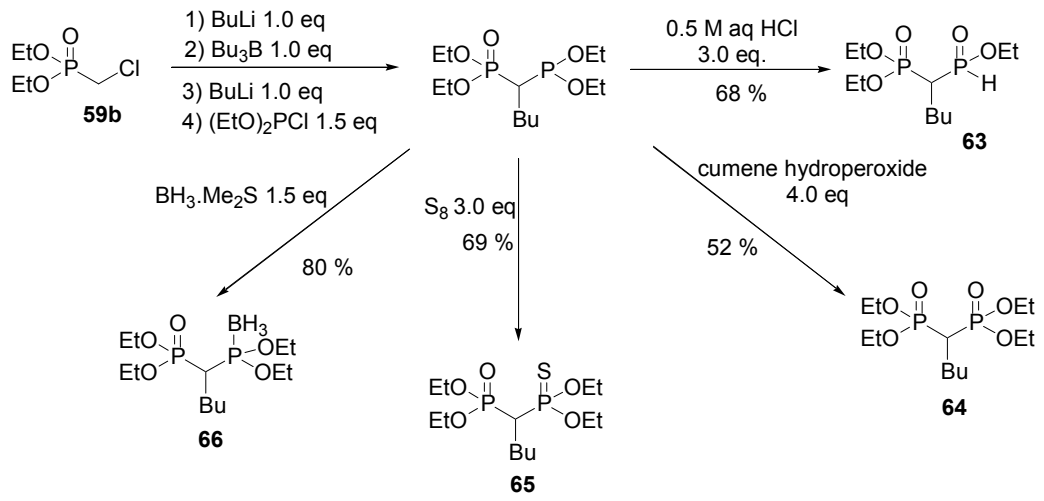
To test the flexibility of our method for the preparation of organophosphorus compounds from organoborates, we investigated phosphorus electrophiles in order to prepare bis-phosphorus compounds (Scheme 4.16). These compounds are important in a variety of applications, from medicines to pesticides, from ligands in catalysis to extractants and flame-retardants.[1,2b,2c,112] Unlike the direct hydrolysis of the α-boranophosphorus intermediate **57**, direct treatment with diethyl chlorophosphite $(EtO)_2PCl$, diethylchlorophosphate $(EtO)_2P(O)Cl$, or chlorodiphenylphosphine Ph_2PCl, did not result in the desired P-C bond formation. However, activation of the intermediate **57** as the borate complex **60** (Scheme 4.16) allowed reaction with the P(III) electrophiles, but not with the less reactive P(V).

Scheme 4.16 Transformation of α-boranophosphorus intermediate **57** into bis-phosphorus compounds



Initially, we focused on diethyl chloromethylphosphonate $(EtO)_2P(O)CH_2Cl$ **59b** as the carbenoid precursor to delineate the scope of the reaction. Since $(EtO)_2P(O)Cl$, did not react, the direct synthesis of bisphosphonates was not possible. However, this does not constitute a major impediment since bisphosphonates can be synthesized easily using literature procedures, such as alkylation of commercially available methylenebisphosphonates.[113] Indeed, other P-C-P functionalities are significantly more interesting since methods for their syntheses either do not exist, or are limited to a handful of compounds.[114]

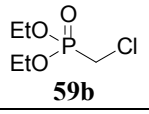
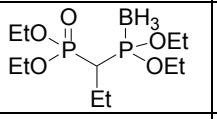
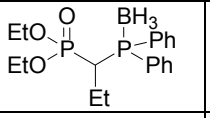
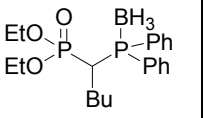
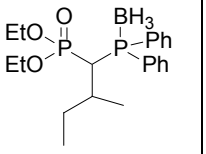
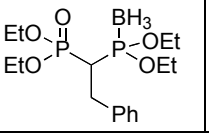
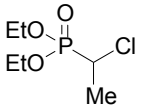
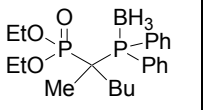
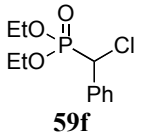
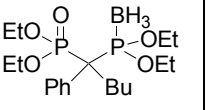
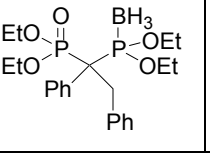
Scheme 4.17 Reactions of diethyl chloromethylphosphonate **59b**



Reaction of **59b** with *n*-butyl lithium at low temperature (- 90 ^{o}C) forms the corresponding carbenoid which then reacts with various organoboranes. Addition of another equivalent of BuLi to the resulting intermediate **57b** formed borate **60b**, which then reacted with diethyl chlorophosphite in good yield. The resulting intermediate could be either hydrolyzed, treated with an oxidant, sulfur, or BH_3 (Scheme 4.17).

Table 4.5 summarizes the results with phosphonate carbenoids using borane complexation of the intermediate P(III) compound. The phosphonate-phosphonite borane complexes were obtained in moderate to good yields. Compound **59b** afforded various substitution patterns (Table 4.5, entries 1 to 5). Entry 5 shows the successful selective transfer of a 9-BBN substituted borane. As expected, substituted phosphonates **59e** and **59f** gave the corresponding dialkylated products in useful yields (entries 6 to 9).

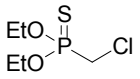
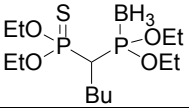
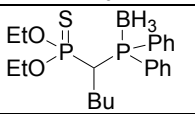
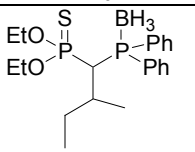
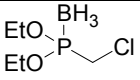
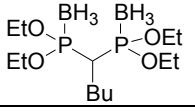
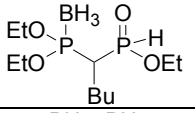
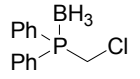
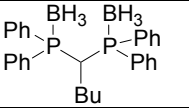
Table 4.5 Reactions of phosphonate carbenoid

Entry	Starting material	Organoborane	Chlorophosphine	Product	Isolated Yield (%)
1	 **59b**	Et_3B	$(EtO)_2PCl$ 1.5 equiv		92
2	**59b**	Et_3B	Ph_2PCl 1.5 equiv		62
3	**59b**	Bu_3B	Ph_2PCl 1.5 equiv		89
4	**59b**	$(sec\text{-}Bu)_3B$	Ph_2PCl 1.5 equiv		69
5	**59b**	Benzyl-9-BBN	$(EtO)_2PCl$ 4.0 equiv		73
6	 **59e**	Bu_3B	Ph_2PCl 1.5 equiv		76
7	 **59f**	Bu_3B	$(EtO)_2PCl$ 1.5 equiv		54
8	**59f**	Benzyl-9-BBN	$(EtO)_2PCl$ 4.0 equiv		64

Based on these results, other carbenoid precursors were examined (Table 4.6). Phosphonothioate **59h**, phosphonite-borane **59i**, and phosphine-borane **59k** could all be employed successfully. As with phosphonate **59b**, hydrolysis of the intermediate

produced the *H*-phosphinate product (Table 4.6, entry 5), and interestingly in this case, simple acid hydrolysis resulted in the cleavage of only one phosphonite-borane group.

Table 4.6. Reactions of other phosphorus carbenoids

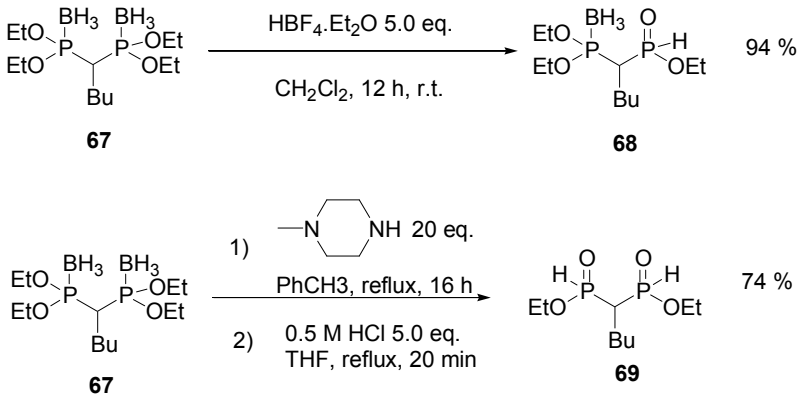
Entry	Starting material	Organoborane	Chlorophosphine	Product	Yield[a] (%)
1	 **59h**	Bu_3B	$(EtO)_2PCl$ 1.5 equiv		69
2	**59h**	Bu_3B	Ph_2PCl 1.5 equiv		89
3	**59h**	$(sec\text{-}Bu)_3B$	Ph_2PCl 1.5 equiv		62
4	 **59i**	Bu_3B	$(EtO)_2PCl$ 1.5 equiv		82
5	**59i**	Bu_3B	$(EtO)_2PCl$ 1.5 equiv		82[b]
6	 **59k**	Bu_3B	Ph_2PCl 1.5 equiv		77

[a] Isolated yields. [b] Obtained after hydrolysis of the intermediate phosphonite with concentrated aqueous HCl.

While the P-C-P(OEt)$_2$ species can be cleaved directly with concentrated HCl (Scheme 4.18, and Table 4. 6, entry 5), borane complexes can also be cleaved using different conditions (Scheme 4.18). While treatment of **67** with HBF_4, cleaves only one group (as with HCl) to form **68**, complete decomplexation to **69** is also possible using an amine base followed by hydrolysis of the intermediate bisphosphonite. 1,1-Bis-*H*-phosphinate esters similar to **69** have been previously synthesized using our radical

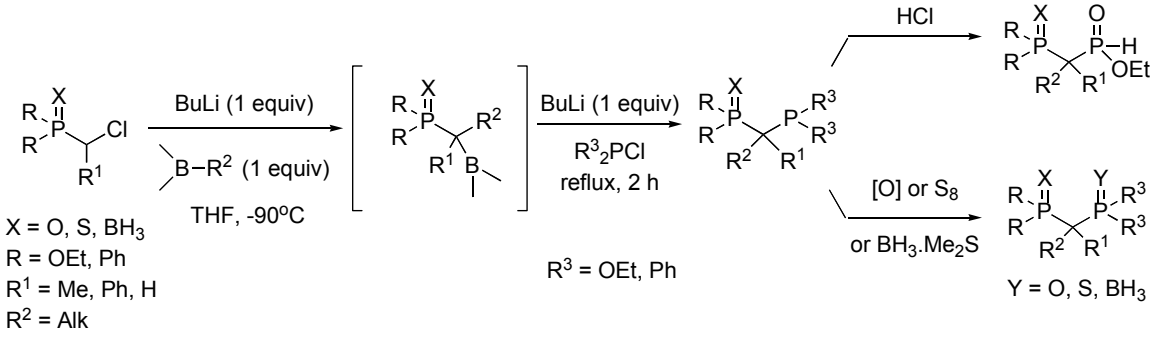
hydrophosphinylation followed by esterification,[10] but the present approach provides added flexibility in the type of accessible phosphorus functionalities.

Scheme 4.18. Decomplexation of phosphonite-boranes



Scheme 4.19 summarizes the present methodology. A wide variety of known bisphosphonate and bisphosphine-borane complexes[114] as well as novel bisphosphorus functionalities can be synthesized in one-pot from readily available reagents.

Scheme 4.19. Overall summary of P-C-P synthesis

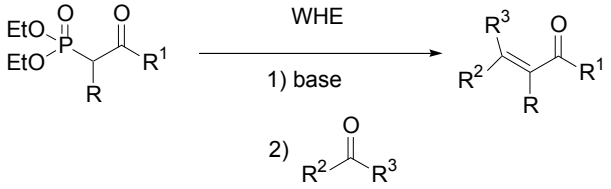


In conclusion, a wide variety of P-C-P compounds can be obtained using our methodology. Because pyrophosphate analogs are common motifs in biologically

important compounds, and because bisphosphines are useful ligands, the present work should be useful for the preparation of a variety of P-C-P functionalities. The advantage of our reaction is that the direct alkylation approach is only well-precedented with methylenebisphosphonates. Because a P(III) intermediate is involved herein, several different organophosphorus functionalities can be prepared from a single intermediate. Therefore, the reaction lends itself to combinatorial approaches. Implementation of this methodology to the preparation of biologically-relevant pyrophosphate analogs can be investigated in the future.

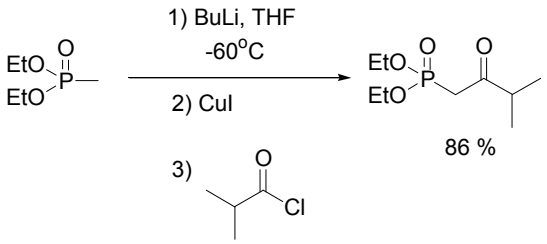
4.3.2 Transformation P-C-B complex into P-C-C *via* acylation, aldol, conjugate adition, radical reaction cross-coupling, *etc.*

Another particularly important set of transformations is C-C bond formation. Encouraged by the successful synthesis of various bis-phosphorus compounds from the borate complex, we turned our attention to β-ketophosphonate esters. β-Ketophosphonates are valuable organic compounds for their metal-complexing ability[115] and more importantly, monoanions derived from β-ketophosphonate esters have been extremely useful in the synthesis of certain olefins from aldehydes and ketones (the "Wadsworth-Horner-Emmons" or WHE reaction, Eq. 4.8).[116]



Eq. 4.8

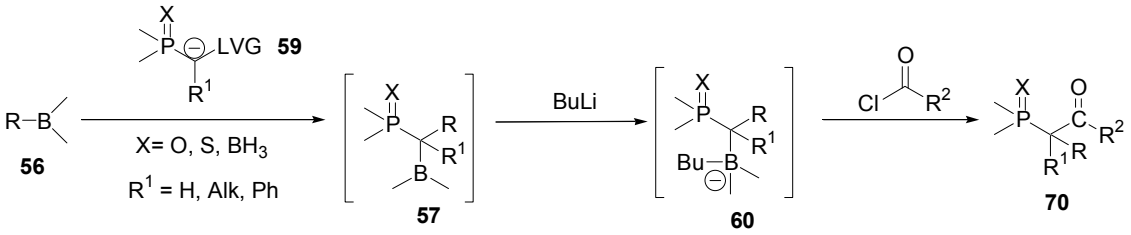
The most convenient way for the synthesis of β-ketophosphonates is acylation of alkylphosphonate anion in presence of CuI as reported by Mathey and Savignac (Eq. 4.9).[117]



Eq. 4.9

In our method, acyl chlorides are also used as electrophiles. Similarly to the synthesis of bisphosphorus derivatives, direct treatment α-boranophosphorus **57** intermediate with acyl chloride did not result in the desired C-C bond formation. Therefore, activation of the intermediate **57** as the borate complex **60** (Scheme 4.20) was required to allow acylation.

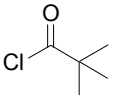
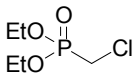
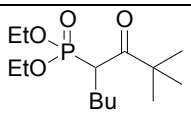
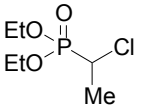
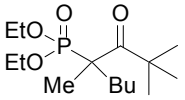
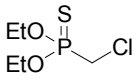
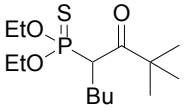
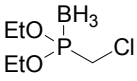
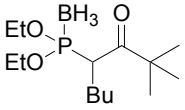
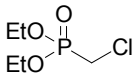
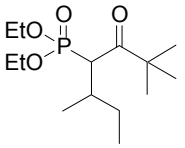
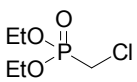
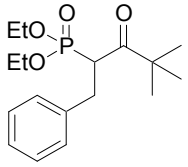
Scheme 4.20 Synthesis of β-ketophosphonates via organoboranes



To test the possibility of the reaction depicted in Scheme 4.20, the reaction of diethylchloromethylphosphonate $(EtO)_2P(O)CH_2Cl$ **59b**, BuLi, Bu_3B, and pivaloyl chloride was investigated (table 4.7, entry 1). Reaction of **59b** with *n*-butyllithium at low temperature (- 90 ^oC) forms the corresponding carbenoid, which then reacts with tributylborane. Addition of another equivalent of BuLi to the resulting intermediate **57**

formed borate **60**, which then reacted with pivaloyl chloride in good yield. Also α-substituted diethyl chloromethylphosphonates **59e** can react with pivaloyl chloride under these same conditions to produce the corresponding α,α-disubstituted β-ketophosphonate esters (Table 4.7, entry 2). Aside from phosphonates derivatives, phosphonothioates and boranophosphonates can be used for this homologation as a starting material (entry 3 and 4).

Table 4.7 Reaction of intermediate **57** with pivaloyl chloride

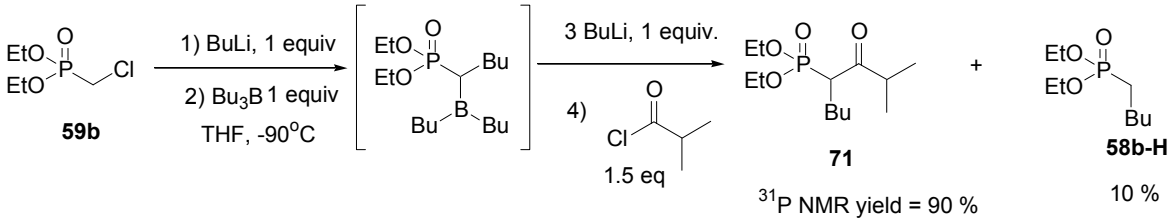
Entry	Starting material	Organoboron compound		Product	Isolated Yield (%)
1		Bu_3B	1.5 equiv		92
2		Bu_3B	1.5 equiv		78
3		Bu_3B	1.5 equiv		87
4		Bu_3B	1.5 equiv		65
5		$(sec\text{-}Bu)_3B$	1.5 equiv		86
6		B-benzyl-9-BBN	4.0 equiv		63

The next question was to determine the reactivity of other organoboron reagents. As shown in Table 4.7, when (*sec*-Bu)$_3$B (entry 5) and B-benzyl-9-BBN (entry 6) are used, the corresponding β-ketophosphonate is obtained in good yields.

Encouraged by these results, we decided to investigate the reactivity of organoborate complex **60** with other acyl chlorides. As expected, reaction with 1.5 eq of isobutyryl chloride gave the desired product **71** in 90 % ^{31}P NMR yield (Scheme 4.21).

However, reaction with 1.5 eq. of benzoyl chloride proceeded with formation of three products in an approximately 1:1:1 ratio by ^{31}P NMR (Table 4.8, entry 1). The desired β-ketophosphonate ester **73** was obtained in only 34 % ^{31}P NMR yield, the formation of compound **74** was due to the reaction of product **73** with benzoyl chloride present in the reaction mixture, product **58b-H** was formed because of simple hydrolysis of borate complex **60**. From our previous study, we established that excess (1.5 eq.) of pivaloyl chloride was necessary to obtain β-ketophosphonates from borate complex **60** in good yield. In the case of benzoyl chloride, 1.0 eq. of this reagent was used to convert borate complex **60** into 34 % of product **73** and 33 % of product **74** (table 4.8 entry 1).

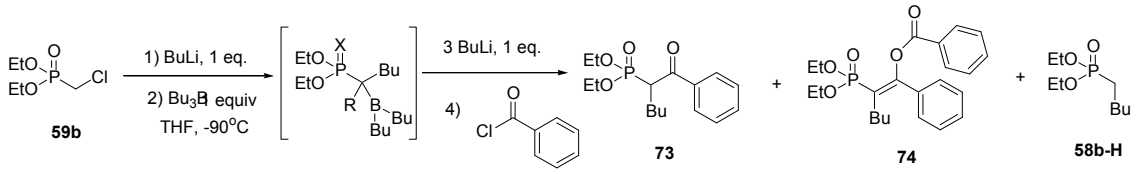
Scheme 4.21 Reaction of intermediate **57** with isobutyryl chloride

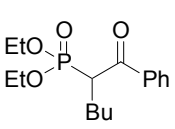
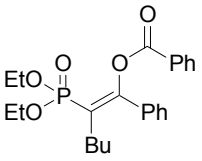
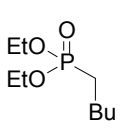


Unreacted benzoyl chloride in the reaction mixture was not sufficient to convert the rest of borate complex **60** (33 %) into products **73** and/or **74**, resulting in 33 % hydrolysis and

the formation of product **59b-H**. In order to investigate other possible distributions of products, we conducted reactions with 1.1 eq. and 4.0 eq. of benzoyl chloride. In the first case (table 4.8, entry 2), 80 % of benzoyl chloride was employed to produce **74** (44 % in ^{31}PNMR), and only 4 % of compound **73** was present in reaction mixture after 2 h of reflux. In the second case (table 4.8, entry 3), a large excess of benzoyl chloride (4.0 eq.) resulted in the formation of 70% of product **73** and 30% of product **74**.

Table 4.8 Reaction of intermediate **57** with benzoyl chloride



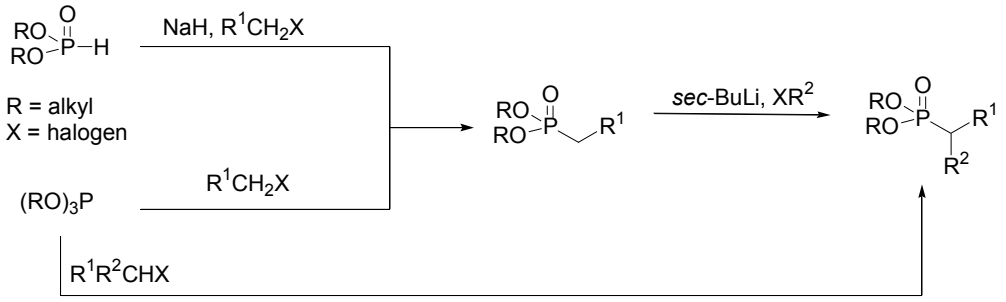
Entry	Number of eq. Benzoyl chloride			
1	1.5 eq.	(34 %) [a] (28 %) [b]	(33 %) [a] (30 %) [b]	(33 %) [a] (18 %) [b]
2	1.0 eq.	(4 %) [a]	(44 %) [a]	(52 %) [a]
3	4.0 eq.	(70 %) [a] (62 %) [b]	(30 %) [a]	(0 %) [a]

[a] ^{31}PNMR yield, [b] Isolated yield.

In conclusion, we demonstrated a novel, potentially important way for the synthesis of α-substituted β-ketophosphonates, β-ketophosphonothioates and β-ketoboranophosphonates. Future investigation will fully explore the scope and limitations of this approach.

Another important set of transformations which were investigated is the synthesis of secondary phosphonates from borate complex **60** (Scheme 4.23). The most convenient way to synthesize these compounds is using the Michaelis-Arbuzov reaction (Scheme 4.22) or by the alkylation of dialkylphosphite with an electrophile, followed by second alkylation in the α-position of phosphorus (Scheme 4.22). It is important to note that the direct alkylation of phosphonate is often inefficient, so that secondary phosphonates are not readily available. The Arbuzov reaction rarely works well to produce secondary phosphonates.

Scheme 4.22 Literature syntheses of secondary phosphonates



Hence, we decided to examine the possibility of converting intermediate **57** into secondary phosphonates. Similar to the synthesis of bis-phosphonates and β-ketophosphonates, direct treatment of α-boranophosphorus **57** intermediate with electrophiles did not result in the desired C-C bond formation. Therefore, activation of the intermediate **57** to the borate complex **60** was required to allow alkylation (Scheme 4.23). To test the possibility of the reaction depicted in Scheme 4.23, the reaction of borate **60**, formed from diethyl chloromethylphosphonate **59b**, Bu_3B, two eq. of BuLi, and alkyl halide (iodomethane, Table 4.9, entry 1, benzyl bromide, Table 4.9, entry 2),

was investigated. Unsurprisingly, the reaction produced secondary phosphonates in good isolated yield (74 % and 60 % respectively). Aside from secondary phosphonates derivatives, secondary boranophosphonate (Entries 3 and 4) could also be prepared in good yield.

Scheme 4.23 Synthesis of secondary phosphonates from intermediate **57**

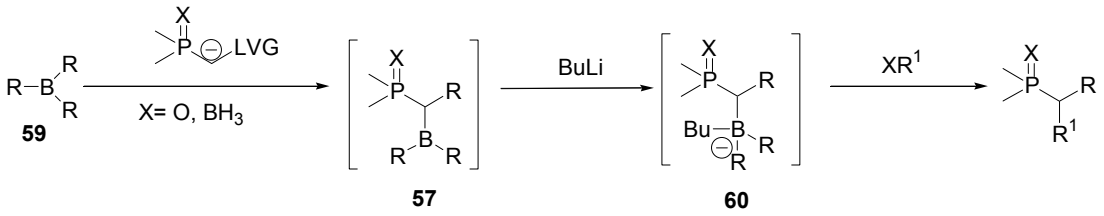
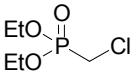
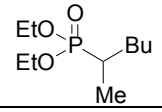
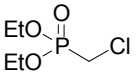
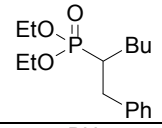
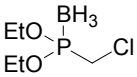
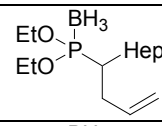
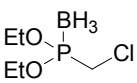
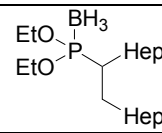


Table 4.9 Synthesis of secondary phosphonates from boranophosphonate **57**

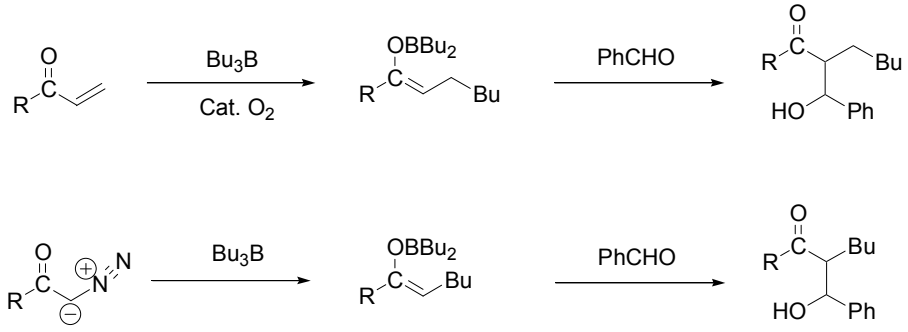
Entry	Starting material	Organoborane Reagent. R_3B	Electrophile R^1X	Product	Isolated yield (%)
1		Bu_3B	Iodomethane		74
2		Bu_3B	Benzyl bromide		60
3		(*n*-Heptyl)$_3$B	Allyl bromide		72
4		(*n*-Heptyl)$_3$B	1-Iodooctane		76

In conclusion, we demonstrated a convenient approach to the synthesis of secondary phosphonates and phosphonite-borane complexes. The present development illustrates that, with a suitable choice of substrates, the simplicity and good yield of this

method allow unambiguous synthesis of certain secondary organophosphorus compounds in “one pot”, which would otherwise not be readily available using conventional methods.

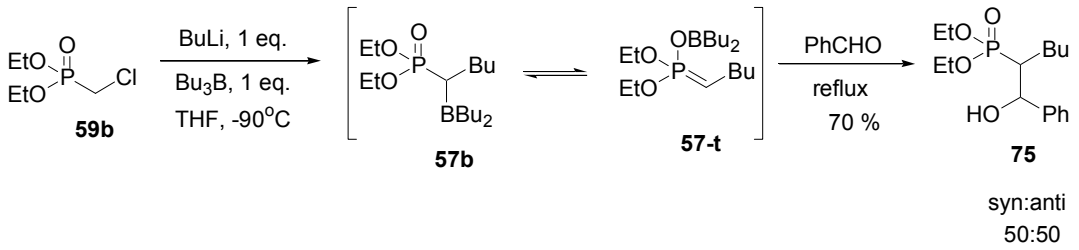
Another very important transformation of the α-boranophosphorus intermediate **57** that we investigated was aldol-like carbonyl addition. The aldol reaction is one of the most powerful methodologies for the formation of β-hydroxy ketones, and boron enolates are important intermediates for this transformation. In 1973 Mukaiyama[118] discovered that boron enolates, prepared from tributylborane and vinyl methyl ketone, or by an alternative pathway from tributylborane and diazo ketone or ester, react with benzaldehyde to give diastereomeric β-hydroxy ketones in high yield (Scheme 4.24)

Scheme 4.24 Synthesis β-hydroxy ketones from organoboranes *via* aldol reaction



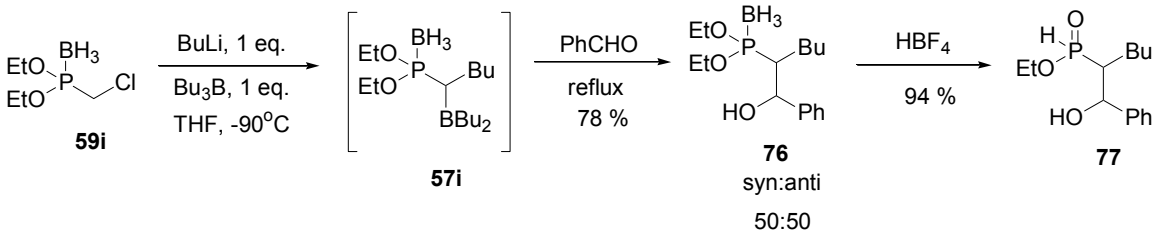
Therefore, the feasibility of the analogous reaction from phosphorus-containing carbenoid seemed reasonable. Hence, the reaction of chloromethylphosphonate, tributylborane and benzaldehyde was investigated (Scheme 4.25).

Scheme 4.25 Aldol reaction of α-boranophonate intermediate **57b**



Deprotonation of **59b** and reaction with Bu_3B at -90 ^oC, followed by addition of benzaldehyde, gave the expected β-hydroxyphosphonate **75** in 70 % yield and 50:50 syn/anti ratio. Furthermore, the similar reaction of chloromethylphosphonite-borane complexes **59i** and benzaldehyde gave β-hydroxyboranophosphonate **76** in good yield (78 %), which can be converted to β-hydroxy *H*-phosphinate ester **77** (Scheme 4.26).

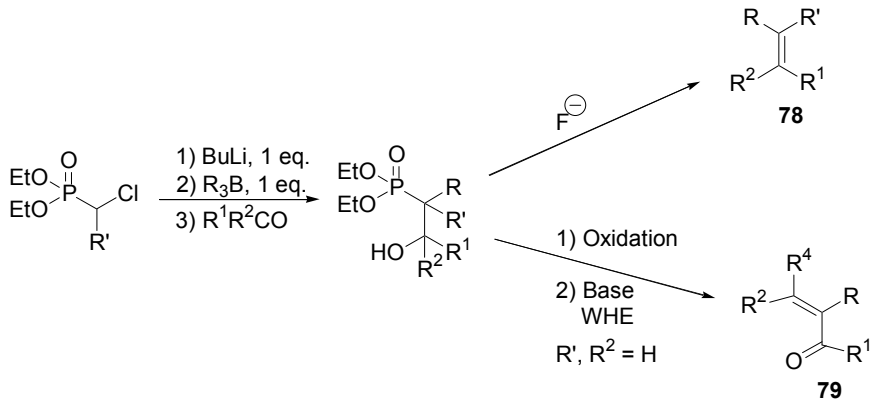
Scheme 4.26 Aldol reaction of α-boranophosphorus intermediate **59i**



Aldol reactions of borane complex **57b** and **57i** remain to be fully investigated. Products of this homologation: β-hydroxyphosphonates **75** and β-hydroxy *H*-phosphinate ester **77** are highly valuable compounds, with potential biological activities, due to their ability to mimic their carboxylic counterparts.[119] Also, the possibility to improve *syn*:*anti* diastereoselectivity in our method will be investigated. It is known from the literature that boron-mediated aldol reaction is one of the most powerful methodologies for the stereodirected formation of a carbon-carbon bond. The transition states of boron enolates

addition reactions to aldehydes and ketones (enolboration) appear tightly organized, transmitting well the spatial arrangement to the aldol product. It has been well demonstrated that *E* enolborinates give *anti*-aldols, and *Z* enolborinates give *syn*-aldols stereoselectively.[120] Control of enolate geometry to achieve the formation of *E* or *Z* isomer stereoselectively is crucial for the enolboration. Thus, the formation of (*E*)-enol borinate using organoborane reagents is favored by a sterically demanding group attached to boron, whereas lesser steric requirements favor in formation of (*Z*)-enol borinates formation. Another factor, such as ketone structure, also influences the stereochemical course of enolization. Therefore, a stereoselective synthesis of β-hydroxyphosphonates using our boranophosphorus intermediate **57** might be feasible. Previously, we demonstrated that phosphorus-containig carbenoids react with organoboron reagents containing sterically demanding groups, as well as lesser steric requirements, to produce a variety of boranophosphorus intermediates (enolborinate-like) **57-t** (Scheme 4.14). In addition, structural flexibility in the phosphorus compound can also lead to successful, stereoselective synthesis of β-hydroxyphosphonates.

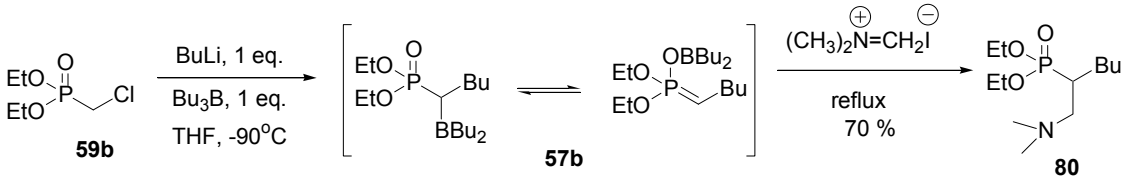
Scheme 4.27 Olefination reactions



Another reason for this homologation to be explored, is the possibility of converting β-hydroxyphosphonates into olefins. For example, aldol reaction followed by oxidation and Wadsworth-Horner-Emmons (WHE) olefination, or by treatment with fluoride could form olefins **78** and **79**, respectively (Scheme 4.27).

Our strategy for the synthesis of β-hydroxyphosphonates from intermediate **57** can also be applied to synthesize β-aminophosphonates, if the aldehyde is replaced by dialkyl(methylene)ammonium iodide. To demonstrate this possibility, the reaction of chloromethylphosphonate anion, tributylborane and dimethyl(methylene) ammonium iodide was investigated (Scheme 4.28).

Scheme 4.28 Reaction of α-boranophosphorus intermediate **57** with dimethyl(methylene) ammonium iodide

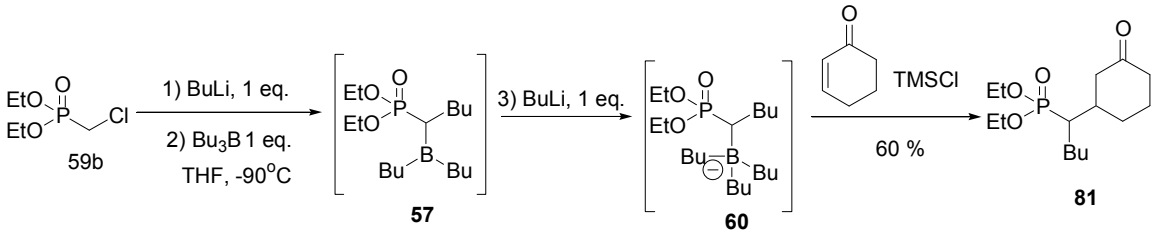


As expected, the desired product **80**, a β-aminophosphonate, was obtained in good isolated yield. The present development, similarly to that of the aldol reaction, remains to be fully investigated. However, the described examples illustrate that this method will presumably enable the synthesis of certain β-hydroxyphosphonates and β-aminophosphonates by suitable choice of substrates (all of which are easily accessible).

The next question was to determine the reactivity of boranophosphorus intermediate **57** toward conjugate addition. Unlike the aldol reaction, direct treatment of

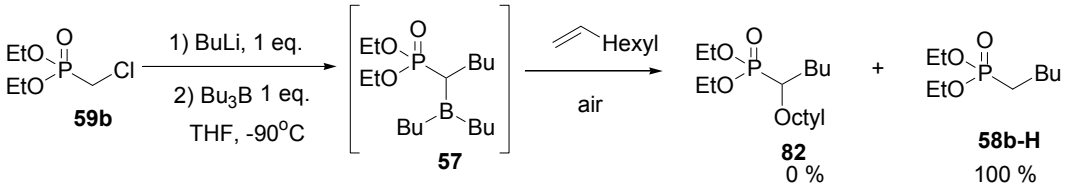
the α-boranophosphorus intermediate with 2-cyclohexanone did not result in the desired C-C bond formation. However, activation of the intermediate **57** as the borate complex **60** (Scheme 4.29) allowed us to obtain the desired conjugate addition product **81**. Unfortunately, this same reaction with acrylates (ethyl, benzyl) did not give any expected product.

Scheme 4.29 Conjugate addition reaction of α-boranophosphorus intermediate **57** with 2-cyclohexanone



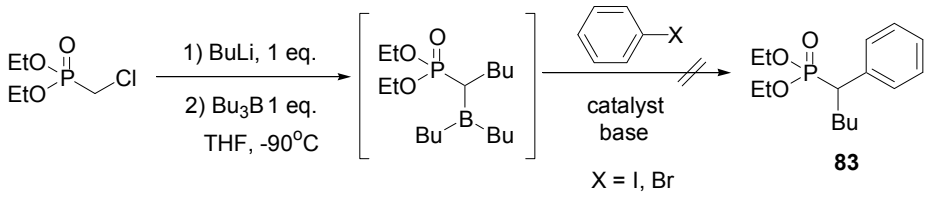
We also investigated the reactivity of α-boranophosphorus intermediate **57** towards free radical reaction. Therefore, reaction of α-boranophosphorus **57**, 1-octene in the presence of air was conducted (Scheme 4.30). Unfortunately, we obtained exclusively diethyl pentylphosphonate **58b-H** due to hydrolysis of α-boranophosphorus intermediate **57**.

Scheme 4.30 Radical reaction of α-boranophosphorus intermediate



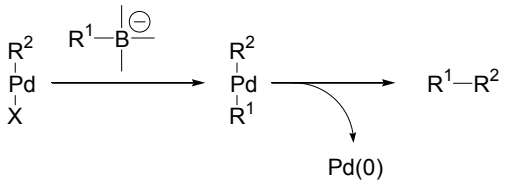
Then, we worked to establish whether or not α-boranophosphonates **57** reacts with aryl halides *via* Suzuki coupling. The palladium-catalyzed cross-coupling of organoboron compounds with organic halides or triflates in the presence of a negatively charged base (such as sodium or potassium carbonate, phosphonate, hydroxide, and alkoxides) has been extensively studied and is known as the Suzuki coupling.[121] Thus, we tested several Pd-catalysts: $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$, $Pd_2(dba)_3$, $Pd(OAc)_2$, which are commonly used in Suzuki reaction with iodobenzene in the presence of alkoxides. We also examined bromobenzene in the presence of Ni catalysts, such as $NiCl_2(PPh_3)_2$, $NiCl_2(dppe)_2$. Unfortunately, the reaction depicted in Scheme 4.31 did not provide any coupling product **83**.

Scheme 4.31 Attempted cross-couping reaction of α-boranophosphonates **57**

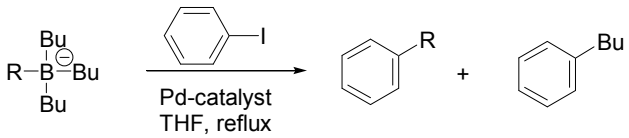


We also conducted reactions without base. However, the transmetalation between organopalladium (II) halides and organoboron compounds does not occur readily due to low nucleophilicity of the organic group on the boron atom. Nonetheless, such nucleophilicity can be enhanced by quaternization of the boron with negatively charged bases giving the corresponding "ate" complexes (Scheme 4.32).[92c, 122]

Scheme 4.32 Cross-coupling reaction of ate complex



In fact, it is reported that ate complexes undergo a clean coupling reaction with iodobenzene (Eq. 4.10)[123]

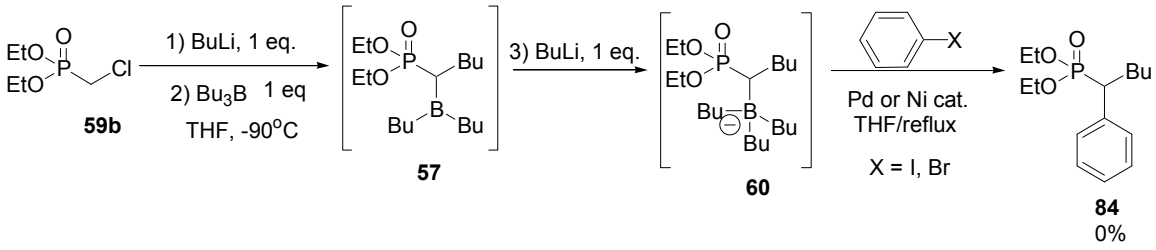


Eq. 4.10

R = Bu	$Pd(PPh_3)_4$		82 %	
	$PdCl_2(dppf)$		81 %	
R = $C_4H_9C\equiv C$	$Pd(PPh_3)_4$	71 %	29 %	overall 98 %
	$PdCl_2(dppf)$	95 %	5 %	overall 81 %

Hence, we performed reactions of activated complex **60** with halobenzenes in the presence of $Pd(PPh_3)_4$, $PdCl_2(dppf)$, $NiCl_2(PPh_3)_2$, $NiCl_2(dppf)$ (Scheme 4.33).

Scheme 4.33 Attempted cross-coupling of borate complex **60** with aryl halides**.**

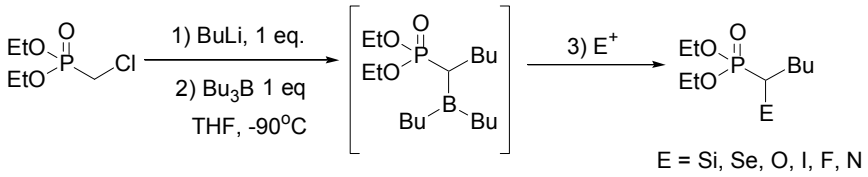


Unfortunately, activated α-boranophosphonates did not couple with iodobenzene under the condition investigated.

4.3.3 Transformation P-C-B complex into P-C-X functionalities (X = Si, Se, O, I, F, N).

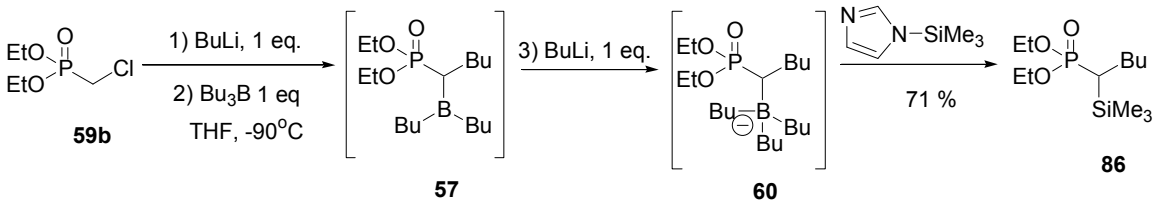
The reactivity of α-boranophosphorus intermediate **57** towards electrophiles other than H, D, P, C was investigated next, in order to further explore the scope and limitations of our method (Scheme 4.34).

Scheme 4.34 Reactivity of α-boranophosphorus intermediate **57** towards E^+: Si, Se, O, I, F, N



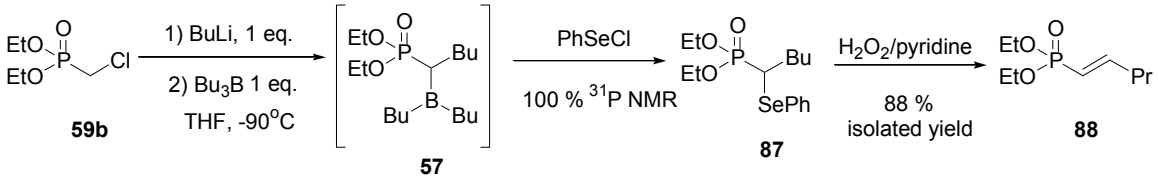
Initially, we investigated the silylation reaction, by treating intermediate **57** with various silylation reagents (e.g., *N*-trimethylsilylimidazole, trimethysilyl chloride, triisopropylsilyl chloride, *t*-butyldimethylsilyl trifluoromethanesulfonate, triisopropylsilyl trifluoromethanesulfonate). However, only the reaction of activated borate complex **60** with *N*-trimethylsilylimidazole resulted in the formation of α-silylated phosphonate **86** (Scheme 4.35).

Scheme 4.35 Reaction of borate complex **60** with N-trimethylsilylimidazole



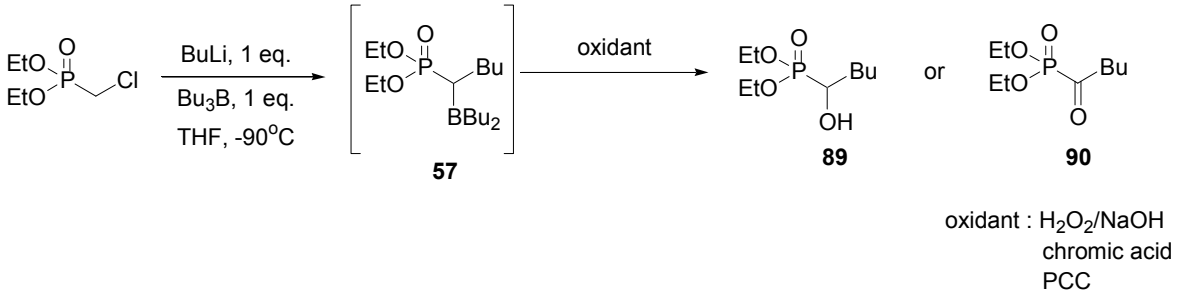
Another interesting transformation is the selenylation reaction (Scheme 4.36). Unactivated α-boranophonate **57** successfully reacts with benzeneselenenyl chloride to yield α-selenophosphonate **87**, which can be isolated if required or oxidized directly (H_2O_2/pyridine) in a simple "one pot" procedure.

Scheme 4.36 Reaction of α-boranophonate **57** with benzeneselenenyl chloride



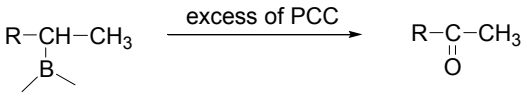
One of the most common functionalizations of the C-B bond is oxidation to alcohols and carbonyl compounds. Hence, we investigated the oxidation of α-boranophosphonate intermediate **57** using reagents known from the literature to oxidize organoboron compounds: H_2O_2/NaOH, chromic acid and pyridine chlorochromate (Scheme 4.37).

Scheme 4.37 Oxidation of α-boranophosphonate intermediate **57**



The standard oxidation reaction procedure for a C-B bond employs 30 % hydrogen peroxide and 3 M sodium hydroxide at 20 – 50 °C.[92a] However, under these conditions,

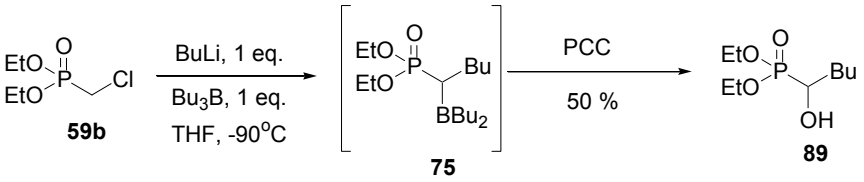
α-boranophosphonate **57** was not converted into the corresponding α-hydroxyphosphonate **89**. Diethyl pentylphosphonate was obtained exclusively, due to faster hydrolysis of the α-boranophosphonate **57**. Also reaction with chromic acid produced only diethyl pentylphosphonate. To avoid hydrolysis of α-boranophosphonate, we turned our attention to pyridine chlorochromate (PCC) as an anhydrous oxidant. Oxidation with this reagent does not require an aqueous solution and a variety of organoboranes containing primary or secondary alkyl groups can be oxidized to corresponding the aldehydes and ketones in excellent yields (Eq. 4.11).[124]



Eq. 4.11

To examine the oxidation of α-boranophosphonate **57** to the corresponding α-ketophosphonate **90** with PCC, we conducted the reaction depicted in Scheme 4.38. Surprisingly, we obtained α-hydroxyphosphonate **89** in 50 % isolated yield (100 % ^{31}PNMR), instead of the expected α-ketophosphonate **90**.

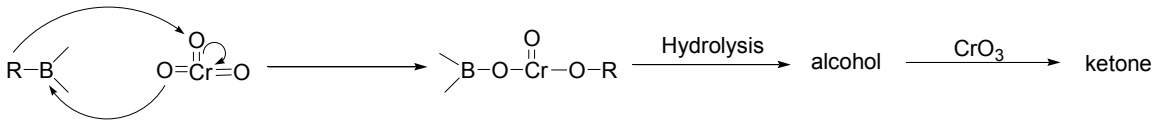
Scheme 4.38 Oxidation of α-boranophosphonate intermediate **57** with PCC



However, the formation of α-hydroxyphosphonate **89** instead of α-ketophosphonate **90** can be explained by a mechanistic study of the original reaction. The oxidation of organoboranes with PCC probably proceeds *via* the formation of alcohols, which are

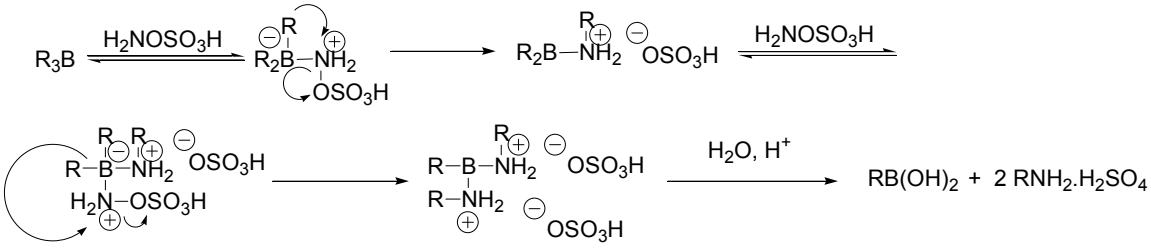
subsequently oxidized to ketones (Scheme 4.39). Analysis of an incomplete reaction by IR and GLC showed the presence of alcohol and ketone.[124c] We can assume that oxidation of the α-boranophosphonate with PCC proceeds via a similar mechanism as Brown's original reaction, but in our case the reaction stops at the alcohol stage. PCC is not efficient enough to oxidize α-hydroxyphosphonate **89** to α-ketophosphonate **90**.

Scheme 4.39 Mechanism of oxidation reaction of organoboranes proposed by Brown



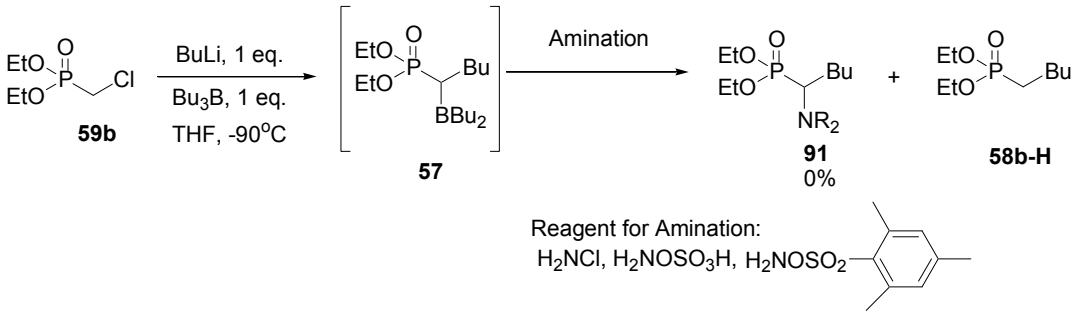
Another particularly important transformation of the C-B bond is amination. Trialkylboranes react rapidly with chloroamine and other ammonia derivatives containing a good leaving group, producing the corresponding amines. Hydroxylamine-*O*-sulfonic acid and *O*-(mesitylsulfonyl)hydroxylamine (MSH) are more stable than chloroamine and are the preferred reagents.[92b,125] A mechanism involving a 1,2-shift of the alkyl group from boron to nitrogen in the organoborane-amine adduct accounts for the results (Scheme 4.40).

Scheme 4.40 Mechanism of amination of organoboranes with hydroxylamine-*O*-sulfonic acid

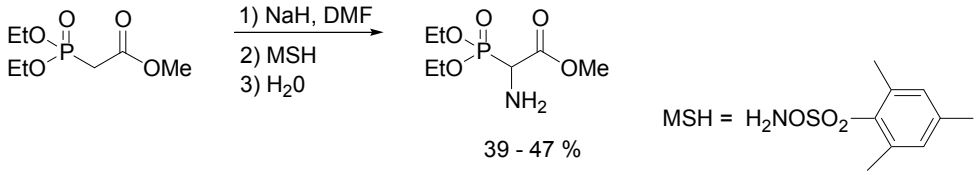


However, these methods for the amination of α-boranophosphonate **57** did not result in the formation of α-aminophosphonate **91**. In all these cases, diethyl pentylphosphonate was obtained instead, due to hydrolysis of α-boranophosphonate (Scheme 4.41).

Scheme 4.41 Attempted amination of α-boranophosphonate **57**



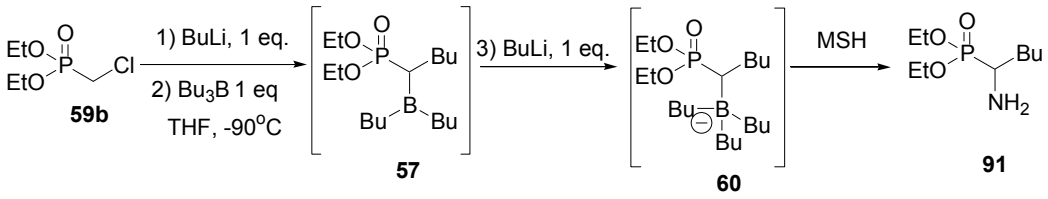
On the other hand, it was demonstrated by Scopes[126] that *O*-(mesitylsulfonyl)hydroxylamine (MSH) reacted with the sodium enolate of methyl diethylphosphonoacetate to give aminated products in moderate yield (Eq. 4.12).



Eq. 4.12

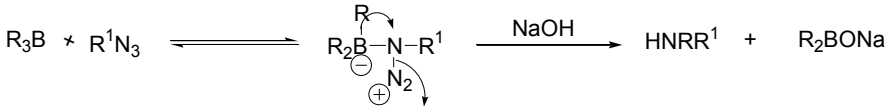
Encouraged by this result, we conducted the reaction of activated intermediate **57** as the borate complex **60** with MSH (Scheme 4.42) However, our strategy failed again, and diethyl pentylphosphonate was again obtained exclusively.

Scheme 4.42 Attempted amination of borate complex **60** with MSH



An alternative way to convert organoboranes into amines is through the reaction with organic azides followed by hydrolysis (Scheme 4.43).[127] However, this method also did not produce α-aminophosphonate from α-boranophosphonate and RN_3 (R = octyl, benzyl).

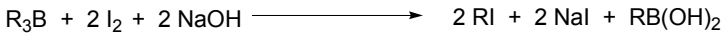
Scheme 4.43 Amination of organoboranes with organic azides



α-Aminophosphonates are highly valuable compounds in medicine and agriculture, due to their biological activities.[128] Therefore, we devoted extensive work to synthesize of α-aminophosphonates from organobonanes. However, the most common methods, known in the literature to convert organoboranes into amines, were unsuccessful in the preparation of α-aminophosphonate **91** from α-boranophosphonate.

In next stage of our work, we studied halogenolysis of α-boranophosphonate intermediate **57**. The carbon-boron bond in trialkylboranes is surprisingly stable to the direct action of halogens, such as bromine and iodine.[129] In the presence of alkali, a reaction readily occurs to give the corresponding alkyl halides.[130,131] For example, iodine

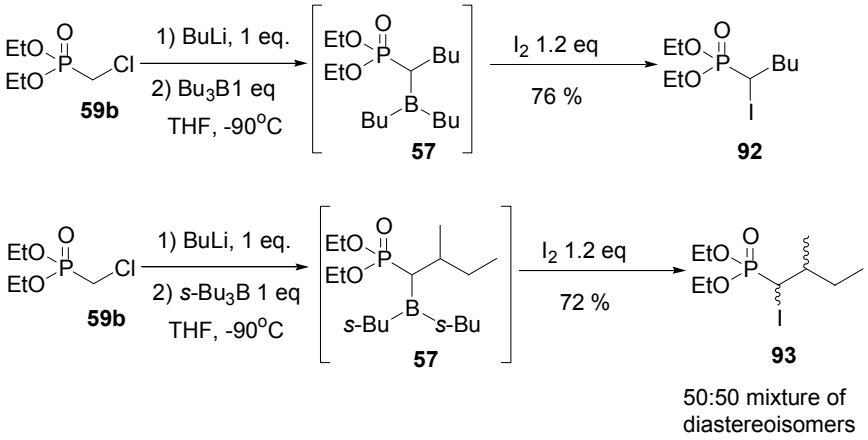
fails to react directly with organoboranes except under relatively drastic conditions.[132] However, the addition of sodium hydroxide in methanol to the organoboranes and iodine brings about a rapid reaction (Eq. 4.13).[92b]



Eq. 4.13

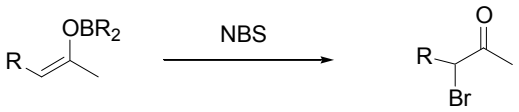
Only two of three primary alkyl groups react, and the situation is even less favorable for secondary alkyl groups. To test the possibility of halogenolysis of α-boranophosphonate intermediate, we conducted reactions depicted in Scheme 4.44. The successful iodination of α-boranophosphonate intermediates **57** provided highly functional α-iodophosphonates **92** and **93** in good yields. It is interesting to note that one C-B bond reacts selectively, as would be expected from some boron enolate character in **57**. These iodophosphonates might also be indirect precursors to valuable compounds such as α-aminophosphonates and related compounds.

Scheme 4.44 Synthesis of α-iodophosphonates



Halogenolysis of α-boranophosphonate intermediates **57** with bromine under similar condition did not provide α-bromophosphonates. However, bromolysis of intermediate

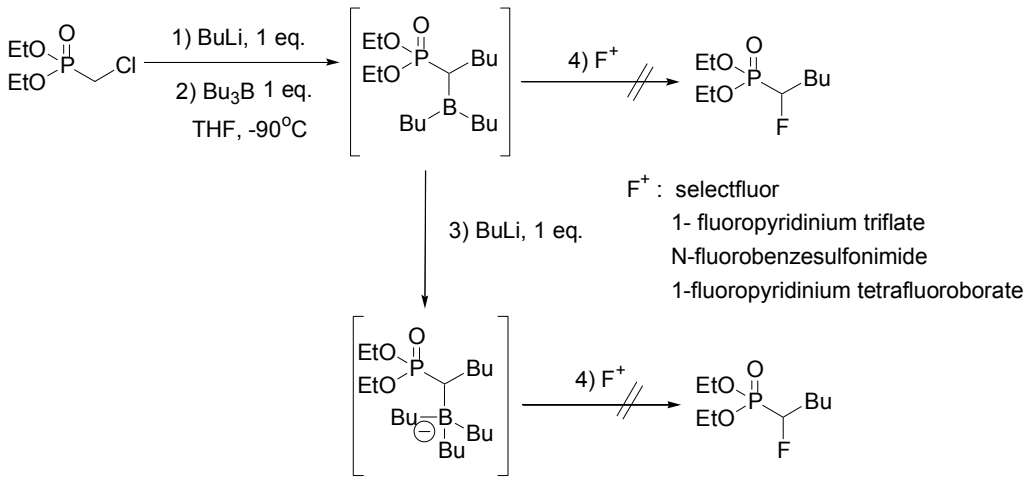
57 might possibly be accomplished by using N-bromosuccinimide (NBS). Since it is known from the literature that enol borinates reacts with NBS to give α-bromoketones (Eq. 4.14),[133] an analogous reaction of α-boranophosphonate intermediates **57** will be investigated in the future.



Eq. 4.14

Additionally, we investigated the possibility of the synthesis of α-fluorophosphonates (Scheme 4.45). Unfortunately, neither α-boranophosphonate **57**, nor activated borate complex **60** reacted with electrophilic fluorinating reagents (selectfluor, 1-fluoropyridinium triflate, N-fluorobenzesulfonimide, 1-fluoropyridinium tetrafluoroborate) commonly used in the fluorination reactions of phosphonate carbanoins.[134] Most of the reactions gave **58b-H**.

Scheme 4.45 Attempted fluorination of α-boranophosphonate **57**



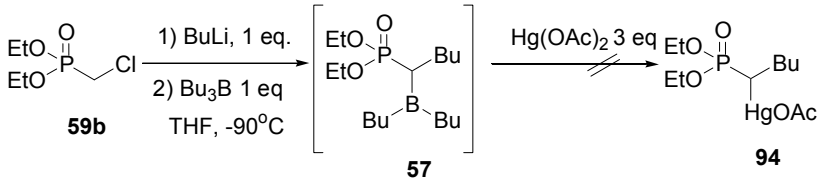
We also studied the transmetallation reaction of α-boranophosphonate **57** with Hg and Zn. Organoboranes derived from terminal olefins *via* hydroboration undergo a

quantitative reaction in a matter of minutes with mercuric acetate at 0 ^{o}C or at rt to give the corresponding alkylmercuric acetates in essentially quantitative yields (Eq 4.15).[135]

$$(RCH_2CH_2)_3B + 3\ Hg(OAc)_2 \xrightarrow{THF} 3\ RCH_2CH_2HgOAc + B(OAc)_3 \qquad \textbf{Eq. 4.15}$$

However, secondary alkyl groups require much more vigorous conditions (longer time at high temperature and low yield) to react and this can be a reason the reaction shown in Scheme 4.46 did not yield product **94**.

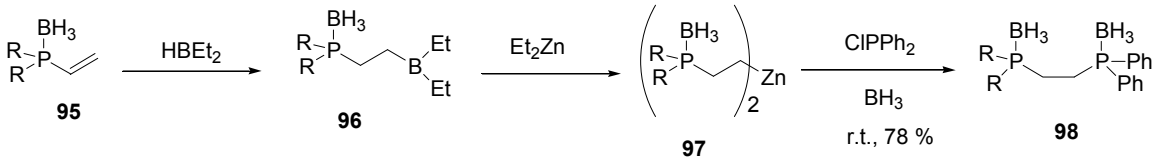
Scheme 4.46 Reaction of α-boranophosphonate **57** with mercury acetate



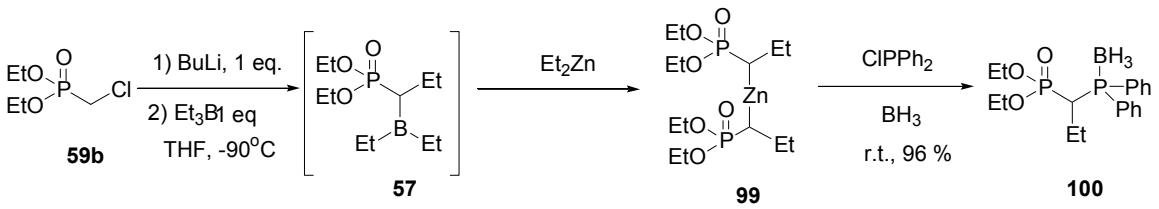
Recently, the boron-zinc transmetallation has been gaining importance for the preparation of organozinc compounds. Dialkylzincs are convenient reagents for the synthesis of ketones, esters, nitroalkenes, alkynes, optically active alcohols and even phosphorus compounds.[136] It was demonstrated by Knochel[137] (Scheme 4.47) that boron intermediate **96** undergoes reaction with diethylzinc to give intermediate **97**, which then reacts with chlorodiphenylphosphine in 78 % yield. Since intermediate **96** is comparable in structure to our α-boranophosphonate **57**, we performed an analogous reaction (Scheme 4.48). We obtained the product **100** in 96 % isolated yield. However, we demonstrated previously that exactly this same compound can be formed from activated borate complex **60** (scheme 4.16). Therefore, at this stage of our investigation we are not able to distinguish whether compound **100** is formed through a true boron-zinc transmetallation or simply by

activation of α-boranophosphonate **57** with diethylzinc. Nonetheless, there is a difference in the reaction conditions - the reaction with activated borate intermediate proceeds during 2 h under reflux, in the reaction with diethylzinc is complete after only 1 h at rt.

Scheme 4.47 Example of Knochel's Boron-Zinc Transmetallation[137]



Scheme 4.48 Synthesis of a Bisphosphorus Compound *via* Boron-Zinc Transmetallation

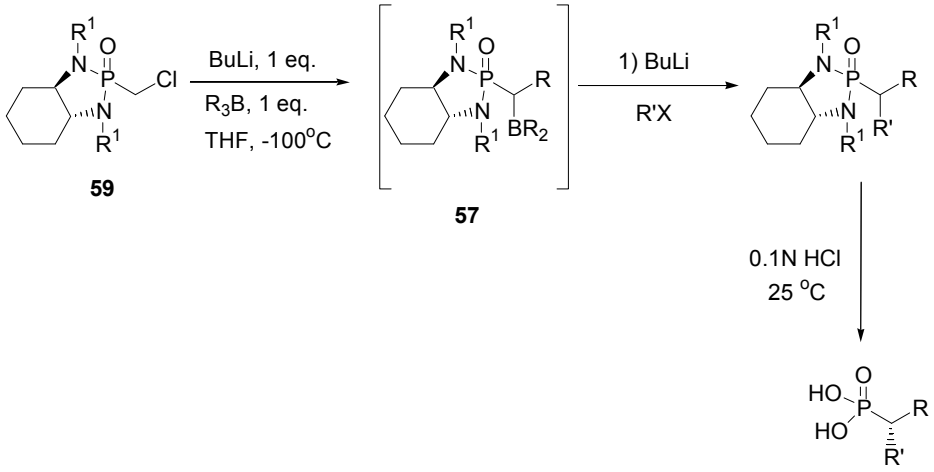


4.4 Asymmetric Synthesis of Functionalized Organophosphorus Compounds *via* Organoboranes.

Implementation of the methodology for asymmetric synthesis is an important objective. Chirality can be either contained in the phosphorus reagent **59**, or in the boron moiety. Since migration from boron to carbon is known to be stereospecific,[92b] it is possible that a product would be obtained in high diastereo- or enantiomeric ratios (depending on where the chiral group initially resides). A general approach to chiral α-

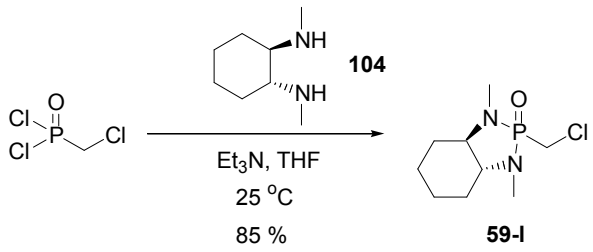
substituted organophosphorus compounds could be a major advance in this field. First, we investigated the reaction where chirality was contained in the phosphorus moiety **59** (Scheme 4.49).

Scheme 4.49 Asymmetric synthesis of functionalized organophosphorus compounds *via* organoboranes.



59 **57**

To test the possibility of the reaction depicted in scheme 4.49, we prepared (chloromethyl)phosphonamides **59-l** (the Hanessian auxiliary)[138] from (*R,R*)-1,2-bis-N-methylamino-cyclohexane **104** and (chloromethyl)phosphonic dichloride, in 85 % isolated yield (Eq. 4.16).

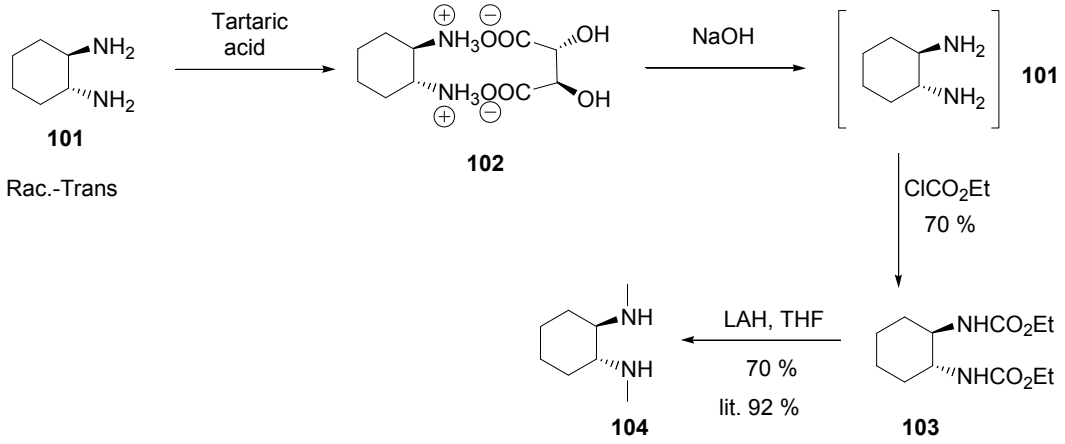


59-l

Eq 4.16

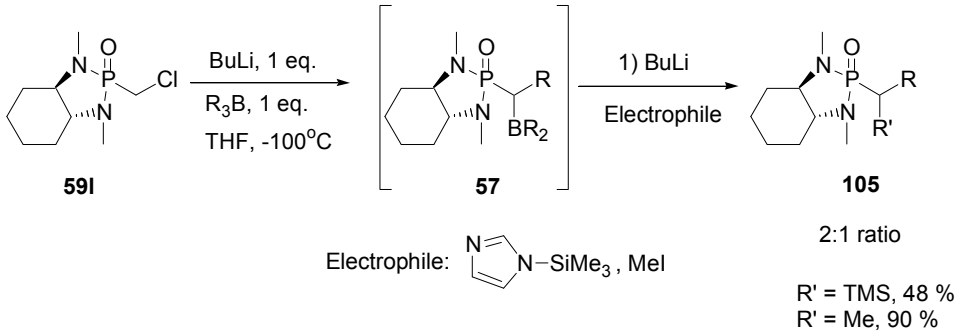
Diamine **104** can be readily obtained from commercial enantiopure (*R,R*)-1,2-diaminocyclohexane **101** by a two-step *N*-methylation procedure,[138] however large-scale processing is severely undermined by the high cost of this starting material. Another possibility involves resolution of (+/-)- *trans*-1,2-diaminocyclohexane with L-(+)-tartaric acid.[139] However, the regeneration of enantiopure free 1,2-diaminocyclohexane, under basic conditions, is troublesome due to its high solubility in water (drying has to be carried out with pieces of sodium) and its sensitivity (it forms carbonates very easily).[139a] In contrast, the tartrate salt **102** is very stable, and can be stored for months at rt and is easy to prepare in large amounts according to a recently improved synthesis.[139b] Taking these factors into account, our strategy was to use the very stable (*R,R*)-1,2-diaminoniumcyclohexane mono-(+)-tartrate salt **102** and regenerate *in situ* the free amine **101** to give desired *N*-substituted diamine directly (Scheme 4.50). Thus, *in situ* trapping of the intermediate free diamine **101** with ethyl chloroformate gave directly the bis-carbamate **103** in 70 % isolated yield. After LAH reduction, pure (*R,R*)-1,2-*N,N*'-(dimethyl)diaminocyclohexane **104** could be obtained as shown in Scheme 4.50.

Scheme 4.50 Synthesis of (*R,R*)-1,2-bis-N-methylamino-cyclohexane **104**

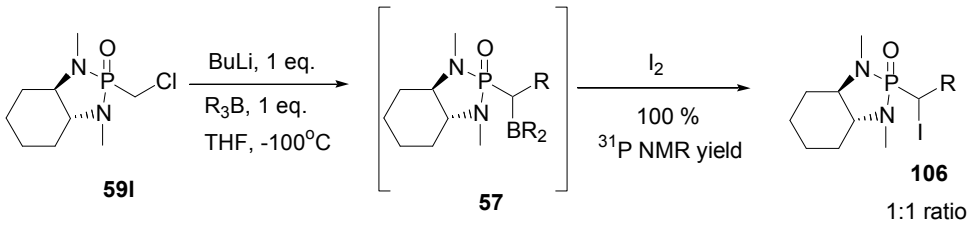


With **104** in hand, we then studied the reaction of (chloromethyl)phosphonamides carbenoid **59-l** with tributylborane and electrophiles (N-trimethylsilylimidazole, iodomethane) (Scheme 4.51). Reaction of **59-l** with *n*-butyllithium at low temperature (-100 ^{o}C) forms the corresponding carbenoid **59-l** which then reacts with Bu_3B. Addition of another equivalent of BuLi to the resulting intermediate **57** formed borate, which then reacted with *N*-trimethylsilylimidazole and iodomethane in 48 % and 90 % yields, respectively. In both cases we obtained the products in a disappointing 2:1 diasteroisomeric ratio (Scheme 4.51).

Scheme 4.51 Reaction of 59l with electrophiles

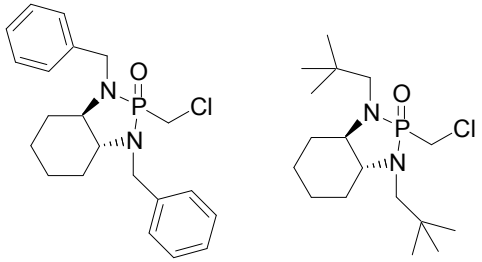


Scheme 4.52 Iodination reaction



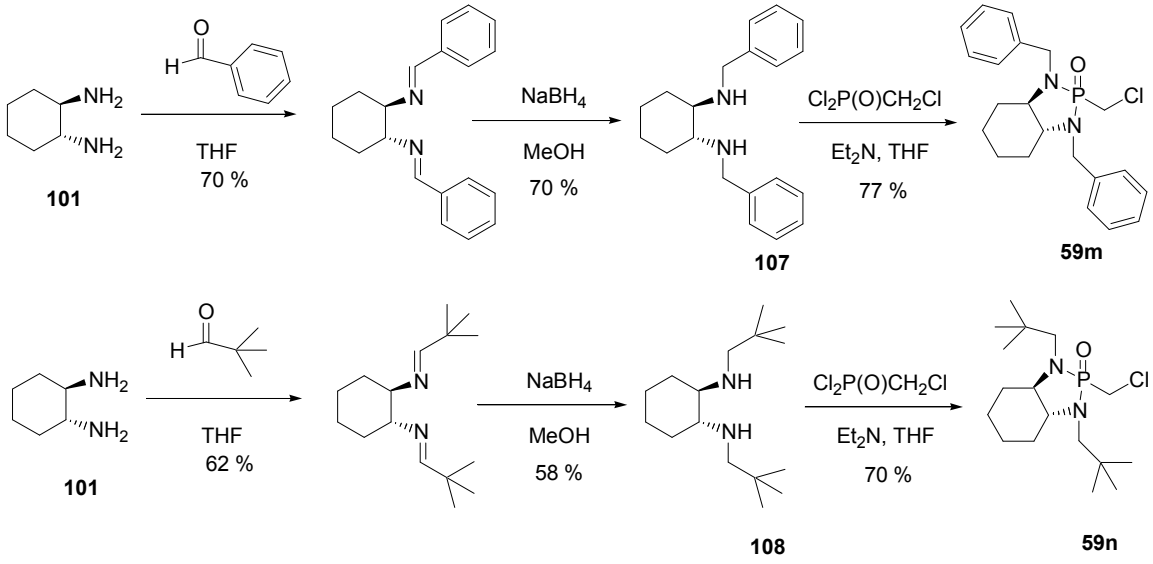
An iodination reaction of the α-boranophosphonamide was also attempted (Scheme 4.52). α-Iodophosphonamide **106** was formed in 100% ^{31}P NMR yield and 1:1 ratio. Since the above results were unsatisfactory, we then turned our attention to other chiral auxiliaries (Figure 4.3).

Figure 4.2 Chiral auxiliaries which were investigated



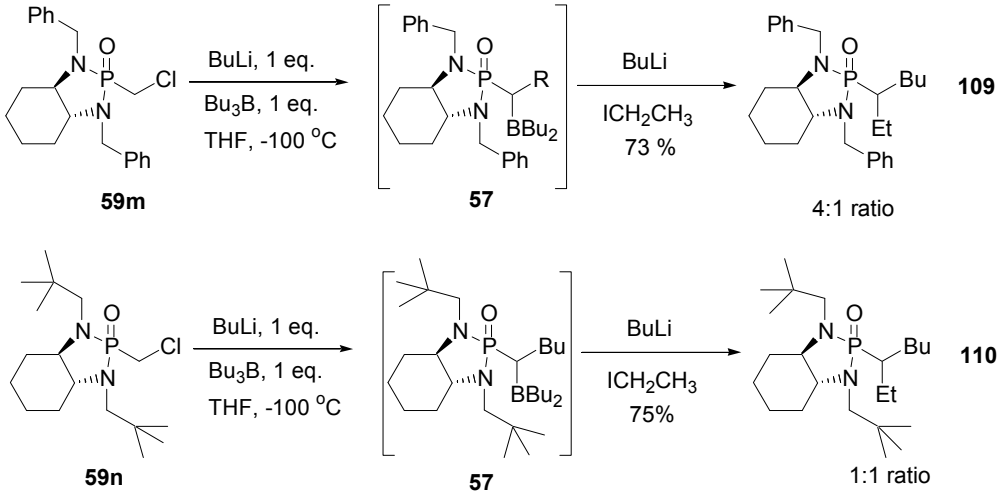
59m **59n**

Scheme 4.53 Synthesis of chiral auxiliary **59m** and **59n**



(Chloromethyl)phosphonamides (**59m** and **59n**) were prepared from (chloromethyl)phosphonic dichloride and the corresponding diamines **107** and **108** in good yields. Diamines **107** and **108** were obtained in two steps from resolved trans-1,2-diaminocyclohexane **101** and an aldehyde (benzaldehyde and pivaldehyde), followed by reduction with $NaBH_4$ (Scheme 4.53). When (chloromethyl)phosphonamides **59m** was used as starting material and iodoethane as the electrophile, product **109** was obatined in 73 % isolated yield and in a 4:1 diastereoisomeric ratio (Scheme 4.54). However, reaction of (Chloromethyl)phosphonamides **59n** and this same electrophile yielded product **110** in 75 % ^{31}PNMR and 1:1 ratio (Scheme 4.54).

Scheme 4.54 Reaction of **59m** and **59n** with Bu_3B, followed by alkylation with EtI



4.5 Conclusion

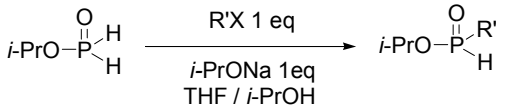
We developed a novel and general methodology for the synthesis of a variety of organophosphorus compounds (phosphonates, phosphinates, phosphonothioates,

boranophophonates, phosphine-boranes, *H*-phosphinates) using organoboron reagents. In some cases, selective transfer of one group attached to the boron atom has been achieved. However, the generality of selective migration might possibly be improved by studying organoboron reagents other than the 9-BBN derivatives, for example: catecholborane, dimesitylborane or dimethylborane *etc.* could be investigated. We also demonstrated that the α-boranophosphorus intermediates can be converted into various functional organophosphorus compounds, for example: phophorylation, acylation, alkylation, aldol, silylation, selenylation, reaction with iminium ions, iodination and oxidation delivered bis-phosphorus, β-ketophosphonates, secondary phosphonates, β- hydroxyphosphonate, α-silanophosphonate, α-selenophosphonate, β-aminophosphonate and α-iodophosphonate, respectively. Therefore, our methodology lends itself to combinatorial approaches. Finally, we investigated asymmetric version of our reaction. The best result, a 4:1 ratio, was obtained using a chiral auxiliary (Scheme 4.53). However, other auxiliaries remain to be investigated and chiral boron reagents possibly might also improve this ratio.

Chapter V: Borane Complexes of the H_3PO_2 P(III) Tautomer

5.1 Introduction

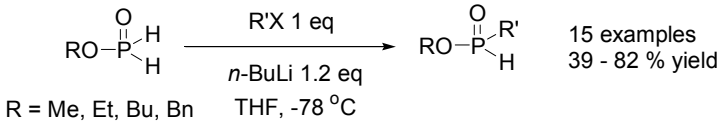
Theoretically, the direct alkylation of alkyl phosphinates ($ROP(O)H_2$) under basic conditions would be an efficient approach for the synthesis of *H*-phosphinic acid esters. However, the anions derived from unhindered esters (R = Me, Et) of hypophosphorous acids, prepared by the Fitch method,[56] were reported to decompose rapidly, and consequently the formation of *H*-phosphinic acid esters did not occur.[140] Alternatively, Gallagher reported the alkylation of isopropyl phosphinate (prepared by the Nifant'ev method) using alkyl halides and sodium isopropoxide as base (Eq. 5.1).[16]



Eq. 5.1

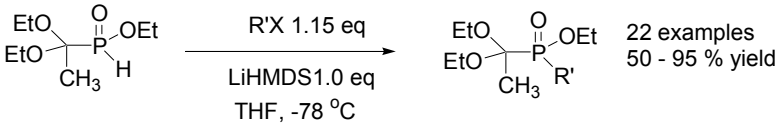
R'X = MeI, AllBr, BnBr, n-PentI, $Br(CH_2)_4Br$

The successful alkylation was attributed to the more hindered nature of the ester, which slowed down decomposition. Unfortunately, this method has not found widespread use. The alkoxysilane-based esterification (Eq. 2.1),[58] developed by Montchamp, provides alkyl phosphinates in excellent yields. Alkyl phosphinates prepared by this method not only have exceptional thermal stability in various solvents, but they are also more robust than prepared with the other methods (Fitch and Nifant'ev). The alkylation of these phosphinates under basic conditions was therefore investigated (Eq 5.2).[23] His method is straightforward and it is compatible with the formation of various esters of *H*-phosphinic acids. However, good yields are only obtained with the more reactive electrophiles such as methyl iodide and allylic bromides.



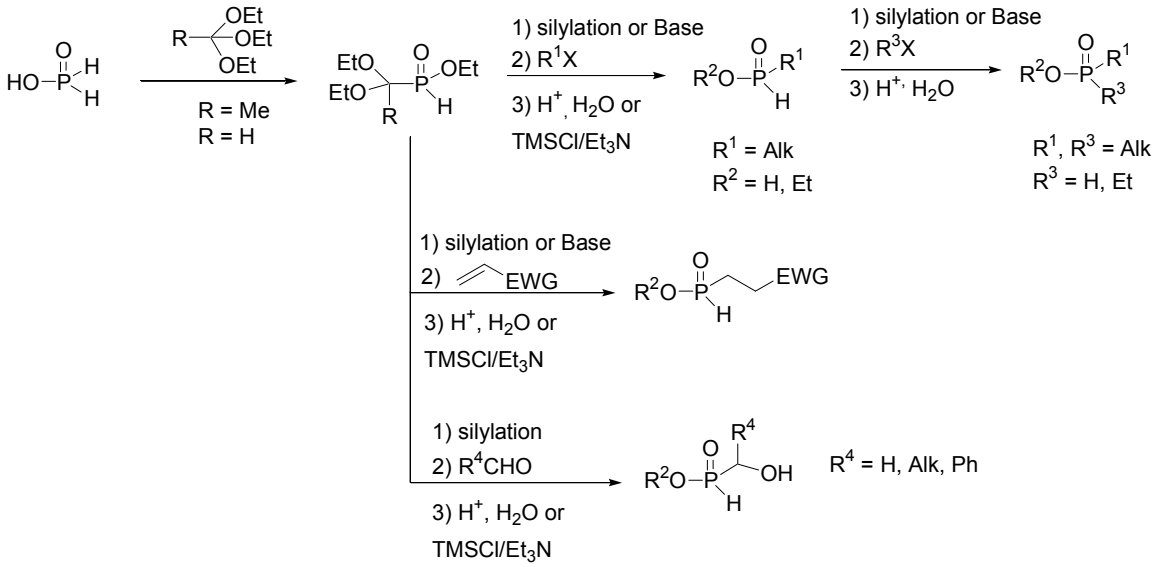
Eq. 5.2

To avoid problems associated with lack of stability of anions derived from alkyl phosphinates, Montchamp reported the alkylation reaction of the "Ciba-Geigy" reagents under basic conditions with various electrophiles (Eq. 5.3).[17]



Eq. 5.3

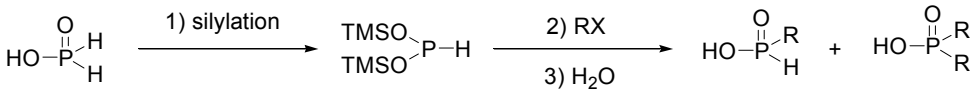
Scheme 5.1 "Ciba–Geigy" reagents in the synthesis of phosphinic acid derivatives



The Ciba–Geigy synthons are commonly used in the preparation of phosphinic acid derivatives (Scheme 5.1),[141] however, these reagents rely on a protection-deprotection strategy, which reduces the compatibility with functionalized compounds since an acidic cleavage of the acetal is required. The first generation uses 1,1-diethoxymethyl as protecting group (Scheme 5.1, R = H), which demands vigorous acidic conditions for its

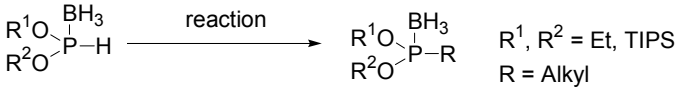
removal (aq. HCl, 100°C).[141a-c] The second generation of reagents (R = Me) uses a slightly modified ketal protecting group (1,1-diethoxyethyl), which can be cleaved under milder conditions (excess TMSCl in $CHCl_3$, rt).[141d]

Similarly, bis(trimethylsiloxy)phosphine ($(TMSO)_2PH$, also called BTSP) has been employed for the preparation of *H*-phosphinic acids, although some problems exist with this approach: the reagent is pyrophoric and it typically requires a large excess of BTSP to favor monosubstitution (Eq. 5.4).[15]



Eq. 5.4

Therefore, we decided to investigate the borane complexes derived from the P(III) form of H_3PO_2, an equivalent to alkyl phosphinates and an alternative to the "Ciba–Geigy" reagent (Eq. 5.5)



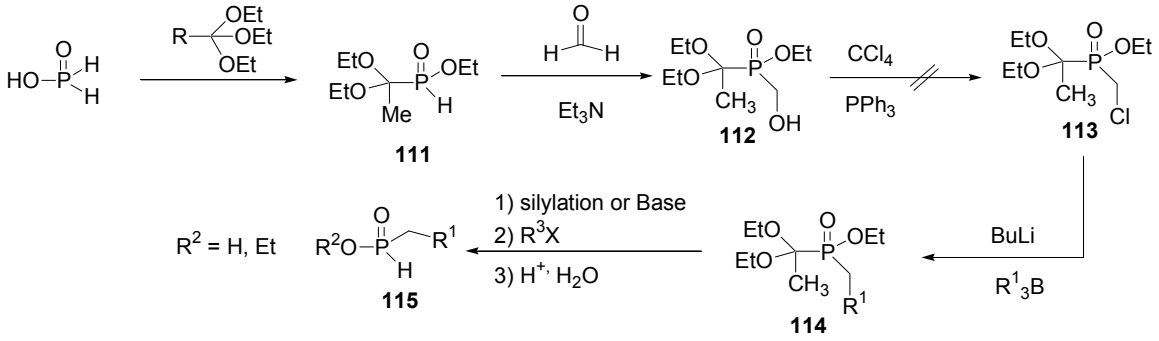
Eq. 5.5

5.2 Synthesis and Reactivity of Diethoxyphosphine-Borane $(EtO)_2P(BH_3)H$

During the development of our methodology for the synthesis of organophosphorus compounds *via* organoboranes (Chapter IV), we have introduced novel phosphonite-borane complexes **59i** (Chapter IV, Scheme 4.8), which are the precursors to *H*-phosphinates (Scheme 4.8). It is important to note that our first approach for the synthesis of *H*-phosphinates **115** *via* organoboranes using the "Ciba–Geigy" reagent **111** (Scheme 5.2) failed, since we were not able to convert compound **112** into product **113**. The "Ciba–Geigy" synthon was not compatible with the reaction conditions

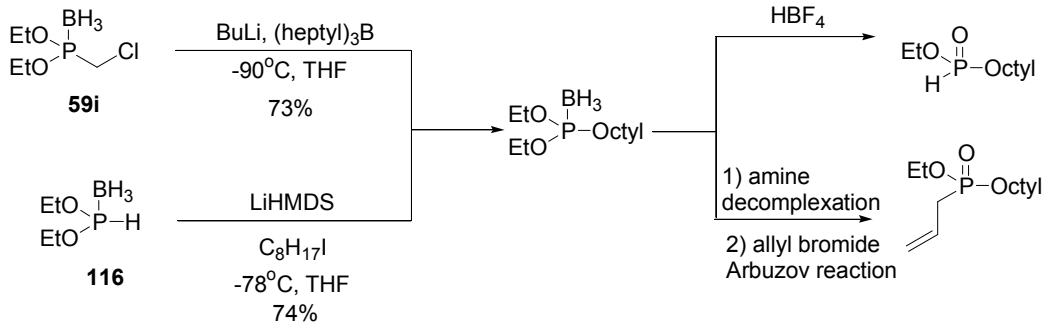
and afforded the formation of several products including the cleavage of 1,1-diethoxymethyl (protection group).

Scheme 5.2 Attempted synthesis of *H*-phosphinates from "Ciba–Geigy" reagent via organoboranes



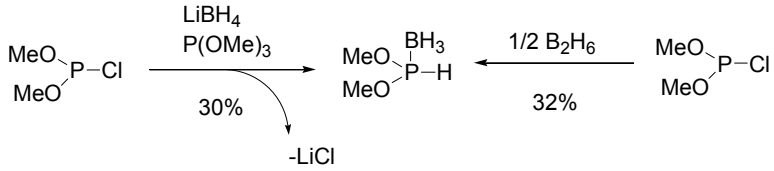
The successful reaction of diethoxy-(chloromethyl)phosphonite-borane **59i** with organoboranes, and more importantly, the development of the straightforward conversion of phosphonite-borane complexes into *H*-phosphinates through decomplexation reaction with HBF_4 (Table 4.3, Chapter IV) encouraged us to investigate an additional and potentially more general way for the synthesis of phosphonite-borane complexes from diethoxyphosphine-borane $(EtO)_2P(BH_3)H$ **116** (Scheme 5.3).

Scheme 5.3 Synthesis of phosphinates from **59i** or alternatively from **116**



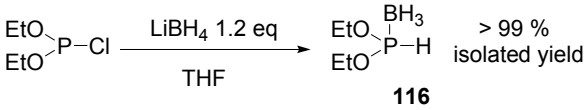
If successful, $(EtO)_2P(BH_3)H$ could become an important alternative to the "Ciba–Geigy" reagents. Although secondary phosphine-boranes are well known,[49,142] the reactivity of dialkoxyphosphine-boranes toward P–C bond formation has never been reported. In fact, we are aware of only one example of a dialkoxyphosphine-borane complex in the literature. Centofanti described the synthesis of pyrophoric $(MeO)_2P(BH_3)H$ (Scheme 5.4), but no further investigation was conducted.[143]

Scheme 5.4 Centofanti's synthesis of $(MeO)_2P(BH_3)H$[143]



We have repeated Centofanti's work and similarly found that the compound is pyrophoric and difficult to purify resulting in a low yield of material, confirming his report. Thus, $(MeO)_2P(BH_3)H$ is ill-suited for use as a practical reagent.

In contrast $(EtO)_2P(BH_3)H$ **116** has remarkable stability and is obtained in nearly qualitative isolated yield (>99 %) from the reduction of commercially viable chlorodiethoxyphosphine with lithium borohydride (Eq. 5.6).

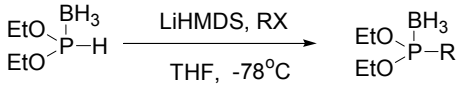


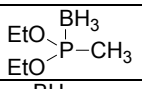
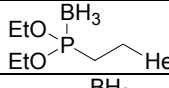
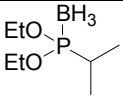
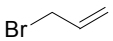
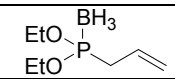
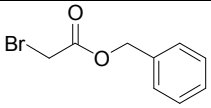
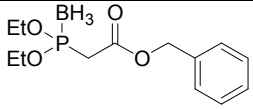
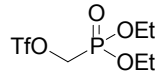
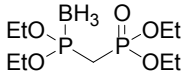
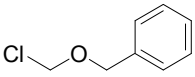
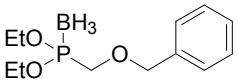
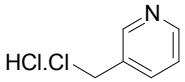
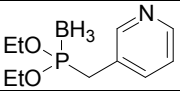
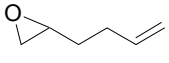
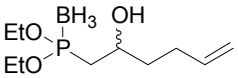
116 **Eq. 5.6**

Reaction with sodium borohydride was also investigated, but the reaction did not produce $(EtO)_2P(BH_3)H$ in acceptable yield, possibly because of the poor solubility of sodium borohydride in THF and other tested solvents. The quantitative NMR yield of the reaction with lithium borohydride makes the purification step very easy, and allows us to obtain

product **116** in very high isolated yield. Furthermore, $(EtO)_2P(BH_3)H$ in contrast to the "Ciba–Geigy" reagent can be stored for at least 4 months at 10 ^oC without any decomposition.

Table 5.1 Scope of the base-promoted alkylation of $(EtO)_2P(BH_3)H$

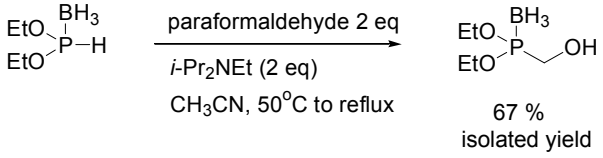


Entry	Electrophile	Reactin time	Product	^{31}P NMR Chemical shift (ppm)	^{11}B NMR Chemical shift (ppm)	Isolated yield
1	MeI	2 h		149.7	- 41.8	80
2a 2b	OctI OctBr	4 h 4 h		148.9	-42.2	74 77
3		4 h		154.8	-45.0	49
4		12 h		144.0	-42.9	69
5		12 h		139.1	-42.2	25
6		12 h		138.8 & 19.9	-41.4	52
7		20 min		138.0	-43.0	89
8[b]		12 h		143.0	-43.0	69
9a 9b	 $+BF_3.Et_2O$	12 h 12 h		146.8	-42.2	36 50

In the next stage, we tested the reactivity of $(EtO)_2P(BH_3)H$ towards alkylation reactions. Similarly to the "Ciba–Geigy" synthon, the anion derived from $(EtO)_2P(BH_3)H$ was generated with LiHMDS as a base, then alkylated with electrophiles. The alkylation products were isolated in moderate to good yields (Table 5.1). Various alkyl halides

reacted uneventfully. Even a secondary iodide (Entry 3) could be employed in moderate isolated yield. These results are at least comparable to those previously reported by our group with the Ciba–Geigy reagents.[17] The reaction of $(EtO)_2P(BH_3)H$ can also produce phosphonate-phosphonite borane complex (Entry 6), which was previously prepared by Bisseret,[144] who demonstrated that this compound can be used for the preparation of various pyrophosphate analogs. $(EtO)_2P(BH_3)H$ can also react with an epoxide, and in this case, the use of a Lewis acid improved the yield significantly (entry 9b *vs* entry 9a).

Since the Ciba–Geigy reagents are commonly used in the reaction with carbonyl compounds (for example: the formation of compound **112** in Scheme 5.2, and Scheme 5.1), we decided to conduct the reaction of $(EtO)_2P(BH_3)H$ with paraformaldehyde, and we obtained product in 67 % isolated yield (Eq. 5.7). It is important to note that the hydroxyl group does not affect the decomplexation process. We have already demonstrated that phosphinite-borane containing an hydroxyl group undergoes the conversion to corresponding hydroxy-*H*-phophinate in high yield (Scheme 4.23). Even if direct addition of alkyl phosphinate (ROP(O)H2) to carbonyl compounds is superior[58,145] the possibility to examine chiral dialkoxyphosphine-borane complexes is still interesting.

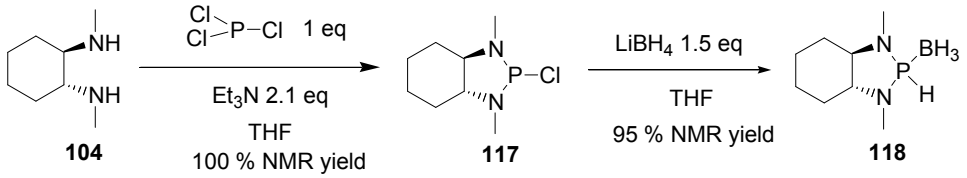


Eq. 5.7

The asymmetric version of these phosphorus synthons remains to be investigated. We have conducted only one attempt for the synthesis of a chiral complex. The reaction of phosphorus trichloride and (*R,R*)-1,2-bis-N-methylamino-cyclohexane **104** (prepared by the method described in chapter IV) in the presence of Et_3N yields intermediate **117**, which was reduced with $LiBH_4$ to give product **118** in 95 % NMR yield (Scheme 5.5).

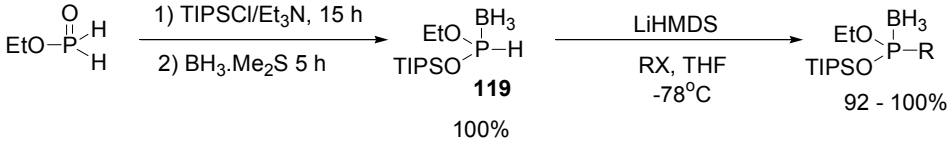
Unfortunately, we were not able to isolate this compound. Purification by chromatography over silica gel gave a mixture of desired compound along with decomposition products containing phosphorus.

Scheme 5.5 Attempted asymmetric synthesis



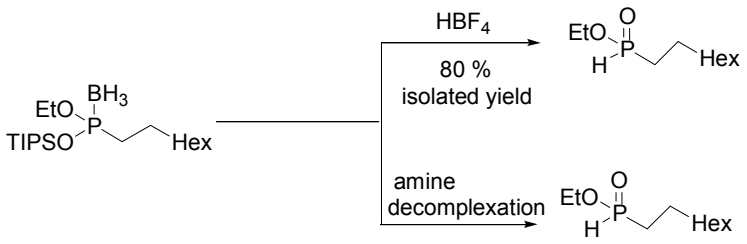
To explore the chemistry of the borane complexes of hypophosphorus acid, the synthesis and the reactivity of the siloxyphosphine-borane complexes of hypophosphorus acid were also investigated in our laboratory. For example, ethoxy(triisopropylsilyloxy)phosphine-borane[146] **119** was prepared from the reaction of ethylphosphinate and triisopropylchlorosilane (1.5 equiv.) in the presence of Et_3N (1.6 equiv.) in quantitative isolated yield (Scheme 5.6, Eq. 1). Similarly to diethoxyphosphine-borane **116**, ethoxy(triisopropylsilyloxy)phosphine-borane **119** undergoes alkylation reaction with various electrophiles in the presence of LiHMDS.[147] Several products are obtained in higher yields probably due to destabilization of anion of ethoxy(triisopropylsilyloxy)phosphine-borane **119** by the isopropylsiloxy group (EDG).

Scheme 5.6 Synthesis and alkylation reaction of (TIPSO)(EtO)P(BH_3)H **119**



The products of this reaction can be easily converted into the corresponding *H*-phosphinates under conditions previously used for synthesis of *H*-phosphinates from diethoxyphosphonite-boranes (Table 4.3, Chapter IV). In contrast to diethoxyphosphonite-boranes (Scheme 4.11, Chapter IV), the decomplexation of ethoxy(triisopropylsilyloxy)phosphonite-boranes with amines did not afford free phosphines and consequently the product of the Arbuzov reaction could not be obtained. The reaction of ethoxy(triisopropylsilyloxy)phosphonite-boranes with amines yields exclusively the corresponding ethyl *H*-phosphinate (Scheme 5.7) or, if reaction is not conducted under anhydrous conditions, the amine salt of the *H*-phosphinate.

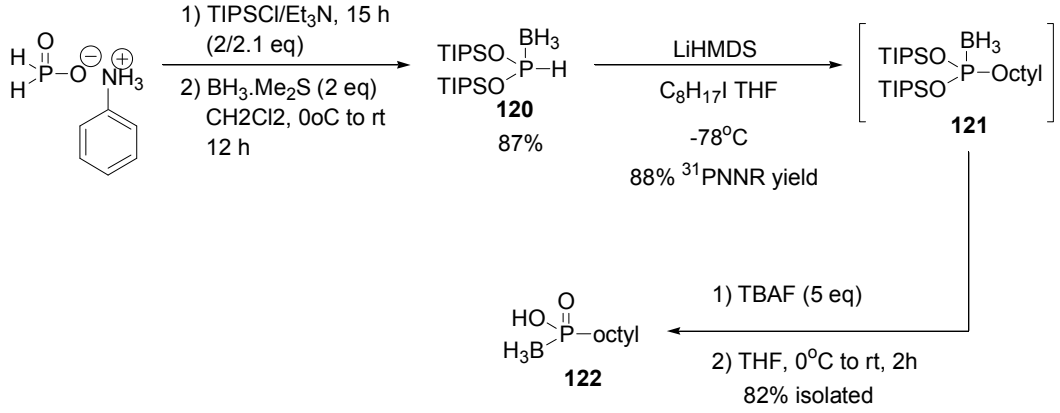
Scheme 5.7 Conversion of (TIPSO)(EtO)P(BH_3)H into *H*-phosphinates



The synthesis and the reactivity of bis(silyloxy)phosphine-boranes[146] were also reported by our group. For example, the reaction of anilinium hypophosphite with 2.0 equiv. of triisopropylchlorosilane and 2.1 equiv. of Et_3N afforded bis(triisopropylsilyloxy)phosphine-borane **120** in 87 % isolated yield (Scheme 5.8, Eq. 2). The alkylation reaction of $(TIPSO)_2P(BH_3)H$ **120** leads to the corresponding bis(triisopropylsilyloxy)phosphonite-borane **121**, which can be converted boranophosphonates **122** (Scheme 5.8).[146] While the chemistry of boranophosphonates is

still currently limited, this class of compounds could constitute biologically active analogs of phosphonates or prodrugs of *H*-phosphinates.

Scheme 5.8 Boranophosphonate synthesis from $(TIPSO)_2P(BH3)H$



5.2 Conclusion

We have developed a straightforward synthesis of novel phosphorus synthons displaying remarkable stability. Diethoxyphosphine-borane taken with siloxyphosphine-borane complexes provides added flexibility for the preparation of organophosphorus compounds. When available, the direct conversion of alkyl phosphinates $ROP(O)H_2$ into *H*-phosphinate esters is always superior to this protecting group strategy. However, limitations still exist, especially for the alkylation reaction of $ROP(O)H_2$ with alkyl halides which is not an efficient method to prepare a variety of *H*-phosphinate esters. The Ciba–Geigy reagents solved a number of problems; however unmasking the P–H bond always requires acidic conditions, which reduces the compatibility with functionalized

compounds. Our method provides not only *H*-phosphinates, but also disubstituted phosphinates and boranophosphonates, depending only on the borane-complexes used as starting material. The alkylated product can be unmasked under either basic or acidic conditions. We also have demonstrated the possibility for tandem decomplexation/Arbuzov functionalization to disubstituted phosphinates and the possibility for the preparation of boranophosphonates. More work will be required to investigate chiral versions of those borane complexes.

Experimental section

Reagents and Solvents. Aqueous hypophosphorous acid (50 wt.%), was purchased from Aldrich and used as received. Concentrated hypophosphorous acid (H_3PO_2) was obtained by rotary evaporation (0.5 mmHg) of the 50 wt.% aqueous solution at rt for 20-30 min before reaction. Stock solutions (0.5 M) of concentrated H_3PO_2 in reagent grade acetonitrile were also prepared and used for three months without any decomposition of the acid. Triethylammonium hypophosphite was prepared according to the method described by Stawinski *et al*,[147] ammonium hypophosphite was prepared as described by Frost *et al*,[15j] anilinum hypophosphite[18a,58] and alkyl phosphinates[18a,19a] were also prepared as previously described, from commercially available alkoxysilanes unless otherwise indicated. Stock solutions (0.5M) of alkyl phosphinates were also prepared from concentrated hypophosphorous acid and an alkoxysilane, and stored under N_2 for over a month (less than 10% decomposition).[20] Unless otherwise stated, HPLC or reagent grade solvents were used. The activation of molecular sieves consisted in flaming them under vacuum (0.5 mmHg) during 20-30 min. When common anhydrous reagents and/or solvents were employed, they were prepared as follows: Et_3N, pyridine, diisopropylethylamine, diisopropylamine were distilled under N_2 from CaH_2 and stored under N_2 over activated 4Å molecular sieves. Tetrahydrofuran (THF) was distilled under N_2 from sodium benzophenone ketyl, and used immediately. Anhydrous acetonitrile, toluene, benzene and dichloromethane were distilled under N_2 from CaH_2, and used immediately. DMF was stored over activated 3Å molecular sieves, under N_2. Strictly anhydrous DMF was distilled under reduced pressure from CaH_2 (45-50°C) and stored under N_2 over activated 4Å molecular sieves. Catalysts and ligands were commonly

purchased from Aldrich, Strem Chemicals or Solvias AG. Bu_3B, (*sec*-Bu)$_3B$, Et_3B, B-benzyl-9-BBN, Alpine-Borane are commercially available. Other organoboranes reagents Cy_3B [92], (heptyl)$_3B$ [92], B–octyl-9-BBN [92] were prepared according to literature procedure. Butyllithium (1.6 M in hexanes), $BH_3.Me_2S$ (2.0 M in THF) and $HBF_4.Et_2O$ were obtained from Aldrich and used as received.

Purification. Radial chromatography was carried out with a Harrison Associates Chromatotron, using 1, 2, or 4 mm layers of silica gel 60 PF_{254} containing gypsum or silica gel - glue plates. Silica gel (200-300 mesh) was used for flash chromatography. Ethyl acetate/hexanes/MeOH mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by UV, then immersed in *p*-anisaldehyde stain (by volume: 93% ethanol, 3.5% sulfuric acid, 1% acetic acid, and 2.5% anisaldehyde) followed by heating.

NMR Dat a. ^1H NMR spectra were recorded on a Varian Mercury 300-MHz spectrometer. Chemical shifts for ^1H NMR spectra are reported (in parts per million) relative to internal tetramethylsilane (Me_4Si, δ = 0.00 ppm) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 121 MHz and/or at 36 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid δ = 0.0 ppm). ^{11}B NMR spectra were recorded at 29 MHz, and chemical shifts reported (in parts per million) relative to external $BF_3.Et_2O$ (δ = 0.0 ppm).The NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra, an approach that is valid if no phosphorus-containing gas (i.e. PH_3) evolves, or if the precipitate in a heterogeneous mixture does not contain

phosphorus. The yields determined by NMR are generally accurate within ~10% of the value indicated, and are reproducible. Some experiments with internal standards and gas chromatography also confirmed the validity of the method,[54] and a careful validation of NMR yield was verified for the hydrophosphinylation of 4-octyne with ethyl phosphinate ($EtOP(O)H_2$) using known amounts of authentic samples and then integrating the spectra (see Supporting Information from Ref. 35). Isolated yields are sometimes significantly lower because *H*-phosphinate esters are highly polar compounds and hydrolytically labile.

Gas Chromatography (GC). Gas chromatographic analyses were conducted on a gas chromatograph equipped with capillary GC and FID detection, and with mesitylene as an internal standard. The column was a 30 m HP5 (crosslinked 5% PH ME siloxane) capillary column (0.25 μm, phase ratio 320, ID 0.32 mm). Conditions: oven 60°C, initial time: 1 min, rate1: 5°C/min, final temperature1: 160°C, final time 1: 0 min, then rate2: 25°C/min, final temperature2: 280°C, final time 2: 20 min. Inlet 200°C, detector 280°C, split mode with constant make-up. For GC analysis, 3 drops of sample are diluted in 1 mL of diethyl ether. The solution is washed with 1 mL of 2 M NaOH, and 1 μL of the organic solution is injected in the GC. For each sampling, the areas of the different peaks are normalized with the area of the mesitylene peak.

High Resolution Mass Spectrometry and Elemental Analysis. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR00954), or by the Mass Spectrometry Facility of the University of South Carolina. Elemental analyses were done at Atlantic Microlab, Inc., Norcross, GA.

Chapter II: Section 2.2. Nickel - Catalyzed Hydrophosphinylation [20]

Preparation of a Stock Solution of AlkOP(O)H_2.[58] In a typical procedure, a solution (or suspension) of concentrated H_3PO_2 (100 mmol), alkoxysilane (70 mmol for $(RO)_4Si$, or 200 mmol for $(RO)_2SiMe_2$) in the appropriate volume of solvent (CH_3CN, toluene or THF) to create a 0.5 M solution, is refluxed for 2 h under a N_2 atmosphere. After cooling to rt, the stock solution was kept at rt under N_2. Less than 10% decomposition was detected after 2 months.

Experimental Procedures for Table 2.3

General Procedure for the Hydrophosphinyla tion of Alkynes w ith a Stock Solution of AlkOP(O)H $_2$. To a mixture of the alkyne (2.5 mmol) and the catalyst (0.05-0.075 mmol, 2-3 mol% relative to the alkyne) was added a solution of EtOP(O)H_2 (5 mmol) in CH_3CN (10 mL, 0.5 M) at rt. The mixture was stirred at reflux until completion of the reaction (NMR monitoring on a sample of the crude reaction mixture). The mixture was then concentrated in vacuo. The residue was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$, then brine. Drying on $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (hexanes, 100% v/v to EtOAc, 100% v/v). The product was generally obtained as light yellow oil.

General Procedure for the Hydrophosphinylation of Alkynes by Heat Activation. To the catalyst (0.05-0.075 mmol, 2-3 mol % relative to the alkyne) was added a solution of EtOP(O)H_2 (5 mmol) in CH_3CN (10 mL, 0.5M) at rt. The mixture was heated for 15min (10 min to reach reflux and 5 min at reflux) then allowed to cool back to rt for 15 min. This orange-red homogeneous mixture was added to the alkyne (2.5 mmol) and stirred at rt until completion of the reaction (NMR monitoring on a sample of the crude reaction

mixture). The mixture was then concentrated in vacuo. The residue was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$, then brine. Drying on $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (hexanes, 100% v/v to EtOAc, 100% v/v).

Representative Procedure for the One-Pot Hydrophosphinylation with Anilinum Hypophosphite: Preparation of Butyl (1-propyl-pent-1-enyl) phosphinate (Table 2.3, entry 1d). To a suspension of $PhNH_3OP(O)H_2$ (0.800 g, 5 mmol), $(BuO)_4Si$ (1.122 g, 3.5 mmol) and 4-octyne (0.37 mL, 2.5 mmol) in CH_3CN (10 mL) was added $NiCl_2$ (0.01 g, 0.075 mmol, 3 mol%). The reaction mixture was then refluxed for 16 h. After cooling to rt, ^{31}P NMR analysis showed the product at 31.2 ppm (100%). The mixture was diluted with EtOAc and washed successively with diluted HCl (1 x). The aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc) afforded the product as a colorless oil (0.521 g, 90%).

Representative Procedure with Aminosilicate/TFA: Preparation of Ethyl (*trans*-2-trimethylsilyl-vinyl) phosphinate (Table 2.3, entry 12). To a solution of concentrated H_3PO_2 (5 mmol) in HPLC grade CH_3CN (10 mL), was added 3-aminopropyltriethoxysilane (1.107 g, 5 mmol), trimethylsilylacetylene (0.35 mL, 2.5 mmol), trifluoroacetic acid (0.39 mL, 5 mmol) and nickel chloride (0.01 g, 0.075 mmol, 3 mol%), at rt. The solution was refluxed under N_2 for 2.5 h. After cooling to rt, ^{31}P NMR analysis showed the product at 25.3 ppm (98%). The mixture was then diluted with EtOAc and washed successively with diluted aqueous HCl (1 x). The aqueous phase was

then extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying and concentration afforded the product as colorless oil (0.350 g, 75%).

Methyl (1-propyl-pent-1-enyl) phosphinate (Table 2.3, entry 1a).

^{1}H NMR ($CDCl_3$) δ 6.96 (d, J = 545 Hz, 1 H), 6.38 (dt, J = 26 Hz, J = 7 Hz, 1 H), 3.67 (d, J = 12 Hz, 3 H), 2.0-2.26 (m, 4 H), 1.41 (q, J = 7 Hz, 4 H), 0.87 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.4 (d, J_{PCC} = 14 Hz), 130.5 (d, J_{PC} = 123 Hz), 51.1 (d, J_{POC} = 7 Hz), 29.4 (d, J_{PCC} = 18 Hz), 27.3 (d, J_{PCCC} = 12 Hz), 20.9, 20.8, 13.1, 12.8; ^{31}P NMR ($CDCl_3$) δ 35.4 (dm, J = 545 Hz). HRMS (EI) calcd. for $C_9H_{19}O_2P$ (M^+) 190.1123, found 190.1116.

***iso*-Propyl (1-propyl-pent-1-enyl) phosphinate (Table 2.3, entry 1b).**

^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 540 Hz, 1 H), 6.35 (dt, J = 27 Hz, J = 6 Hz, 1 H), 4.45-4.7 (m, 1 H), 2.0-2.25 (m, 4 H), 1.34-1.53 (m, 4 H), 1.07-1.34 (m, 6 H), 0.7-1.0 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 14 Hz), 132.2 (d, J_{PC} = 125 Hz), 70.7 (d, J_{POC} = 7 Hz), 30.5 (d, J_{PCC} = 19 Hz), 28.4 (d, J_{PCCC} = 12 Hz), 24.2 (d, J_{POCC} = 4 Hz), 23.5 (d, J_{POCC} = 4 Hz), 22.5 (d, J_{PCCC} = 2 Hz), 21.9 (d, J_{PCCCC} = 1 Hz), 14.1, 13.9; ^{31}P NMR ($CDCl_3$) δ 30.0 (dm, J = 539 Hz). HRMS (EI) calcd. for $C_{11}H_{23}O_2P$ (M^+) 218.1436, found 218.1440.

Butyl (1-propyl-pent-1-enyl) phosphinate (Table 2.3, entries 1c & 1d).[18c]

^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 542 Hz, 1 H), 6.37 (dt, J = 33 Hz, J = 7 Hz, 1 H), 3.88-4.0 (m, 2 H), 2.0-2.2 (m, 4 H), 1.55-1.63 (m, 2 H), 1.3-1.45 (m, 6 H), 0.87 (t, J = 7 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, J_{PCC} = 14 Hz), 131.19 (d, J_{PC} = 124 Hz), 65.7 (d, J_{POC} = 7 Hz), 32.6 (d, J_{POCC} = 7 Hz), 30.5 (d, J_{PCC} = 18 Hz), 28.4 (d, J_{PCCC} = 12 Hz), 22.6,

21.9, 18.9, 14.2, 13.9, 13.7; ^{31}P NMR ($CDCl_3$) δ 33.4 (dm, J = 543 Hz). HRMS (EI) calcd. for $C_{12}H_{25}O_2P$ (M^+) 232.1592, found 232.1590.

Ethyl (1-propyl-pent-1-enyl) phosphinate (Table 2.3, entries 2a & 2b).

^{1}H NMR ($CDCl_3$) δ 6.99 (d, J = 542 Hz, 1 H), 6.36 (dt, J = 26 Hz, J = 6 Hz, 1 H), 3.89-4.1 (m, 2 H), 2.0-2.27 (m, 4 H), 1.3-1.52 (m, 4 H), 1.12-1.3 (m, 3 H), 0.72-1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.9 (d, J_{PCC} = 14 Hz), 131.6 (d, J_{PC} = 124 Hz), 61.7 (d, J_{POC} = 7 Hz), 30.3 (d, J_{PCC} = 18 Hz), 28.1 (d, J_{PCCC} = 12 Hz), 22.4, 21.7, 16.1 (d, J_{POCC} = 3 Hz), 13.9, 13.6; ^{31}P NMR ($CDCl_3$) δ 32.2 (dm, J = 543 Hz). HRMS (EI) calcd. for $C_{10}H_{21}O_2P$ (M^+) 204.1279, found 204.1275.

Ethyl (1-butyl-hex-1-enyl) phosphinate (Table 2.3, entry 3).

^{1}H NMR ($CDCl_3$) δ 7.0 (d, J_{PH} = 545 Hz), 6.36 (dt, J = 26.4 Hz, J = 7.0 Hz, 1 H), 3.95-4.1 (m, 2 H), 2.05-2.25 (m, 4 H), 1.2-1.4 (m, 11 H),0.84 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 14 Hz), 130.7 (d, J_{PC} = 124 Hz), 61.3 (d, J_{POC} = 7 Hz), 30.7 (d, J_{PCCCC} = 2 Hz), 30.0 (d, J_{PCCC} = 2 Hz), 27.4 (d, J_{PCCC} = 18 Hz), 25.3 (d, J_{PCC} = 12 Hz), 22.0, 21.7, 15.6 (d, J_{POCC} = 6Hz), 13.1, 13.1; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 33.05 (d, J_{PH} = 545 Hz). MS (EI^+): *m/z* 232 ([*M*]$^+$); HRMS (EI^+): calcd. for $C_{12}H_{25}O_2P$ 232.1592, found 232.1594.

Ethyl vinylphosphinate (Table 2.3, entry 4a). [18c,148] Hydrophosphinylation of acetylene: Acetylene is produced by a slow addition of water over calcium carbide (40g, 0.62 mol) in a system previously flushed with N_2. A sulfuric acid trap followed by a drierite trap dries the resulting gas. Acetylene is bubbled gently for 2h at rt through a solution of pre-activated catalyst (0.01 g, 0.075 mmol, 1.5 mol%) and $ROP(O)H_2$ (0.5 M,

10 mL, 5 mmol) in CH_3CN, produced either from the appropriate alkoxysilane or the aminosilicate. The whole system is then flushed again with N_2.

^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 558 Hz, 1 H), 6.1-6.4 (m, 3 H), 4.0-4.2 (m, 2 H), 1.41 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.4 (d, J_{PCC} = 4 Hz), 128.7 (d, J_{PC} = 125 Hz), 62.1 (d, J_{POC} = 7 Hz), 16.3 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.06 (d, J_{PH} = 558 Hz).

2-Ethyl-butyl vinylphosphinate (Table 2.3, entry 4b).

^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 558 Hz, 1 H), 6.1-6.5 (m, 3 H), 3.9-4.1 (m, 2 H), 1.45-1.6 (m, 1 H), 1.3-1.45 (m, 4 H), 0.91 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 136.3 (d, J_{PCC} = 4 Hz), 128.8 (d, J_{PC} = 125 Hz), 67.7 (d, J_{POC} = 6 Hz), 41.7 (d, J_{POCC} = 7 Hz), 22.8, 10.9; ^{31}P NMR ($CDCl_3$) δ 25.78 (d, J_{PH} = 558 Hz).

Ethyl (1,3,3-trimethyl-but-1-enyl) phosphinate (Table 2.3, entry 5).

^{1}H NMR ($CDCl_3$) δ 6.94 (d, J_{PH} = 546 Hz, 1 H), 6.38 (dm, J = 29.9 Hz, 1 H), 4.0-4.2 (m, 2 H), 1.92 (dd, J = 1.5 Hz, J_{PCC} = 16.1 Hz, 3 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.18 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.2 (d, J_{PCC} = 12 Hz), 125.3 (d, J_{PC} = 125 Hz), 62.0 (d, J_{POC} = 6 Hz), 34.8 (d, J_{PCCC} = 20 Hz), 30.1, 16.5 (d, J_{POCC} = 6 Hz), 11.8 (d, J_{PCC} = 13 Hz); ^{31}P NMR ($CDCl_3$) δ 35.79 (d, J_{PH} = 546 Hz). MS (EI^+): *m/z* 190 ($[M]^+$); HRMS (EI^+): calcd. for $C_9H_{19}O_2P$ 190.1123, found 190.1118.

Ethyl (*trans*-styryl) phosphinate (Table 2.3, entries 6a & 6b).[149]

^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 561 Hz, 1 H), 7.2-7.55 (m, 5 H), 6.2-6.4 (m, 2 H), 4.0-4.2 (m, 2 H), 1.33 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.9 (d, J_{PCCC} = 7 Hz), 134.6 (d, J_{PCC} = 21 Hz), 130.8, 129.1 (2 C), 128.1 (2 C), 116.5 (d, J_{PC} = 133 Hz), 62.2 (d, J_{POC} = 6 Hz), 16.6 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.7 (dm, J = 561 Hz), ^{31}P NMR ($CDCl_3$) δ 28.4. HRMS (EI) calcd. for $C_{10}H_{13}O_2P$ (M^+) 196.0653, found 196.0650.

Ethyl (1-phenyl-vinyl) phosphinate (Table 2.3, entries 6a & 6b).[150]

^{1}H NMR ($CDCl_3$) δ 7.33-7.5 (m, 5 H), 7.32 (d, J = 564 Hz, 1 H), 6.24 (d, J = 47 Hz, 1 H), 6.18 (d, J = 24 Hz, 1 H), 4.0-4.1 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.7 (d, J_{PC} = 119 Hz), 135.4 (d, J_{PCC} = 13 Hz), 130.5 (d, J_{PCC} = 13 Hz), 129.0 (2 C), 128.6, 127.3 (d, J_{PCCC} = 6 Hz, 2 C), 62.5 (d, J_{POC} = 7 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.4 (dm, J = 564 Hz). HRMS (EI) calcd. for $C_{10}H_{13}O_2P$ (M^+) 196.0653, found 196.0650.

Ethyl (1,2-diphenyl-vinyl) phosphinate (Table 2.3, entries 7a & 7b).

^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 25 Hz, 1 H), 7.29-7.44 (m, 3 H), 7.19 (d, J = 562 Hz, 1 H), 7.0-7.3 (m, 7 H), 4.1 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.4 (d, J_{PCC} = 13 Hz), 134.4 (d, J_{PCC} = 6 Hz), 134.2 (d, J_{PCCC} = 4 Hz), 132.1 (d, J_{PC} = 123 Hz), 130.6 (2 C), 129.7, 129.5, 129.4, 129.3, 129.2, 128.6 (2 C), 128.5, 62.5 (d, J_{POC} = 7 Hz), 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 29.1 (dm, J = 562 Hz). HRMS (EI) calcd. for $C_{16}H_{17}O_2P$ (M^+) 272.0966, found 272.0964.

Ethyl (1-ethylidene-but-2-ynyl) phosphinate (Table 2.3, entry 8).

^{1}H NMR ($CDCl_3$) δ 6.94 (d, J_{PH} = 577 Hz, 1 H), 6.85 (dq, J = 19.9 Hz, J = 6.7 Hz, 1 H), 4.03 (dq, J = 9.1 Hz, J = 7.0 Hz, 2 H), 1.98 (d, J = 5.0 Hz, 3 H), 1.95 (dd, J = 7.0 Hz, J = 2.9 Hz, 3 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.2 (d, J_{PCC} = 10 Hz), 117.9 (d, J_{PC} = 134 Hz), 96.5 (d, J_{PCCC} = 8 Hz), 71.9 (d, J_{PCC} = 14 Hz), 62.1 (d, J_{POC} = 7 Hz), 17.4 (d, J_{PCCC} = 15 Hz), 16.5 (d, J_{POCC} = 6 Hz), 4.8 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 24.141 (d, J_{PH} = 577 Hz). MS (EI^+): *m/z* 172 ($[M]^+$); HRMS (EI^+): calcd. for $C_8H_{13}O_2P$ 172.0653, found 172.0651.

Ethyl (2-cyclohex-1-enyl-vinyl) phosphinate (Table 2.3, entry 9). (linear isomer): ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 555 Hz, 1 H), 7.08 (dd, J = 17.3 Hz, J = 23.5 Hz, 1 H), 6.18 (s br, 1 H), 5.64 (dd, J = 17.3 Hz, J = 21.6 Hz, 1 H), 4.05-4.2 (m, 2 H), 2.1-2.3 (m, 4 H), 1.5-1.75 (m, 4 H), 1.37 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.7 (d, J_{PCC} = 7 Hz), 139.1, 135.2 (d, J_{PCCC} = 22 Hz), 113.1 (d, J_{PC} = 137 Hz), 61.9 (d, J_{POC} = 6 Hz), 37.1 (d, J_{PCCCC} = 3 Hz), 26.6, 24.1, 22.2, 16.7 (d, J_{POCC} = 7 Hz); ^{31}P NMR ($CDCl_3$) δ 27.60 (d, J_{PH} = 555 Hz).

Ethyl (1-cyclohex-1-enyl-vinyl) phosphinates (Table 2. 3, entry 9). (branched isomer): ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J_{PH} = 550 Hz, 1 H), 6.37 (s br, 1 H), 5.91 (d, J = 50.4 Hz, 1 H), 5.86 (d, J = 26.9 Hz, 1 H), 4.05-4.2 (m, 2 H), 2.1-2.25 (m, 4 H), 1.55-1.75 (m, 4 H), 1.38 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.0 (d, J_{PC} = 118 Hz), 132.2 (d, J_{PCCC} = 10 Hz), 130.8 (d, J_{PCCCC} = 7 Hz), 124.7 (d, J_{PCC} = 15 Hz), 62.4 (d, J_{POC} = 6 Hz), 26.2 (d, J_{PCCC} = 7 Hz), 26.7, 22.6, 22.0, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 32.28 (d, J_{PH} = 558 Hz).

Ethyl (1-ethoxy-vinyl) phosphinate (Table 2.3, entry 10).

^{1}H NMR ($CDCl_3$) δ 7.01 (dd, J = 581 Hz, J = 1.2 Hz, 1 H), 5.15 (dd, J = 13.2 Hz, J = 3.2 Hz, 1 H), 4.91 (ddd, J = 35 Hz, J = 3.2 Hz, J = 1.2 Hz, 1 H), 4.1-4.2 (m, 2 H), 3.86 (q, J = 7.0 Hz, 2 H), 1.35-1.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.3 (d, J_{PC} = 160 Hz), 98.2 (d, J_{PCC} = 25 Hz), 64.4 (d, J_{POC} = 9 Hz), 62.3 (d, J_{PCOC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz), 14.2; ^{31}P NMR ($CDCl_3$) δ 19.23 (d, J_{PH} = 581 Hz).

Ethyl (*trans*-oct-1-enyl) phosphinate (Table 2.3, entry 11). (major isomer, 68%).

^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 555 Hz, 1 H), 6.7-6.9 (m, 1 H), 5.78 (m, 1 H), 4.0-4.2 (m, 2 H), 2.15-2.3 (m, 2 H), 1.2-1.55 (m, 8 H), 1.37 (t, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz,

3 H); ^{13}C NMR ($CDCl_3$) δ 155.1 (d, J_{PCC} = 5 Hz), 119.7 (d, J_{PC} = 131 Hz), 61.8 (d, J_{POC} = 6 Hz), 34.3 (d, J_{PCC} = 20 Hz), 31.6, 28.7, 27.7, 22.6, 16.4 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 25.56 (dm, J = 547 Hz). Minor isomer: Ethyl (1-hexyl-vinyl) phosphinate (21%): ^{31}P NMR ($CDCl_3$) δ 30.3 (dm, J = 553 Hz).

Ethyl (*trans*-2-trimethylsilyl-vinyl) phosphinate (Table 2.3, entry 12).

^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 558 Hz, 1 H), 7.13 (dd, J = 37 Hz, J = 21 Hz, 1 H), 6.29 (ddd, J = 32 Hz, J = 21 Hz, J = 1.5 Hz, 1 H), 4.01 (q, J = 7 Hz, 2 H), 1.24 (t, J = 7 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.0 (d, J_{PCC} = 3 Hz), 136.2 (d, J_{PC} = 119 Hz), 64.7 (d, J_{POC} = 7 Hz), 18.4 (d, J_{POCC} = 6 z), 0.0 (s, 3 C); ^{31}P NMR ($CDCl_3$) δ 27.0 (dt, J = 558 Hz, J = 32 Hz).

Ethyl (1-butyl-2-trimethylsilyl-vinyl) phosphinate (Table 2.3, entry 13a).

^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 544 Hz, 1 H), 6.46 (d, J = 46 Hz, 1 H), 3.9-4.1 (m, 2 H), 2.2-2.4 (m, 2 H), 1.2-1.5 (m, 4 H), 1.22 (t, J = 7.0 Hz, 3 H), 0.80 (t, J = 7 Hz, 3 H), 0.07(s, 9 H); ^{13}C NMR ($CDCl_3$) δ 149.6 (d, J_{PC} = 95 Hz), 146.8 (d, J_{PCC} = 3 Hz), 62.3 (d, J_{POC} = 7 Hz), 32.6, 31.7 (d, J_{PCC} = 15 Hz), 23.3, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 0.0; ^{31}P NMR ($CDCl_3$) δ 40.16 (d, J_{PH} = 544 Hz).

Ethyl (1-propyl-2-trimethylsilyl-vinyl) phosphinate (Table 2.3, entry 13b).

^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 544 Hz, 1 H), 6.61 (d, J = 38.7 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.25-2.5 (m, 2 H), 1.5-1.65 (m, 2 H), 1.37 (t, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 150.3 (d, J_{PC} = 110 Hz), 147.3 (d, J_{PCC} = 5 Hz), 62.7 (d, J_{POC} = 7 Hz), 34.3 (d, J_{PCC} = 16 Hz), 24.1, 17.0(d, J_{POCC} = 6 Hz), 14.9, 0.4; ^{31}P NMR ($CDCl_3$) δ 33.52 (d, J_{PH} = 543 Hz).

Ethyl (3-methyl-but-2-enyl) phosphinate (Table 2.3, entry 14).

^{1}H NMR ($CDCl_3$) δ 6.95 (d, J = 538 Hz, 1H), 5.11 (q, J = 7 Hz, 1H), 4.0-4.25 (m, 2H), 2.45-2.65 (m, 2H), 1.77 (d, J = 6 Hz, 3H), 1.67 (d, J = 4Hz, 3H), 1.36 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4 (d, J_{PCCC} = 14 Hz), 110.5 (d, J_{PCC} = 9 Hz), 62.5 (d, J_{POC} = 7 Hz), 30.0 (d, J_{PC} = 92 Hz), 25.9 (d, J_{PCCCC} = 4 Hz), 18.2 (d, J_{PCCCC} = 3 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 40.2 (d, J = 538 Hz); HRMS (EI) calcd. for $C_7H_{15}O_2P$ (M^+) 162.0810, found 162.0802.

Butyl (2-pyridin-2-yl-ethyl) phosphinate (Table 2.3, entry 15).

^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 4.7 Hz, 1 H), 7.62 (td, J = 7.6 Hz, J = 1.7 Hz, 1 H), 7.20 (d, J = 7.9 Hz, 1 H), 7.18 (d, J_{PH} = 538 Hz, 1 H), 7.15 (dd, J = 4.7 Hz, J = 7.6 Hz, 1 H), 3.9-4.2 (m, 2 H), 3.05-3.2 (m, 2 H),2.2-2.35 (m, 2 H), 1.6-1.75 (m, 2 H), 1.3-1.5 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.8, 149.6, 136.8, 123.1, 121.9, 66.4 (d, J_{POC} = 7 Hz), 32.6 (d, J_{PCC} = 6 Hz), 29.4 (d, J_{POCC} = 2 Hz), 28.2 (d, J_{PC} = 94 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 39.36 (d, J_{PH} = 538 Hz). HRMS (ES^+): calcd. for $C_{11}H_{19}NO_2P$ (M^+) 228.1153, found 228.1146.

Ethyl (3-cyclohexyl-propen-2-yl) phosphinate (Eq. 2.4) (linear isomer)**.**

^{1}H NMR ($CDCl_3$) δ 6.94 (dt, J_{PH} = 540 Hz, J = 2.0 Hz, 1 H), 5.50-5.65 (m, 1 H), 5.20-5.35 (m, 1 H), 4-4.25 (m, 2 H), 2.57 (ddm, J = 19.0Hz, J = 7.4 Hz, 2 H), 1.9-2.05 (m, 1 H), 1.6-1.75 (m, 5 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.0-1.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 143.9 (d, J_{PCC} = 14 Hz), 114.2 (d, J_{PCCC} = 9 Hz), 62.6 (d, J_{POC} = 7 Hz), 41.1 (d, J_{PCCCC} = 3 Hz), 33.7 (d, J_{PC} = 91 Hz), 33.0, 26.3, 26.1, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 39.10 (dm, J_{PH} = 539 Hz).

Ethyl (2-cyclohexyl-1-methyl-vinyl) phosphinate (Eq. 2.4) (branched isomer).

^{1}H NMR ($CDCl_3$) δ 7.00 (d, J_{PH} = 544 Hz, 1 H), 6.28 (ddd, J = 26.1 Hz, J = 9.4 Hz, J = 1.5 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.3-2.45 (m, 1 H), 1.81 (dd, J = 15.0 Hz, J = 1.5 Hz, 3 H), 1.6-1.8 (m, 5 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.1-1.4 (m, 5 H); 31P NMR ($CDCl_3$, Me_4Si) δ 33.44 (dm, J_{PH} = 554 Hz).

Preparation of EtOP(O)D $_2$. Aqueous hypophosphorous acid (50 wt.%, 13.2g, 100 mmol) was concentrated on a rotary evaporator at rt for 30 min then the remaining water (around 2 wt.%) was coevaporated with toluene. Deuterated water (9 mL) is added to the residue, and the solution is stirred at rt for 10 min then concentrated. This cycle is repeated 4 more times. D_3PO_2, monitored by ^{31}P NMR, is obtained 97% pure at the end of the 5th cycle. To this compound is added dimethyldiethoxysilane (29.7g, 198 mmol) and 165 mL of dry CH_3CN. The solution is refluxed for 2 h under N_2 to afford a solution of 0.5 M of $D_2P(O)OEt$, 94% pure (6% of DHP(O)OEt). D_3PO_2 ^{31}P NMR (CH_3CN) δ 11.46 (quintet, J_{DP} = 87 Hz). $D_2P(O)OEt$; ^{31}P NMR (CH_3CN) δ (quintet of triplet, J_{PD} = 86 Hz, J_{POCH} = 10 Hz).

Hydrophosphinylation with EtOP(O)D $_2$. Deuterated ethyl (1-propyl-pent-1-enyl) phosphinate (Eq. 2.5). General procedure for hydrophosphinylation is used on 4-octyne (279 mg, 2.53 mmol) using a stock solution of $(EtO)P(O)D_2$. After 3 h at reflux, the mixture is concentrated and directly purified by radial chromatography (EtOAc/Hexanes, 50/50 % v/v to EtOAc, 100% v/v) to afford the expected compound (370 mg, 71%, %D > 80%). Measurements for deuterium incorporation were conducted by integration of the ^{1}H NMR spectra. Mass spectrometric determination is problematic because the exchange of P(O)(OEt)D to P(O)(OEt)H in the product must be complete.

^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 543 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.15-2.3 (m, 4 H), 1.4-1.6 (m, 4 H), 1.37 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 6 H).^{13}C NMR ($CDCl_3$) δ 147.0 (dt, J_{PCC} = 13 Hz, J_{CD} = 35 Hz), 131.9 (d, J_{PC} = 123 Hz), 61.9 (d, J_{POC} = 7 Hz), 30.6 (d, J_{PCCC} = 18 Hz), 28.5 (d, J_{PCC} = 12 Hz), 22.7 (d, J_{PCCC} = 2 Hz), 22.1 (d, J_{PCCC} = 2 Hz), 16.5 (d, J_{POCC} = 6 Hz), 14.3, 14.1. ^{31}P NMR ($CDCl_3$) δ 32.78 (d, J = 542 Hz).

Tandem Reactions (Table 2.5).

Diethyl (1-propyl-pent-1-enyl)phosphonate (Table 2.5, Entry 1). To 4-octyne (0.275 g, 2.50 mmol) and $NiCl_2$ (9.7 mg, 0.076 mmol, 3.0 mol%) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux overnight. To the reaction mixture was added CCl_4 (8 mL, 12.7g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9g, 29mmol) at rt. The resulting mixture was stirred at rt for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with EtOAc The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (299 mg, 48%) as an oil.

^{1}H NMR ($CDCl_3$) δ 6.48 (dt, J = 24 Hz, J = 7 Hz, 1 H), 3.97 (q, J = 7 Hz, 4 H), 2.05-2.18 (m, 4 H), 1.25-1.40 (m, 4 H), 1.24 (t, J = 7 Hz, 6 H), 0.86 (dt, J =3 Hz, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 147.6 (J_{PCC} = 10 Hz), 129.4 (J_{PC} = 175 Hz), 61.5 (J_{POC} = 6 Hz), 30.7 (J_{PCCC} = 19 Hz), 29.6 (J_{PCC} = 11 Hz), 22.6 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.5 (J_{POCC} = 7 Hz), 14.3, 14.0; ^{31}P NMR ($CDCl_3$) δ 23.47. MS (EI^+) m/z 248 (M^+); HRMS (EI^+) calcd. for $C_{12}H_{25}O_3P$ 248.1541, found 248.1534.

Ethyl phenyl-(1-propyl-pent-1-enyl)phosphinate (Table 2.5, Entry 2). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5

mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux for 3 h. To the reaction mixture was added iodobenzene (1.5 g, 7.51 mmol), $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol, 1.9 mol%), and triethylamine (1.52 g, 15.1 mmol) at rt. The resulting mixture was stirred at reflux overnight. The solution was concentrated, partitioned between 1 M $NaHSO_4$ and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (419 mg, 58%) as an oil.

^{1}H NMR ($CDCl_3$) δ 7.64 (ddd, J = 11.7 Hz, J = 1.5 Hz, J = 0.6 Hz, 2 H), 7.29-7.45 (m, 3 H), 6.39 (dt, J = 22.28 Hz, J = 7.33 Hz, 1 H), 3.91 (ddq, J = 22.4 Hz, J = 10.1 Hz, J = 7.04 Hz, 2 H), 1.96-2.10 (m, 4 H), 1.25-1.40 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.0-1.2 (m, 2 H), 0.79 (t, J = 7.33 Hz, 3 H), 0.70 (t, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.4 (J_{PCC} = 10 Hz), 131.9 (J_{PC} = 127.5 Hz), 131.5 (J_{PCCCC} = 3 Hz), 131.3 (J_{PCC} = 10 Hz), 131.0 (J_{PC} = 131 Hz), 128.0 (J_{PCCC} = 12 Hz), 60.2 (J_{POC} = 6 Hz), 30.3 (J_{PCCC} = 17 Hz), 28.9 (J_{PCC} = 12 Hz), 22.5 (J_{PCCC} = 2 Hz), 21.6 (J_{PCCCC} = 1 Hz), 16.1 (J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$) δ 35.89. MS (EI^+): *m/z* 280 (M^+); HRMS (EI^+): calcd. for $C_{16}H_{25}O_2P$ 280.1592, found 280.1588.

Ethyl (2-cyano-ethyl)-(1-propyl-ent-1-enyl)phosphinate (Table 2.5, Entry 3). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 2.9 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux for 3 h. To the reaction mixture was added acrylonitrile (0.403g, 7.6 mmol) and DBU (1.1g, 7.36 mmol) at rt. The resulting mixture was stirred at rt for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was

washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (415 mg, 63%) as an oil.

^{1}H NMR ($CDCl_3$) δ 6.58 (dt, J = 21.40 Hz, J = 7.33 Hz, 1 H), 3.95-4.16 (m, 1 H), 3.82-3.96 (m, 1 H), 2.56-2.70 (m, 6 H), 1.35-1.60 (m, 6 H), 1.32 (t, J = 7.33 Hz, 3 H), 0.98 (t, J = 7.04 Hz, 3 H), 0.95 (t, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.8 (J_{PCC} = 9 Hz), 130.7 (J_{PC} = 118 Hz), 119.0 (J_{PCCC} = 17 Hz), 60.7 (J_{POC} = 6 Hz), 31.1 (J_{PCCC} = 16 Hz), 29.5 (J_{PCC} = 12 Hz), 24.5 (J_{PC} = 97 Hz), 23.2 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.7 (J_{POCC} = 6 Hz), 14.5, 14.1, 10.8 (J_{PCC} = 2 Hz); ^{31}P NMR ($CDCl_3$) δ 43.25. MS (EI^+): *m/z* 257 (M^+); HRMS (EI^+): calcd. for $C_{13}H_{24}NO_2P$ 257.1545, found 257.1547.

Ethyl ally l-(1-propyl-pent-1-enyl)phosphinate (Table 2.5, Entry 4). To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.1 mg, 0.078 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux for 3 h. To the reaction mixture was added at rt BSA (1.46g, 7.2 mmol) and after 5 min of stirring allyl chloride (0.582g, 7.61 mmol) was added. The mixture was stirred at reflux for 3 h. The reaction mixture was then cooled down, quenched by saturated $NaHCO_3$, extracted with EtOAc and the combined organic phases washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (475 mg, 76%) as an oil.

^{1}H NMR ($CDCl_3$) δ 6.48 (dt, J = 21.1 Hz, J = 7.3 Hz, 1 H), 5.7-5.85 (m, 1 H), 5.1-5.22 (m, 2 H), 3.85-4.2 (m, 2 H), 2.5-2.75 (m, 2 H), 2.1-2.25 (m, 4 H), 1.35-1.55 (m, 4 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR

($CDCl_3$) δ 147.7 (d, J_{PCC} = 9 Hz), 130.7 (d, J_{PC} = 116 Hz), 127.3 (d, J_{PCC} = 9 Hz), 119.5 (d, J_{PCCC} = 13 Hz), 59.9 (d, J_{POC} = 6 Hz), 34.0 (d, J_{PC} = 94 Hz), 30.1 (d, J_{PCCC} = 13 Hz), 29.1 (d, J_{PCC} = 12 Hz), 22.4 (d, J_{PCCCC} = 1 Hz), 21.6 (d, J_{PCCC} = 1 Hz), 16.8 (d, J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$) δ 45.18. MS (EI^+): *m/z* 244 (M^+); HRMS (EI^+): calcd. for $C_{13}H_{25}O_2P$ 244.1592, found 244.1587.

Ethyl methyl-(1-propyl-pent-1-enyl)phosphinate (Table 2. 5, Entry 5). To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux overnight. To the reaction mixture was added at rt BSA (1.46g, 7.2 mmol) and, after 5 min of stirring, dimethyl sulfate (0.633g, 5.02 mmol). To the mixture was stirred at rt for 2 h. The reaction mixture was then quenched by saturated $NaHCO_3$, extracted with EtOAc and the combined organic phases washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (343 mg, 62%) as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 6.55 (dt, J = 21.4 Hz, J = 7.3 Hz, 1 H), 3.8-4.05 (m, 2 H), 2.1-2.25 (m, 4 H), 1.49 (d, J = 13.8 Hz, 3 H), 1.35-1.55 (m, 4 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.0 (d, J_{PCC} = 9 Hz), 132.5 (d, J_{PC} = 118 Hz), 59.9 (d, J_{POC} = 6 Hz), 30.9 (d, J_{PCCC} = 16 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.0 (d, J_{PCCCC} = 1 Hz), 22.2 (d, J_{PCCC} = 1 Hz), 14.5, 14.5 (d, J_{PC} = 99 Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 45.77. MS (EI^+): *m/z* 218 (M^+); HRMS (EI^+): calcd. for $C_{11}H_{23}O_2P$ 218.1436, found 218.1438.

Benzyl 3-[ethoxy-(1-ethylidene-bu t-2-ynyl)-phosphinoyl] propionate (Table 2.5, Entry 6). To 2,4-hexadiyne (0.199 g, 2.55 mmol) and $NiCl_2$ (7.0 mg, 0.054 mmol, 2.1 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux overnight. To the reaction mixture was added benzyl acrylate (1.22g, 7.5 mmol) and DBU (1.12g, 7.36 mmol) at rt. The resulting mixture was stirred at rt for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (271 mg, 32%) as an oil. ^1H NMR ($CDCl_3$) δ 7.3-7.4 (br, 5 H), 6.9-7.1 (m, 1 H), 5.13 (s, 2 H), 3.85-4.2 (m, 2 H), 2.55-2.8 (m, 2 H), 2.1-2.3 (m, 2 H), 1.95-2.05 (m, 6 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2 (d, J_{PCCC} = 19 Hz), 152.1 (d, J_{PCC} = 8 Hz), 135.7, 128.6, 128.3, 128.2, 117.3 (d, J_{PC} = 128 Hz), 95.5 (d, J_{PCCC} = 8 Hz), 73.1 (d, J_{PCC} = 13 Hz), 66.6, 60.7 (d, J_{POC} = 7 Hz), 26.7 (d, J_{PCC} = 2 Hz), 22.5 (d, J_{PC} = 106 Hz), 17.3 (d, J_{PCCC} = 14 Hz), 16.4 (d, J_{POCC} = 7 Hz), 4.7 (d, J_{PCCCC} = 2 Hz); ^{31}P NMR ($CDCl_3$) δ 41.41. MS (EI^+): *m/z* 334 (M^+); HRMS (EI^+): calcd. for $C_{18}H_{23}O_4P$ 334.1334, found 334.1340.

Diethyl (1,3,3-trimethyl-but-1-en yl)phosphonate (Table 2.5, Entry 7). To 4,4-dimethyl-2-pentyne (0.240 g, 2.50 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux for 24 h. To the reaction mixture was added CCl_4 (8 mL, 12.7g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9g, 29mmol) at rt. The resulting mixture was stirred at rt for 12 h. The solution was quenched with 1M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried

over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (354 mg, 57%) as an oil.

^{1}H NMR ($CDCl_3$) δ 6.54 (ddd, J = 27 Hz, J = 1.47 Hz, J = 0.59 Hz, 1 H), 3.9-4.1 (m, 4 H), 1.88 (ddd, J = 15.8 Hz, J = 1.47 Hz, J = 0.59 Hz, 3 H), 1.28 (t, J = 7 Hz, 6 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.8 (d, J_{PCC} = 4 Hz), 123.2 (d, J_{POC} = 175 Hz), 61.7 (d, J_{POC} = 6 Hz), 34.5 (d, J_{PCCC} = 21 Hz), 30.2, 16.5 (d, J_{POCC} = 6Hz), 13.5 (d, J_{PCC} = 10 Hz); ^{31}P NMR ($CDCl_3$) δ 24.44. MS (EI^+): *m/z* 234 (M^+); HRMS (EI^+) calcd. for $C_{11}H_{23}O_3P$ 234.1585, found 234.1380.

(1-Propyl-pent-1-enyl)-phosphonothioic acid *O*-ethyl ester (Scheme 2.7, eq. 1). To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.0 mg, 0.077 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux overnight. To the reaction mixture were added at rt sulfur (0.24g, 7.5 mmol) and triethylamine (0.762g, 7.53 mmol), and the resulting mixture was stirred at rt overnight. The solution was extracted with hexane, the acetonitrile layer was partitioned between 1 M HCl and EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to hexanes/EtOAc, 90/10% v/v) produced the expected compound (424 mg, 70%) as a brown oil. ^{1}H NMR ($CDCl_3$) δ 6.66 (dt, J = 27.5 Hz, J = 7.2 Hz, 1 H), 6.4-6.65 (bs, 1 H), 4.05-4.2 (m, 2H), 2.25-2.4 (m, 2 H), 2.1-2.25 (m, 2 H), 1.4-1.6 (m, 4 H), 1.33 (t, J = 7.0 Hz, 3 H), 0.95 (dt, J = 2.3 Hz, J = 7.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 13.8 Hz), 134.1 (d, J_{PC} = 141 Hz), 62.3 (d, J_{POC} = 6 Hz), 30.9 (d, J_{PCCC} = 20 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1,

22.2, 16.3 (d, J_{POCC} = 8 Hz), 14.5, 14.2; ^{31}P NMR ($CDCl_3$) δ 85.69. MS (EI^+): *m/z* 236 (M^+); HRMS (EI^+): calcd. for $C_{10}H_{21}O_2PS$ 236.1000, found 236.0992.

Methyl-phenyl-(1-propyl-pent-1-enyl)phosphine oxide (Scheme 2.7, eq. 2). To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at rt. The solution was stirred at reflux overnight. The mixture was then concentrated in high vacuo. The residue was diluted with 5 mL of dry THF. To the mixture at 0°C was added 7.5 mL (7.5 mmol) of phenylmagnesium bromide (1 M solution in THF). The mixture was warmed to rt and then stirred at reflux for 1.5 h. After addition of methyl iodide at 0°C (1.08 g, 7.61 mmol), the mixture was warmed to rt and stirred for 2 h. The reaction mixture was then quenched with 10 mL of 1 M HCl, extracted with EtOAc and the combined organic phases were washed with 1 M sodium thiosulfate, and then brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (334 mg, 53%) as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 7.65-7.8 (m, 2 H), 7.4-7.55 (m, 3 H), 6.41 (dt, J = 21.1 Hz, J = 7.3 Hz, 1 H), 2.0-2.25 (m, 4 H), 1.8 (d, J = 12.9 Hz, 3 H), 1.42-1.46 (m, 2 H), 1.20-1.35 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.5 (d, J_{PCC} = 9 Hz), 134.4 (d, J_{PC} = 94 Hz), 133.9 (d, J_{PC} = 98 Hz), 131.4 (d, J_{PCCCC} = 3 Hz), 130.4 (d, J_{PCC} = 10 Hz), 128.5 (d, J_{PCCC} = 12 Hz), 30.8 (d, J_{PCCC} = 15 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1, 22.1, 14.9 (d, J_{PC} = 72 Hz), 14.3, 13.9; ^{31}P NMR ($CDCl_3$) δ 33.74. MS (EI^+): *m/z* 250 (M^+); HRMS (EI^+): calcd. for $C_{15}H_{23}OP$ 250.1487, found 250.1488.

Chapter II: Section 2.3. Radical Hydrophosphinylation. [22]

Experimental Procedures for Table 2.6 and 2.8

General Procedure for the Radical Hydrophosphinylation of Alkenes and Alkynes with a Stock Solution of AlkOP(O)H$_2$. A 0.5 M solution of EtOP(O)H_2 (6.25 mmol, 1.0 equiv.) in CH_3CN (reagent grade 12.5 mL) was added to the alkyne, alkene (2.5 mmol) and heated to reflux. AIBN (0.045 g, 0.25 mmol, 0.1 equiv) was than added to the reaction flask and the mixture heated under N_2. After 6 h at reflux, another portion of AIBN (0.045 g, 0.25 mmol, 0.1 equiv) was added and the mixture was stirred at reflux overnight. After cooling to rt, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and washed with sat. aq $NaHSO_4$ (1 X). The aqueous phase was then extracted with EtOAc and the combined organic fractions were washed with aq sat. $NaHCO_3$ (1X) and brine. Drying ($MgSO_4$) and concentration afforded the crude compound, which was purified by chromatography (hexanes, 100% to EtOAc, 100% v/v). The product was generally obtained as oil.

Ethyl octylphosphinate[18c] **(Table 2.6, Entry 1).**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (d, J = 526 Hz, 1 H), 4.03 - 4.23 (m, 2 H), 1.21 - 1.82 (m, 14 H), 1.36 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ40.3 (dm, J_{PH} = 524 Hz). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 7 Hz), 31.8, 30.4 (d, J_{PCCC} = 15 Hz), 29.1, 29.0, 28.6 (d, J_{PC} = 93 Hz), 22.6, 20.7, 16.2 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ40.7 (dm, J = 530 Hz).

Ethyl decylphosphinate (Table 2.6, Entry 2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J = 558 Hz, 1 H), 4.02 - 4.23 (m, 2 H), 1.24 - 1.82 (m, 18 H), 0.88 (t, J = 7 ,3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.4 (d, J_{POC} = 7

Hz), 31.9, 30.4 (d, J_{PCCC} = 16 Hz), 28.1, 22.7, 20.7, 16.2 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.2 (dm J_{PH} = 524 Hz).

Ethyl (hex-5-enyl)phosphinate (Table 2.6, Entry 3).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, J = 526 Hz), 5.72-6.21 (m, 1 H), 4.95 - 5.05 (m, 2 H), 4.26 - 4.03 (m, 2 H), 2.10 - 2.05 (m, 2H), 1.81-1.51 (m, 6 H), 1.43 (t, J = 6 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.8 (dm, J_{PH} = 525 Hz).

Ethyl (4-oxiranyl-butyl)phosphinate (Table 2.6, Entry 4a).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, J = 527, 1 H), 3.98 - 4.17 (m, 2 H), 2.92 - 2.94 (m, 1 H), 2.76-2.79 (m, 1 H), 2.47 - 2.50 (m, 1 H), 1.27 - 1.73 (m, 8 H), 0.96 (t, J = 7, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.6 (dm, J_{PH} = 527 Hz).

Butyl (4-Oxiranylbutyl)phosphinate (Table 2.6, entry 4b).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, J = 527, 1 H), 3.98 - 4.17 (m, 2 H), 2.92 - 2.94 (m, 1 H), 2.76 - 2.79 (m, 1 H), 2.47 - 2.50 (m, 1 H), 1.27 - 1.73 (m, 15 H), 0.96 (t, J = 7.2, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 66.4 (d, J_{POC} = 7 Hz), 52.1, 47.2, 32.6 (d, J_{POCC} = 6 Hz), 32.2, 28.8 (d, J_{PC} = 93 Hz), 27.1 (d, J_{PCCC} = 16 Hz), 20.8 (d, J_{PCC} = 3 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.8 (dm, J_{PH} = 522 Hz).

Ethyl (3-*tert*-Butoxycarbonylaminopropyl)phosphinate[54] (Table 2.6, Entry 5).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 532 Hz, 1 H), 5.20 (m, 5 H), 5.10 (br s, 1 H), 4.00 - 4.30 (m, 2 H), 3.20 (m, 2 H), 1.80 (m, 4 H), 1.70 (t, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 156.6 (C=O), 79.5, 62.0 (d, J_{POC} = 7 Hz), 40.2 (d, J_{PCCC} = 16 Hz), 28.0 25.7 (d, J_{PC} = 95 Hz), 21.1 (d, J_{PCC} = 3 Hz), 15.8 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.4 (dt, J_{PH} = 531 Hz).

Ethyl (3-benz yloxycarbonylamino-propyl)phosphinate (Table 2.6, Entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (d, J = 532 Hz,1 H,), 7.37 - 7.32 (m, 5H), 5.10 (s, 2 H), 4.19 - 4.3 (m, 2 H), 3.30 (d, J = 6 Hz, 2 H,), 1.83 (m, 4 H), 1.35 (t, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 156.6 (C=O), 136.5, 128.5, 128.1, 66.6, 62.6 (d, J_{POC} = 7 Hz), 41.0 (d, J_{PCCC} = 16 Hz), 26.0 (d, J_{PC} = 94 Hz), 21.3, 16.2 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.7 (dt, J_{PH} = 530 Hz).

Ethyl cyclohexylphosphinate[151] (Table 2.6, Entry 7).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (d, J = 519 Hz, 1 H), 4.02 - 4.23 (m, 2 H), 1.77 - 1.92 (m, 6 H), 1.24 - 0.90 (m, 8 H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ = 44.2 (dm, J_{PH} = 523 Hz).

Ethyl (bicyclo[2.2.1]hept-2-yl)phosphinate (Table 2.6, Entry 8).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (d, J = 521Hz, 1 H), 6.87 (d, J = 520 Hz, 0.5 H,), 4.00 - 4.20 (m, 2 H), 2.67 (d, J = 8.7 Hz, 0.5 H), 2.55 (d, J = 10 Hz, 0.5H), 1.23-1.95 (m, 10 H), 1.36 (t, J = 7 Hz, 1.5 H), 1.35 (t, J = 7.2 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (t, J_{POC} = 7.7 Hz), 40.4 (dd, J_{PC} = 96 Hz), 37.4 (d, J_{PCCC}=19 Hz), 36.4 (d, J_{PCCC} = 14 Hz), 31.62 (d, J_{PCC} = 4 Hz), 30.26 (d, J_{PCC} = 4 Hz), 16.50 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 44.4 (dm J_{PH}= 519 Hz) 42.6 (dm J_{PH} = 519 Hz).

Ethyl cyclooctylphosphinate (Table 2.6, Entry 9).

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.86 (d, J = 519 Hz, 1 H), 4.03 - 4.2 (m, 2 H), 1.79-2.05 (m, 15 H), 1.33 - 1.38 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.4, 37.5, 36.3, 35.6, 33.7, 26.7, 26.7, 26.2, 26.0, 24.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 46.9 (dm, J_{PH} = 513 Hz).

Ethyl (octahydropentalen-1-yl)phosphinate (Table 2.6, Entry 10).

^{1}HNMR ($CDCl_3$, 300 MHz) δ 6.97 (d, J = 520 Hz, 1 H), 4.07 - 4.21(m, 2 H), 2.62 (d, J = 7 Hz), 1.20 - 2.72 (m, 12 H), 1.35 (t, J = 7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 45.1 (47%), (dm, J = 519 Hz), 44.4 (53%), (dm, J = 514 Hz). HRMS - FAB calcd. for $C_{10}H_{19}O_2P$, 202.1123, found 202.1127.

Ethyl (oct-1-enyl)phosphinate[20] (Table 2.8, Entry 1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J = 555 Hz, 1 H) 6.72 - 6.90 (m,1 H), 5.71 - 5.85 (m, 1H), 3.98 - 4.18 (m, 2 H), 2.25 - 2.32 (m, 2H), 1.11 - 1.60 (m, 8 H), 0.89 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.9 (dm, J_{PH} = 551 Hz).

Ethyl (dec-1-enyl)phosphiniate[19a] (Table 2.8, Entry 2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 552 Hz, 1 H), 6.64 - 6.82 (m, 1 H), 5.63 - 5.78 (m, 1 H), 4.01 - 4.10 (m, 2 H), 2.08 - 2.22 (m, 2 H), 1.2 - 1.36 (m, 14 H), 1.30 (t, J = 7 Hz, 3 H), 0.81 (t, J = 6 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.8 (dm, J_{PH} = 551 Hz), (70%), 21.5 (dm, J_{PH} = 551 Hz), (30%).

Ethyl (1-Propylpent-1-enyl)phosphinate[20] (Table 2.8, Entry 3).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J = 542, 1 H), 6.38 - 6.51 (m, 1 H), 4.06 - 4.14 (m, 2 H), 2.18 - 2.26 (m, 4 H), 1.47-1.49 (m, 4 H), 1.36 (t, J = 7 Hz, 3 H), 0.95 (t , J = 7 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 32.9 (dm J_{PH} = 525 Hz).

Acetic acid 3-ethoxyphosphinoyl-allyl ester (Table 2.8, Entry 4a).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, J = 564 Hz, 1 H), 6.74 - 6.89 (m, 1 H), 5.81 - 6.11 (m, 1 H), 4.77 (m, 2 H), 4.11 - 4.18 (m, 2 H), 2.14 (s, 3 H), 1.76 - 1.72 (m, 2 H), 1.39 (t, J = 15 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 170.7 (d, J = 5 Hz), 147.1 (d,

J_{PCC} = 7 Hz), 120.7 (d, J_{PC} = 129 Hz), 63.5 (d, J_{PCCC} = 21 Hz), 62.4 (d, J_{POC} = 6 Hz), 20.9, 16.6 (d, J_{POCC} = 7 Hz). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.6 (dm, J_{PH} = 521 Hz).

Acetic acid 3-butoxyphosphinoyl-allyl ester (Table 2.8, Entry 4b).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, J = 561 Hz, 1 H), 6.74 - 6.90 (m, 1 H), 5.98 - 6.30 (m, 1 H), 4.78 (m, 2 H), 4.02 - 4.17 (m, 2 H), 2.14 (m, 2 H) 2.05 (s, 3 H), 1.69 - 1.74 (m, 2 H), 1.40 - 1.47 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 0.97 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 170.3 (C=O), 147.0 (d, J_{PCC} = 7 Hz), 120.7 (d, J_{PC} = 129 Hz), 66.1 (d, J_{POC} = 6.5 Hz), 63.5 (d, J_{PCCC} = 21 Hz), 32.64(d, J_{POCC} = 6 Hz), 20.9, 19.0, 13.8. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ = 24.0 (dm, J_{PH} = 560 Hz).

Butyl (3-*tert*-butoxycarbonylaminopropenyl)phosphinate. (Table 2.8, Entry 5b).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, J = 560, 1 H), 6.69 - 6.85 (m, 1 H), 5.88 - 6.02 (m, 1 H), 4.86 (s, 1 H), 4.05 - 4.15 (m, 2 H), 3.96 (m, 2 H), 2.05 (s, 2 H), 1.71 - 1.67 (m, 2 H), 1.45 (s, 9H), 1.28 - 1.24 (m, 2 H) 0.95 (t, J = 7 Hz, 3 H), ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.7 (C=O), 150.8 (d, J_{PCC} = 6 Hz), 119.3 (d, J_{PC} = 130 Hz), 79.8, 65.8 (d, J_{POC} = 6 Hz), 42.7 (d, J_{PCCC} = 22 Hz), 32.4 (d, J_{POCC} = 6 Hz), 28.3, 18.7, 13.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.1 (dm, J = 559 Hz); HRMS-FAB: *m/z* calcd for $C_{12}H_{24}NO_4P$, (M+Na): 300.1341; found 300.1350.

Prop-2-ynylcarbamic acid *tert*-butyl ester[152] (Scheme 2.10). To a solution of prop-2-ynylamine (2.5 ml, 36.3 mmol) in dry THF (40 ml), was added di-*tert*-butyl dicarbonate (7.92 g, 40.0 mmol). The reaction mixture was then cooled to 0 °C and Et_3N (5.6 ml, 40.0 mmol) was slowly added. The resulting mixture was allowed to warm up to rt overnight under N_2, and then concentrated under reduced pressure to afford the crude compound,

which was purified by chromatography (hexanes, 100% to EtOAc/hexanes, 15:85, v/v). The product was obtained as white solid (5.6 g, 95%).

Synthesis of GABA Analogs 11 and 12 (Scheme 2.10).

Ethyl (3-*tert*-butoxycarbonylaminopropenyl)phosphinate (10, Scheme 2.10).

Propyl-2-ynyl-carbamic acid *tert*-butyl ester (388 mg, 2.50 mmol) and a 0.5 M solution of $EtOP(O)H_2$ in CH_3CN (6.25 mmol, 12.5 mL) was heated to reflux. AIBN (45 mg, 0.25 mmol) was then added and the mixture was heated under N_2. After 6 h at reflux, another portion of AIBN (45 mg, 0.25 mmol) was added. The mixture was stirred at reflux overnight. After cooling to rt, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and washed with sat. aq $NaHSO_4$ (1 X). The aqueous phase was then extracted with EtOAc and combined organic fractions were washed with aq sta. $NaHCO_3$ (1 X) and brine. Drying ($MgSO_4$) and concentration afforded the crude compound, which was purified by chromatography (hexanes, 100 % to EtOAc, 100 %) to produce **10** as an oil (392 mg, 63%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, J = 561, 1 H), 6.70 - 6.87 (m, 1 H), 5.90 - 6.03 (m, 1H), 4.87 (s, 1 H), 4.13 - 4.18 (m, 2 H), 3.97 (m, 2 H), 2.48 (d, J = 60 Hz, 2 H), 1.46 (s, 9 H), 1.38 (t, J = 12, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.8 (C=O), 150.8 (d, J_{PCC} = 10 Hz), 119.6 (d, J_{PC} = 130 Hz), 80.3, 62.37 (d, J_{POC} = 6.6 Hz), 42.9 (d, J_{PCCC} = 21 Hz), 28.5, 16.6 (d, J_{POCC} = 6.5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.8 (dm, J = 561 Hz); HRMS-FAB: *m/z* calcd for $C_{10}H_{20}NO_4P$, (M + Na): 272.1028, found 272.10301.

(3-Aminopropenyl)phosphinic acid. (11, Scheme 2.10).[76] A solution of **10** (340 mg, 1.36 mmol) and concd hydrochloric acid was refluxed overnight. The mixture was cooled to rt, concentrated under vacuum, diluted with water and extracted with EtOAc (3 X).

The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH (3 X) and dried in vacuo to give the hydrochloride salt **11** as a oil. Treatment of the oily hydrochloride with propylene oxide in MeOH at rt give **11**; yield 92 mg (56%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J = 535 Hz, 1 H), 6.48 - 6.31 (m, 1 H), 6.20 (m, 1 H), 3.80 (d, J = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.5 (dt, J = 550 Hz).

(3-Aminopropenyl)methylphosphinic acid.[76] **(12, Scheme 2.10).** To a solution of **10** (0.40 g, 1.60 mmol) in CH_2Cl_2 (8 mL) at -78 °C were added successively DBU (1.46 g, 1.43 mL, 9.60 mmol), MeI (2.27 g, 1.00 mL, 16.0 mmol), and Me_3SiCl (1.04 g, 1.20 mL 9.60 mmol). The mixture was warmed to rt overnight, and concentrated under vacuum. The crude was dissolved in EtOAc and washed with aq 1M HCl (1 X). The aqueous phase was then extracted with EtOAc (3 X) and combined organic fractions were washed with aq sat. $NaHCO_3$ (1 X) and brine. Drying ($MgSO_4$) and concentration afforded the crude ethyl (3-*tert*-butoxycarbonylaminopropenylmethyl)phosphinate and (3-*tert*-Butoxycarbonylaminopropenylmethyl)phosphinic acid. The residue was dissolved in concd HCl (16 mL) and refluxed overnight. It was then concentrated under vacuum, diluted with water and extracted EtOAc (3 X). The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH and dried in vacuo. Recrystallization from absolute EtOH to give hydrochloride salt **12**. The hydrochloride salt was dissolved in MeOH and treated with propylene oxide at rt The crystals were collected by filtration and dried under high vacuum to give **12**; yield 0.147g (68%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.15 - 6.34 (m, 1 H), 5.90 - 6.02 (m, 1 H), 3.57 (d, J = 6, 2 H), 1.21 (d, J = 14, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 31.5 (s).

Chapter III: Section 3.2. Synthesis of GABA Analogs.

Synthesis of Methyl-piperidin-4-ylmethyl-phosphinic acid 45 (Scheme 3.3).

3-Methanol-piperidine-1-carboxylic acid benzyl ester 32 (Scheme 3. 3). To a solution of 3-piperidine methanol **31** (10 g, 86.8 mmol) in 200 mL of dry THF, was added benzyl chloroformate (16.3 g, 13.6 mL, 95.4 mmol). The reaction mixture was then cooled to 0 °C and Et_3N (9.64 g, 13.3 ml, 95.4 mmol) was slowly added. The resulting mixture was allowed to warm up to rt overnight under N_2, and then concentrated under reduced pressure to afford the crude compound, which was purified by chromatography (hexanes, 100% to EtOAc/hexanes, 15:85, v/v). Compound **32** was obtained in 90 % isolated yield (19.5 g, 78.2 mmol).

3-Bromomethyl-piperidine-1-carboxylic acid benzyl ester 33 (Scheme 3.3). A mixture of compound **32** (18.0 g, 72.2 mmol), CBr_4 (53.4 g, 161 mmol) and PPh_3 (44.2 g, 168 mmol) in THF (350 mL), was stirred at rt for 24 h. The resulting suspension was filtered, concentrated and purified. Column chromatography (EtOAc/Hexanes 5 : 95, v/v to EtOAc/Hexanes 1 : 9, v/v) afforded compound **33** (16.3 g, 52.0 mmol, 72 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 - 7.37 (m, 5 H), 5.14 (s, 2 H), 4.00 (d, J = 13 Hz, 2 H), 3.30 (d, J = 5 Hz, 2 H), 2.88 (t, J = 10 Hz, 2 H), 1.24 - 1.83 (m, 5 H).

3-Methylene-piperidine-1-carboxylic acid benzyl ester 34 (Scheme 3.3). To a solution of compound **33** (15.0 g, 46.8 mmol) in 150 mL of dry CH_3CN, was added DBU (14.2 g, 93.6 mmol). The reaction mixture was refluxed for 24 h. After cooling to rt, the mixture

was concentrated in vacuo and purified by column chromatography (EtOAc/Hexanes 2 : 8, v/v to EtOAc/Hexanes 8 : 2, v/v) to afford the title compound as a yellow oil (6.86 g, 29.5 mmol, 63 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 - 7.37 (m, 5 H), 5.13 (s, 2 H), 4.77 (s, 2 H), 3.96 (s, 2 H), 3.53 (t, J = 6 Hz, 2 H), 2.45 – 2.65 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.4, 142.0, 137.1, 128.7, 128.1, 128.0, 110.4, 67.2, 50.8, 44.5, 32.9, 26.8.

3-Butoxyphosphinoylmethyl-piperidine-1-carboxylic acid benz yl ester 35 (Scheme 3.3). A solution of Compound **34** (1.95 g, 8.42 mmol) and a 0.5 M solution of $BuOP(O)H_2$ in CH_3CN (21.0 mmol, 42.0 mL, 2.5 equiv.) was heated to reflux. AIBN (138 mg, 0.84 mmol) was then added, and the mixture was heated under N_2. After 6h at reflux, another portion of AIBN (138 mg, 0.84 mmol) was added. The mixture was stirred at reflux overnight. After cooling to rt, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and washed with sat. aq $NaHSO_4$. The aqueous phase was then extracted with EtOAc, and the combined organic phases were washed with sat. aq $NaHCO_3$ and brine. Drying ($MgSO_4$) and concentration afforded the crude compound **35**, which was purified by column chromatography (EtOAc/Hexanes 3 : 7 v/v to MeOH: EtOAc 1:9 v/v) to give compound **35** in 70 % isolated yield (2.07 g, 5.89 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 - 7.40 (m, 5 H), 7.20 (d, J_{PH} = 530 Hz, 1 H), 5.15 (s, 2 H), 4.10 - 4.19 (m, 2 H), 3.97 - 4.08 (m, 2 H), 2.80 - 2.84 (m, 2 H), 1.99 - 2.05 (m, 3 H), 1.16 - 1.86 (m, 10 H), 0.98 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ (d, J_{PH} = 532 Hz).

3-(Butoxy-methyl-phosphinoylmethyl)-piperidine-1-carboxylic acid benzyl ester 36

(Scheme 3.3). Compound **35** (989 mg, 2.80 mmol) was placed under vacuum in a dry two neck flask 10 min before use. Dry THF (10 mL) was then added under N_2. The flask was then placed at -78 °C and deoxygenated under vacuum for 5 min. The reaction flask was backfilled with nitrogen, and LHMDS (2.80 mmol, 2.80 mL, 1.0 M in THF) was added at -78 °C. After 15 min, iodomethane (397 mg, 175 μL, 2.80 mmol) was added under N_2. After the addition of the electrophile, the temperature of the solution was slowly allowed to warm to rt. The reaction mixture was quenched with a saturated solution of NH_4Cl/brine, extracted with EtOAc (3 X), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel EtOAc/Hexanes 3:7, v/v to MeOH/EtOAc 1:9, v/v)to give compound **36** in 51 % isolated yield (524 mg, 1.43 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 - 7.42 (m, 5 H), 5.14 (s, 2 H), 4.11 - 4.15 (m, 2 H), 3.90 - 4.10 (m, 2 H), 2.82 - 2.86 (m, 2 H), 1.15 - 2.00 (m, 11 H), 1.48 (d, J = 13 Hz, 3 H), 0.93 (t, J = 7.6, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 128.4, 128.0, 127.9, 67.2 (d, J_{POC} = 7 Hz), 63.9(d, J_{POC} = 7 Hz), 51.1, 45.9, 36.5 (d, J_{PC} = 91 Hz), 33.5, 32.7, 30.6, 18.9, 13.8, 13.7 (d, J_{PC} = 90 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 54.6 (s).

Methyl-piperidin-3-ylmethyl-phosphinic acid 37 (Sche me 3.3). A solution of **36** (514 mg, 1.40 mmol) and concd hydrochloric acid was refluxed overnight. The mixture was cooled to rt, concentrated under vacuum, diluted with water and extracted with EtOAc (3 X). The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH (3 X) and dried in vacuo to give the hydrochloride salt **37** as a oil. Treatment of the oily hydrochloride with propylene oxide in MeOH at rt give **37**; yield: 174 mg, 0.98 mmol, 70 %.

^{1}H NMR (D_2O, 300 MHz) δ 3.26 - 3.30 (m, 2 H), 2.83 - 2.96 (m, 2 H), 1.68 - 2.04 (m, 7 H), 1.38 (d, J = 14, 3 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 49.8, 44.1, 33.0 (d, J_{PC} = 88 Hz), 30.1, 28.4, 18.4, 13.0 (d, J_{PC} = 87 Hz); ^{31}P NMR (D_2O, 121.5 MHz) δ 46.3 (s).

Synthesis of Methyl-piperidin-4-ylmethyl-phosphinic acid 45 (Scheme 3.4).

4-Methanol-piperidine-1-carboxylic acid benzyl ester 39 (Scheme 3. 4). To a solution of 4-piperidine methanol **38** (5.0 g, 43.4 mmol) in 100 mL of dry THF, was added benzyl chloroformate (8.14 g, 6.80 mL, 47.7 mmol). The reaction mixture was then cooled to 0 °C and Et_3N (4.82 g, 6.64 ml, 47.7 mmol) was slowly added. The resulting mixture was allowed to warm up to rt overnight under N_2, and then concentrated under reduced pressure to afford the crude compound, which was purified by chromatography (hexanes, 100% to EtOAc/hexanes, 15:85, v/v). Compound **39** was obtained in 85 % isolated yield (9.20 g, 36.9 mmol).

4-Bromomethyl-piperidine-1-carboxylic acid benzyl ester 40 (Scheme 3.4). A mixture of compound **39** (9.00 g, 36.1 mmol), CBr_4 (26.7 g, 80.4 mmol) and PPh_3 (22.1 g, 84.2 mmol) in THF (200 mL), was stirred at rt for 24 h. The resulting suspension was filtered, concentrated and purified. Column chromatography (EtOAc/Hexanes 5 : 95, v/v to EtOAc/Hexanes 1 : 9, v/v) afforded compound **40** (7.6 g, 24.2 mmol, 67 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 - 7.36 (m, 5 H), 5.13 (s, 2 H), 3.96 - 4.23 (m, 2 H), 3.24 (d, J = 5 Hz, 2 H), 2.79 - 2.91 (m, 2 H), 1.24 - 1.83 (m, 5 H).

4-Methylene-piperidine-1-carboxylic acid benzyl ester 41 (Scheme 3.4). To a solution of compound **40** (7.5 g, 23.4 mmol) in 100 mL of dry CH_3CN, was added DBU (7.1 g, 46.8 mmol). The reaction mixture was refluxed for 24 h. After cooling to rt, the mixture was concentrated in vacuo and purified by column chromatography (EtOAc/Hexanes 2 :

8, v/v to EtOAc/Hexanes 8 : 2, v/v) to afford the title compound as a yellow oil (3.0 g,12.9 mmol, 52 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 - 7.37 (m, 5 H), 5.14 (s, 2 H), 4.76 (s, 2 H), 3.51 (t, J = 6 Hz, 4 H), 2.10 – 2.30 (m, 4 H).

4-Butoxyphosphinoylmethyl- piperidine-1-carboxylic acid benzyl ester 42 (Scheme 3.4). A solution of Compound **41** (975 mg, 4.21 mmol) and a 0.5 M solution of $BuOP(O)H_2$ in CH_3CN (10.5 mmol, 21.1 mL, 2.5 equiv.) was heated to reflux. AIBN (69.0 mg, 0.42 mmol) was then added, and the mixture was heated under N_2. After 6h at reflux, another portion of AIBN (69.0 g, 0.42 mmol) was added. The mixture was stirred at reflux overnight. After cooling to rt, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and washed with sat. aq $NaHSO_4$. The aqueous phase was then extracted with EtOAc, and the combined organic phases were washed with sat. aq $NaHCO_3$ and brine. Drying ($MgSO_4$) and concentration afforded the crude compound **42**, which was purified by column chromatography (EtOAc/Hexanes 3 : 7 v/v to MeOH: EtOAc 1:9 v/v) to give compound **42** in 68 % isolated yield (1.02 g, 2.9 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 - 7.40 (m, 5 H), 7.19 (d, J_{PH} = 529 Hz, 1 H), 5.12 (s, 2 H), 4.08 - 4.18 (m, 2 H), 3.93 - 4.04 (m, 2 H), 2.78 - 2.82 (m, 2 H), 1.96 - 2.03 (m, 3 H), 1.16 - 1.86 (m, 10 H), 0.94 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ (d, J_{PH} = 532 Hz).

4-(Butoxy-methyl-phosphinoylmethyl)-piperidine-1-carboxylic acid benzyl ester 43 (Scheme 3.4). Compound **42** (989 mg, 2.80 mmol) was placed under vacuum in a dry two neck flask 10 min before use. Dry THF (10 mL) was then added under N_2. The flask was then placed at -78 °C and deoxygenated under vacuum for 5 min. The reaction flask

was backfilled with nitrogen, and LHMDS (2.80 mmol, 2.80 mL, 1.0 M in THF) was added at -78 °C. After 15 min, iodomethane (397 mg, 175 μL, 2.80 mmol) was added under N_2. After the addition of the electrophile, the temperature of the solution was slowly allowed to warm to rt. The reaction mixture was quenched with a saturated solution of NH_4Cl/brine, extracted with EtOAc (3 X), dried over anhydrous MgSO4, and concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel EtOAc/Hexanes 3:7, v/v to MeOH/EtOAc 1:9, v/v)to give compound **43** in 50 % isolated yield (514 mg, 1.40 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 - 7.42 (m, 5 H), 5.12 (s, 2 H), 4.11 - 4.16 (m, 2 H), 3.89 - 4.09 (m, 2 H), 2.82 - 2.86 (m, 2 H), 1.15 - 2.00 (m, 11 H), 1.46 (d, J = 13 Hz, 3 H), 0.94 (t, J = 7.6, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 128.5, 128.0, 127.9, 67.0 (d, J_{POC} = 7 Hz), 63.9(d, J_{POC} = 7 Hz), 43.9, 36.5 (d, J_{PC} = 91 Hz), 33.5, 32.7, 30.6, 18.9, 13. 8, 13.7 (d, J_{PC} = 89 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 54.2 (s).

Methyl-piperidin-4-ylmethyl-phosphinic acid 45 (Sche me 3.4). A solution of **43** (257 mg, 0.70 mmol) and concd hydrochloric acid was refluxed overnight. The mixture was cooled to rt, concentrated under vacuum, diluted with water and extracted with EtOAc (3 X). The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH (3 X) and dried in vacuo to give the hydrochloride salt **49** as a oil. Treatment of the oily hydrochloride with propylene oxide in MeOH at rt give **49**; yield: 64 mg, 0.36 mmol, 51 %.

^{1}H NMR (D_2O, 300 MHz) δ 3.23 - 3.27 (m, 2 H), 2.82 - 2.94 (m, 2 H), 1.66 - 2.00 (m, 7 H), 1.36 (d, J = 14, 3 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 44.0, 32.0 (d, J_{PC} = 88 Hz), 30.1, 28.4, 18.4, 12.9 (d, J_{PC} = 87 Hz); ^{31}P NMR (D_2O, 121.5 MHz) δ 46.1 (s).

Synthesis of Piperidin-3 and -4-ylmethyl-phosphinic acid (Scheme 3.5)

3-Hydroxyphosphinoylmethyl-piperidine-1-carboxylic acid benzyl ester 46 (Scheme 3.5).

To a solution of NaH_2PO_2 (880 mg, 10 mmol, 2.5 equiv.) and compound **34** (926 mg, 4.0 mmol, 1.0 equiv.) in methanol (20 mL) was added Et_3B (4.0 mL, 4.0 mmol, 1.0 M, 1.0 equiv.), at rt in an open reaction vessel. The solution was stirred at rt for 2 h. The reaction mixture was concentrated on a rotary evaporator, and the residue was partitioned between aq $KHSO_4$ and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried and concentrated to afford compound **46** (1.19 mg, 4.0 mmol, 100 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5 H), 7.18 (d, J_{PH} = 547 Hz, 1 H), 6.05 (br. s, 1 H), 5.12 (s, 2 H), 3.89 - 4.01 (m, 2 H), 2.74 – 2.94 (m, 2 H), 1.98 - 2.10 (m, 3 H), 1.25 - 1.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 158.4, 138.7, 128.2, 128.1, 67.5, 50.1, 44.9, 36.5 (d, J_{PC} = 90.6 Hz), 32.0, 29.8; ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 36.7 (d, J_{PH} = 546 Hz).

Piperidin-3-yl-methyl-phosphinic acid 47 (Scheme 3.5) A solution of **46** (1.19 mg, 4.0 mmol) and concd hydrochloric acid was refluxed overnight. The mixture was cooled to rt, concentrated under vacuum, diluted with water and extracted with EtOAc (3 X). The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH (3 X) and dried in vacuo to give the hydrochloride salt **47** as a oil. Treatment of the oily hydrochloride with propylene oxide in MeOH at rt to give **47**; yield 92 mg (455 mg, 2.8 mmol, 70 %).

^{1}H NMR (D_2O, 300 MHz) δ 6.90 (d, J_{PH} = 505 Hz, 1 H), 3.20 - 3.22 (m, 2 H), 2.80 - 2.89 (m, 2 H), 1.76 - 1.87 (m, 3 H), 1.29 - 1.44 (m, 4 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 49.8, 44.5, 37.1 (d, J_{PC} = 89 Hz), 31.3 (d, J_{PCCC} = 10 Hz), 28.8; ^{31}P NMR (D_2O, 121.5 MHz) δ 27.4 (d, J_{PH} = 507 Hz).

4-Hydroxyphosphinoylmethyl-piperidine-1-carboxylic acid benzyl ester 48 (Scheme 3.5).

To a solution of NaH_2PO_2 (440 mg, 5.0 mmol, 2.5 equiv.) and compound **41** (463 mg, 2.0 mmol, 1.0 equiv.) in methanol (10 mL) was added Et_3B (2.0 mL, 2.0 mmol, 1.0 M, 1.0 equiv.), at rt in an open reaction vessel. The solution was stirred at rt for 2 h. The reaction mixture was concentrated on a rotary evaporator, and the residue was partitioned between aq $KHSO_4$ and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried and concentrated to afford compound **48** (595 mg, 2.0 mmol, 100 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5 H), 7.28 (d, J_{PH} = 544 Hz, 1 H), 6.20 (br. s, 1 H), 5.12 (s, 2 H), 3.09 - 4.16 (m, 2 H), 2.81 - 3.00 (m, 2 H), 1.96 - 2.18 (m, 3 H), 1.65 - 1.85 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.4, 128.7, 128.2, 128.1, 67.3, 44.1, 36.4 (d, J_{PC} = 90.6 Hz), 31.2, 30.2; ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 37.4 (d, J_{PH} = 546 Hz).

Piperidin-4-yl-methyl-phosphinic acid 49 (Scheme 3.5) A solution of **48** (595 mg, 2.0 mmol) and concd hydrochloric acid was refluxed overnight. The mixture was cooled to rt, concentrated under vacuum, diluted with water and extracted with EtOAc (3 X). The aqueous layer was evaporated to dryness. The residue was co-evaporated with water (3 X) and absolute EtOH (3 X) and dried in vacuo to give the hydrochloride salt **49** as a oil.

Treatment of the oily hydrochloride with propylene oxide in MeOH at rt give **49**; yield 92 mg (104 mg, 0.64 mmol, 32 %).

^{1}H NMR (D_2O, 300 MHz) δ 6.84 (d, J_{PH} = 502 Hz, 1 H), 3.18 - 3.20 (m, 2 H), 2.77 - 2.86 (m, 2 H), 1.76 - 1.87 (m, 3 H), 1.26 - 1.41 (m, 4 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 43.9, 37.6 (d, J_{PC} = 89 Hz), 29.7 (d, J_{PCCC} = 10 Hz), 28.3; ^{31}P NMR (D_2O, 121.5 MHz) δ 27.3 (d, J_{PH} = 508 Hz).

Synthesis of 4-oxo-4λ^5-[1,2,4] Diazaphospholidin-4-ol 52 (Scheme 3.6).

Benzyl [bis(chloromethyl)]phosphinate 50 (Scheme 3.6). Anhydrous Et_3N (7.84 g, 10.8 mL, 77.5 mmol, 1.2 equiv) was added dropwise to the solution of bis(chloromethyl)phosphinic chloride (11.6 g, 64.5 mmol, 1.0 equiv) in dry THF (300 mL) at 0 ^{o}C. Absolute ethanol (8.38 g, 8.03 mL, 77.5 mmol, 1.2 equiv) was added dropwise and the mixture stirred at rt, for 4 h. The precipitate was filtered and the filtrate evaporated. Purification of the crude product by distillation at 104-106 ^{o}C /1 torr gave ethyl [bis(chloromethyl)]phosphinate (11.4 g, 45.2 mmol, 70 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 - 7.46 (m, 5 H), 5.19 (d, J = 10 Hz, 2 H), 3.72 (dd, J = 9 Hz, J = 6 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.9, 131.7, 131.1, 130.6, 72.0 (d, J_{POC} = 7 Hz), 33.5 (d, J_{PC} = 106 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 30.6.

4-Oxo-4λ^5-[1,2,4] diaz aphospholidin-4-ol 52 (Scheme 3.6). A mixture of **50** (1.50 g, 5.94 mmol, 1.0 equiv.) and hydrazine (1.90 g, 59.4 mmol, 1.88 mL, 10 equiv.) in 150 mL of EtOH was refluxed for 36 h. After cooling to rt, the mixture was concentrated in high vacuo to remove EtOH and an access of hydrazine and afford compound **51** as a thick oil in 96 % purity. The recrystallization of compound **51** from hot EtOH gave compound **52** as colorless crystals; yield: 1.19 mmol, 145 mg, 20 %.

^{1}H NMR (D_2O, 300 MHz): δ 2.72 (d, J = 7 Hz, 4 H); ^{13}C NMR (D_2O, 75.45 MHz) δ 44.6 (d, J_{PC} = 90 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 62.5.

4-Benzyloxy [1,2,4] diazaphospolidine-4-oxide 51 (Scheme 3.6).

^{1}H NMR (D_2O, 300 MHz): δ 7.29 - 7.48 (m, 5 H), 5.11 (d, J = 10, 2 H), 3.58 (d, J = 9 Hz, 4 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 69.0.

Chapter IV: Section 4.2.1.[47]

General P rocedure for the Reaction of Halomethylphosphorus Anions (59b-59g) with Organoboranes.

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b-59g** (4.0 mmol, 1.0 equiv) and dry THF (20 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe followed by organoboranes (4.0 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then quenched by addition of water. The resulting biphasic mixture was then stirred at reflux for 2 h. After cooling to rt, the layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and the solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes) yielded the described compounds.

General Procedure fo r the Reaction of Halomethylphosphorus Anions (59i, 59j) with Organoboranes.

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59i** or **59j** (3.2 mmol, 1.0 equiv) and dry THF (15 mL). The solution was

cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllithium (2.0 mL, 1.6 M solution in hexane, 3.2 mmol, 1.0 equiv) was added slowly *via* syringe followed by organoboranes (3.2 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and was quenched by addition of water. The resulting biphasic mixture was stirred for 30 min at rt. The layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes) yielded the described compounds.

General Procedure for the Reaction of Diphenyl (chloromet hyl)phosphine-borane 59k with (Alkyl)$_3$B.

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diphenyl (chloromethyl)phosphine-borane **59k** (2.1 mmol, 521 mg, 1.0 equiv) and dry THF (15 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *sec*-butyllithium (1.5 mL, 1.4 M solution in cyclohexane, 2.1 mmol, 1.0 equiv) was added slowly *via* syringe followed by (Alkyl)$_3$B (2.1 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and was quenched by addition of water. The resulting biphasic mixture was stirred for 30 min at rt. The layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes) yielded the described compounds.

(Diazomethyl)phosphonate 4a[101] **(Scheme 4.3)** was prepared according to the literature. A flame-dried 250 mL round-bottomed flask was charged with 40 mL of dry THF.

Dimethyl methylphosphonate (2.29 g, 2.00 mL, 18.4 mmol) was added, and the mixture was cooled to -78 °C. *n*-Butyllithium (7.66 mL of a 2.40 M solution in hexanes, 18.4 mmol) was added over 5 min, and the solution was allowed to stir at -78 °C for 15-30 min. 2,2,2-Trifluoroethyl trifluoroacetate (5.41 g, 3.73 mL, 27.6 mmol) was added rapidly (1-2 s), and the resulting mixture was stirred at -78 °C for 15 min. The solution was then warmed to rt. The crude reaction mixture was partitioned between diethyl ether (250 mL) and 3 % HCl (10 mL).11 The combined ether layers were washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried with $MgSO_4$, and concentrated to give dimethyl (3,3,3-Trifluoro-2,2-dihydroxypropyl)phosphonate as a pale yellow oil which was used without purification in the next step. The crude sample was immediately dissolved in dry CH3CN (40 mL). 4-Acetamidobenzenesulfonyl azide (3.97 g, 16.5 mmol) was added, and the solution was cooled to 0 °C. Triethylamine (1.66 g, 2.29 mL, 16.5 mmol) was slowly added (ca. 5 min). The mixture was allowed to warm to rt and was stirred overnight. Solvent was removed by rotary evaporation from the resulting slurry, which contained precipitated 4-acetamidobenzenesulfonamide. The residual orange oily solid was suspended in $CHCl_3$ and filtered through a coarse glass frit to remove the 4-acetamidobenzenesulfonamide, which was washed with a small portion of additional $CHCl_3$. Column chromatography of the concentrated filtrate gave **59a** (1.23 g, 8.25 mmol, 50%). Spectral data were identical with those from an authentic sample. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79 (d, J = 12 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.6.

Diethyl (chloromethyl)phosphonat e 59b (Scheme 4.5). Anhydrous Et_3N (38.45 g, 52.96 mL, 0.38 mol, 2.1 equiv) was added dropwise to the solution of

(chloromethyl)phosphonic dichloride (30.00 g, 0.18 mol, 1.0 equiv) in dry THF (300 mL) at 0 ^{o}C. Absolute ethanol (17.49 g, 22.14 mL, 0.38 mol, 2.1 equiv) was added dropwise and the mixture stirred at rt, for 10 h. The precipitate was filtered and the filtrate evaporated. Purification of the crude product by distillation at 105-110 ^{o}C /10 torr gave diethyl (chloromethyl)phosphonate (28.20 g, 0.17 mol, 94 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (quin, J = 7 Hz, 4 H), 3.57 (d, J = 10 Hz, 2 H), 1.38 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.4 (d, J_{POC} = 6 Hz), 33.4 (d, J_{PC} = 160 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 19.8.

Dibenzyl (chloromethyl)phosphonate 4c[103] **(Scheme 4.7)** was prepared according to the literature. Anhydrous Et_3N (10.30 mL, 73.9 mmol, 3.0 equiv) was added dropwise to the solution of chloromethylphosphonic dichloride (4.1 g, 24.5 mmol, 1.0 equiv) in dry THF (200 mL) at 0 ^{o}C. Benzyl alcohol (5.60 mL, 53.9 mmol, 2.2 equiv) was added dropwise and the mixture stirred at 0 ^{o}C for 1 h and then at rt, for 4 h. The precipitate was filtered, the filtrate evaporated. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded dibenzyl (chloromethyl)phosphonate (6.05 g, 19.5 mmol, 80%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 - 7.37 (m, 10 H), 4.05 - 5.18 (m, 4 H), 3.49 (d, J = 11, Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.8, 128.0, 127. 9, 69.1 (d, J_{POC} = 7 Hz), 33.9 (d, J_{PC} = 160 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 20.8.

Tri(chloromethyl)phosphonate 59d (Scheme 4.7) was prepared according to the literature.[104]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37 - 4.52 (m, 4 H), 1.45 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 92,1 (d, J_{PC} = 198 Hz), 67.1 (d, J_{POC} = 7 Hz), , 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 6.5.

Diethyl (1-chloroethyl)phosphonate 59e and diethyl 1-chloro-benzylphosphonate 59f (Scheme 4.7) were prepared according to literature[105] from diethyl (hydroxyethyl)phosphonate and 1-hydroxy-benzylphosphonate respectively, triphenylphosphine and carbon tetrachloride.

Diethyl (hydroxyethyl)phosphonate[153] and 1-hydroxy-benzylphosphonate[6] were prepared according to the literature from diethyl phosphite and the appropriate aldehyde in the presence of Et_3N.

Diethyl (1-chloroethyl)phosphonate 59e. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17 - 4.29 (m, 4 H), 4.10 (dq, J_{HH} = 7 Hz, J_{HP} = 9 Hz, 1 H), 1.70 (dd, J_{HH} = 7 Hz, $J_{HP=}$ 16.6 Hz, 3 H), 1.37 (t, J = 7 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.2.

Diethyl 1-chloro-benzylphosphonate 59f. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 – 7.56 (m, 5 H), 4.90 (d, J = 14 Hz, 1 H), 3.85 - 4.24 (m, 4 H), 1.33 (t, J = 7 Hz, 3 H), 1.18 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.1, 129.0, 128.9 (d, J_{PCCC} = 6 Hz, 2 C),128.5 (2 C), 64.1 (d, J_{POC} = 7 Hz), 63.9 (d, J_{POC} = 7 Hz), 53.6 (d, J_{PC} = 160 Hz), 16.4 (d, J_{POCC} = 6 Hz), 16.2 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 18.3.

Ethyl [bis(chloromethyl)]phosphinate 59g.[106] (Scheme 4.7). Anhydrous Et_3N (15.68 g, 21.60 mL, 0.155 mol, 1.2 equiv) was added dropwise to the solution of bis(chloromethyl)phosphinic chloride (23.20 g, 0.129 mol, 1.0 equiv) in dry THF (300 mL) at 0 ^{o}C. Absolute ethanol (7.14 g, 9.04 mL, 0.155 mol, 1.2 equiv) was added dropwise and the mixture stirred at rt, for 4 h. The precipitate was filtered and the filtrate

evaporated. Purification of the crude product by distillation at 104-106 ^{o}C /1 torr gave ethyl [bis(chloromethyl)]phosphinate (20.83 g, 0.110 mol, 85 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.16 - 4.26 (m, 2 H), 3.72 (d, J = 9 Hz, 4 H), 1.36 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.2 (d, J_{POC} = 7 Hz), 33.3 (d, J_{PC} = 106 Hz), 16.7 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.7.

Bis(chloromethyl)phosphinic chloride[107] was prepared according to the literature. A mixture of H_3PO_2 (30.50 g, 0.32 mol, 50 % aqueous solution), 17.5 mL concentrated HCl and 14.5 g of paraformaldehyde was stirred at 40 - 45 ^{o}C until a clear solution was obtained and then refluxed for 30 h. Evaporation under reduced pressure gave crude bis(hydroxymethyl)phosphinic chloride, which was used in next step without purification.

To 176.0 g of refluxing $SOCl_2$ was added slowly with stirring crude bis(hydroxymethyl)phosphinic chloride (30.00 g, 0.25 mol). After completion of the addition, refluxing was continued for 3 h until gas evolution ceased. Purification of the crude product by distillation b.p. 80-85 ^{o}C /0.1 torr gave bis(chloromethyl)phosphinic chloride (32.38 g, 0.18 mol, 72 %).

Diethyl (chloromethyl)phosphonothioate 59h[108] **(Scheme 4.7)** was prepared according to the literature from (chloromethyl)phosphonic dichloride and sodium ethoxide.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.14 - 4.27 (m, 4 H), 3.70 (d, J = 7 Hz, 2 H), 1.36 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.0 (d, J_{POC} = 6 Hz), 41.0 (d, J_{PC} = 124 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 85.5.

Diethoxy-(chloromethyl)phosphine-borane 59i (Scheme 4.9). To a solution of dichloro-(chloromethyl)phosphine (66.1 mmol, 10.00 g, 1.0 equiv) in dry THF (150 mL),

was added absolute ethanol (132.1 mmol, 6.10 g, 7.70 mL, 2.0 equiv) under nitrogen. The reaction mixture was then cooled to 0 °C and Et_3N (132.1 mmol, 18.4 mL, 2.0 equiv) was slowly added. After the solution has been stirred for 10 min at rt, it was again cooled to 0° C and borane-methyl sulfide (36.5 mL of a 2.0 M solution in THF, 73 mmol, 1.1 equiv) was added. The solution was allowed to warm up to rt and stirring was continued for 15 min. The precipitate was removed by filtration, the filtrate diluted with EtOAc and washed with water (1 X). The resulting organic layer was dried with $MgSO_4$, and the solvent removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:99, v/v) yielded diethoxy-(chloromethyl)phosphine-borane **59i** (62.5 mmol, 11.5 g, 95 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03 - 4.26 (m, 4 H), 3.55 (d, J = 3 Hz, 2 H), 1.35 (t, J = 7 Hz, 6 H), 0.50 (qd, J_{BH} = 96 Hz, J_{PBH} = 16 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.5 (d, J_{POC} = 4 Hz), 37.5 (d, J_{PC} = 55 Hz), 16.5 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 137.5 (q, J_{PB} = 76 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 44.2 (dq, J_{BP} = 76 Hz, J_{BH} = 96 Hz); HRMS calcd. for $C_5H_{19}BClNO_2P$, ($[M + NH_4]^+$) 202.0937, found 202.0935.

Dichloro-(chloromethyl)phosphine[154] was prepared by the sulfur exchange reaction as reported in the literature. The mixture of chloromethylphosphonothioic dichloride (17.50 g, 96.2 mmol, 1.0 equiv) and dichlorophenylphosphine (19.80 g, 110.6 mmol, 1.15 equiv) was heated at 175 ^{o}C under an atmosphere of nitrogen in sealed tube for 3 h. It was then cooled and distilled. The fraction collected boiling at 67-132 ^{o}C at 100 torr was then carefully fractioned under atmospheric pressure (128-132 ^{o}C) to give dichloro-(chloromethyl)phosphine (10.24 g, 68.3 mmol, 71 %).

^{31}P NMR (36 MHz) δ 165.

(Chloromethyl)phosphonothioic dichloride[154] was prepared according to the literature. A mixture of posphorus pentasulfide (8.05 g, 18.1 mmol, 0.12 equiv) and chloromethylphosphonic dichloride (25.00 g, 150.7 mmol, 1.0 equiv) was heated to reflux at 174-179 ^{o}C under nitrogen for 6 h, and then distilled at 50 ^{o}C/10 torr to give (chloromethyl)phosphonothioic dichloride (102.5 mmol, 18.64 g, 68 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29 (d, J = 3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 41.0 (d, J_{PC} = 87 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 75.1.

(Chloromethyl)phosphonic dichloride[155] was prepared according to the literature. Dichloromethane (34.98 g, 0.4 mol, 25.7 mL, 1.0 equiv), phosphorus trichloride (54.93 g, 0.4 mol, 34.89 mL, 1.0 equiv) and aluminium chloride (53.34 g, 0.4 mmol, 1.0 equiv) were mixed and heated at 100 ^{o}C in sealed tube for 24 h. After cooling to rt, the reaction mixture was dissolved in dichloromethane and the solution was cooled to about - 20 ^{o}C. Water (79.2 mL, 4.4 mol, 11.0 equiv) was then added in small portions with vigorous stirring. The solution was filtered, the solvent removed in vacuo and the residue distilled at 50 ^{o}C/ 0.5 torr to give (chloromethyl)phosphonic dichloride (33.28 g, 0.2 mol, 50 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17 (d, J = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 45.5 (d, J_{PC} = 117 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.2.

Diethoxy (1-chloroethyl)phosphine-borane 59j (Scheme 4.9). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethoxy (chloromethyl)phosphine-borane (4.0 mmol, 736 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled to - 78 ^{o}C and *n*-butyllithium (3.0 mL, 1.6 M solution in hexane, 4.8 mmol, 1.2 equiv) was added slowly *via* syringe. The reaction mixture was stirred at -

78 °C for 5 min, then iodomethane (4.8 mmol, 681 mg, 1.2 equiv) was added. The reaction was warmed slowly to rt and was quenched by addition of H_2O. The layers were separated and the aqueous phase was extracted with EtOAc (3 X). The combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:99, v/v) yielded diethoxy (1-chloroethyl)phosphine-borane **59j** (3.60 mmol, 713 mg, 90 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 - 4.24 (m, 4 H), 3.93 (q, J = 7 Hz, 1 H), 1.66 (d, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 0.50 (qd, J_{BH} = 94 Hz, J_{PBH} = 16 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.6, 37.5 (d, J_{PCC} = 58 Hz), 18.3, 16.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 141.4 (q, J_{PB} = 75 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 44.4 (dq , J_{BP} = 75Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_6H_{21}BClNO_2P$, ($[M + NH_4]^+$) 216.1092, found 216.1089.

(Chloromethyl)diphenylphosphine[109] was prepared according to the literature.

(Chloromethyl)diphenylphosphine-borane 59k. A solution of KOH (53.5 mmol, 3.00 g, 5.0 equiv) in H_2O (2.5 mL) was mixed with a solution of *n*-Bu_4NCl (1.8 mmol, 500 mg, 0.17 equiv) in CH_2Cl_2 (30 mL) and toluene (5 mL). Diphenylphosphine (10.7 mmol, 2.00 g, 1.0 equiv) dissolved in CH_2Cl_2 (5 mL) was then added under nitrogen to the emulsion, under vigorous stirring, over 2 h. The reaction mixture was stirred for 14 h at rt, washed with H_2O, the organic layer separated and transferred to the round-bottomed flask. $BH_3.Me_2S$ (2.0 M solution in THF, 8.0 mL, 16 mmol, 1.5 equiv) was then added and the reaction mixture was stirred at rt, for 1 h. The solvent was removed in vacuo and the residue diluted with EtOAc then washed with water. The organic layer was dried with $MgSO_4$, and the solvent removed in vacuo. Purification of the crude product by

chromatography on silica gel (EtOAc/hexanes 1:9, v/v) yielded (chloromethyl)diphenylphosphine-borane **59k** (9.6 mmol, 2.38 g, 90 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.70 (m, 10 H), 4.09 (d, J = 7 Hz, 2 H), 0.7 (q, J_{BH} = 100 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.1 (d, J_{PCCC} = 10 Hz, 4 C), 132.3 (d, J_{PCCCC} = 2.5 Hz, 2 C), 129.9 (d, J_{PC} = 55 Hz), 129.3 (d, J_{PCC} = 10 Hz, 4 C), 126.4 (d, J_{PC} = 57 Hz), 37.1 (d, J_{PC} = 32 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.6 (d, J_{PB} = 60 Hz); ^{11}B NMR $CDCl_3$, 28.88 MHz) δ - 39.8 (dd , J_{BP} = 60 Hz, J_{BH} = 100 Hz); HRMS calcd. for $C_{13}H_{17}BClNP$, [M + NH_4^+ - H_2] 264.0880, found 264.0888.

Dimethyl pentylphosphonate (58a-H, Scheme 4.4) .[156] A flame-dried, 25 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with dimethyl (diazomethyl)phosphonate **59a** (2.0 mmol, 300 mg, 1.0 equiv) and dry THF (10 mL). Bu_3B (2.0 mL, 1.0 M solution in diethyl ether, 2.0 mmol, 1.0 equiv) was then added in one portion. An exothermic reaction ensued and nitrogen evolved. The reaction was then stirred at rt for 1 h, and quenched by addition of water. The resulting biphasic mixture was heated at reflux for 2 h. After cooling to rt, the layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and the solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes, 1:1, v/v) yielded dimethyl pentylphosphonate **58a-H** (1.72 mmol, 310 mg, 86 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ3.74 (d, J = 11 Hz, 6 H), 1.31 - 1.80 (m, 8 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 52.5 (d, J_{POC} = 7 Hz), 33.0 (d, J_{PCCC} = 17 Hz), 24.9 (d, J_{PC} = 140 Hz), 22.4, 22.2 (d, J_{PCC} = 5 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.3.

Monodeuterated dimethyl pentylphosphonate (58a-D, Scheme 4.4) . A flame-dried, 25 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with dimethyl (diazomethyl)phosphonate **59b** (2.0 mmol, 300 mg, 1.0 equiv) and dry THF (10 mL). Bu_3B (2.0 mL, 1.0 M solution in diethyl ether, 2.0 mmol, 1.0 equiv) was then added in one portion. An exothermic reaction ensued and nitrogen evolved. The reaction was then stirred at rt for 1 h, then quenched by addition of D_2O (99.9 mol % of D). The resulting biphasic mixture was stirred for 12 h at rt. The layers were separated and the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and the solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded dimethyl pentylphosphonate **58a-D** (1.6 mmol, 290 mg, 80%). Deuterium incorporation 98 %.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (d, J = 11 Hz, 6 H), 1.24 - 1.75 (m, 7 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 52.5 (d, J_{POC} = 7 Hz), 33.0 (d, J_{PCCC} = 17 Hz), 24.9 (dt, J_{PC} = 140 Hz, J_{DC} = 19 Hz), 22.4, 22.1 (d, J_{PCC} = 5 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.4; HRMS (EI^+) calcd. for $C_7H_{17}DO_3P$, ($[M]^+$) 182.1056, found 182.1056.

Diethyl pentylphosphonate (58b-H, Scheme 4.6).[157] The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes, 1:1, v/v) yielded diethyl pentylphosphonate **58b-H** (3.84 mmol, 800 mg, 96 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03 - 4.16 (m, 4 H), 1.25 - 1.77 (m, 8 H), 1.32 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.6 (d, J_{POC} = 6

Hz), 33.0 (d, J_{PCCC} = 17 Hz), 25.5 (d, J_{PC} = 140 Hz), 22.3, 22.2 (d, J_{PCC} = 5 Hz), 16.6 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.8.

Monodeuterated diethyl pentylphosphonat e (58b-D, Scheme 4.6). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). The reaction mixture was quenched by addition of D_2O (99.9 mol % of D) at rt. The resulting biphasic mixture was stirred for 12 h at rt. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl pentylphosphonate **58b-D** (3.56 mmol, 745 mg, 89 %). Deuterium incorporation 95 %.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 - 4.17 (m, 4 H), 1.25 - 1.66 (m, 7 H), 1.35 (t, J = 7 Hz, 6 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.6 (d, J_{POC} = 7 Hz), 32.9 (d, J_{PCCC} = 17 Hz), 25.9 (d, J_{PC} = 140 Hz), 22.4, 22.3 (d, J_{PCC} = 5 Hz), 16.7 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.8; HRMS (EI^+) calcd. for $C_9D_{21}DO_3P$, ($[M]^+$) 210.1369, found 210.1367.

Dibenzyl pentylphosphonate (Table 4.1, entry 1).[158] The title compound was prepared from dibenzyl (chloromethyl)phosphonate **59c** (4.0 mmol, 1.24 g, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded dibenzyl pentylphosphonate (3.40 mmol, 1.13 g, 85 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 - 7.42 (m, 10 H), 4.93 – 5.14 (m, 4 H), 1.20 - 1.79, (m, 8 H), 0.85 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.4 (d, J_{PCC} = 6 Hz, 2 C), 128.6 (4 C), 128.4 (2 C),127.9 (4 C), 67.0 (d, J_{POC} = 7 Hz), 32.6 (d, J_{PCCC} = 15 Hz), 25.9 (d, J_{PC} = 140 Hz), 22.0, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.0.

Diethyl 1-chloropentylphosphonat e (Table 4.1, entry 2). [159] A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl tri(chloromethyl)phosphonate **59d** (4.0 mmol, 1.01 g, 1.0 equiv) and dry THF (20 mL). The solution was cooled below - 100 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllithium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe followed by Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv) in one portion. The reaction mixture was slowly warmed to - 50 ^{o}C and was quenched by addition of water. The resulting biphasic mixture was stirred at reflux for 2 h. The layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 3:7, v/v) yielded diethyl 1-chloropentylphosphonate (2.8 mmol, 678 mg, 70 %), 90 % purity (10 % diethyl 1-butylpentylphosphinate).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19 - 4.30 (m, 4 H), 3.85 (td, J = 11 Hz, J = 3 Hz, 1H), 1.28 - 2.11 (m, 6 H), 1.38 (t, J = 7 Hz, 6 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.7 (d, J_{POC} = 7 Hz), 63.2 (d, J_{POC} = 7 Hz), 52.4 (d, J_{PC} = 160 Hz), 31.8 , 28.6 (d, J_{PCCC} = 12 Hz), 21.9, 16.6 (d, J_{POCC} = 5 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ21.8.

Diethyl 1-butylpentylphosphina te (Table 4.1, entry 3). [160] A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (trichloromethyl)phosphonate **59d** (4.0 mmol, 1.01 g, 1.0 equiv) and dry THF (20 mL). The solution was cooled below - 100 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllithium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe

followed by Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to - 50 ^oC and then was cooled down to - 78 ^oC and *n*-butyllithium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly. After the addition the reaction mixture was quenched with water at rt The resulting biphasic mixture was stirred at reflux for 2 h. After cooling to rt, the layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1 v/v) yielded diethyl 1-butylpentylphosphinate (2.08 mmol, 549 mg, 52 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 4.03 - 4.14 (m, 4 H), 2.10 - 2. 25 (m, 1 H), 1.25 - 1.77 (m, 12 H), 1.30 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.2 (d, J_{POC} = 7 Hz), 35.9 (d, J_{PC} = 138 Hz), 29.8 (d, J_{PCCC} = 9 Hz), 28.0 (d, J_{PCC} = 4 Hz), 22.8, 16.5 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.2.

Diethyl 1-methyl-pentylphosphonate. (Table 4.1, entry 4).[161] The title compound was prepared from diethyl (1-chloroethyl)phosphonate **4e** (4.0 mmol, 800 mg, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 1-methyl-pentylphosphonate (2.52 mmol, 560 mg, 63 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 4.04 - 4.16 (m, 4 H), 1.36 – 1.79 (m, 7 H) 1.26 - 1.34 (t, J = 7 Hz, 6 H), 1.12 -1.20 (dd, J_{HH} = 7 Hz, $J_{HP=}$ 18 Hz, 3 H), 0.88 - 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.6 (t, J_{POC} = 6 Hz), 30.9 (d, J_{PC} = 140 Hz), 29.8 (2 C), 29.7, 29.6, 22.7, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 13.3 (d, J_{PCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.7.

Diethyl 1-phenyl-pentylphosphonate (Table 4.1, entry 5). [162] The title compound was prepared from diethyl 1-chloro-benzylphosphonate **59f** (4.0 mmol, 1.05 g, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 1-phenyl-pentylphosphonate (2.4 mmol, 682 mg, 60 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 - 7.34 (m, 5 H), 3.66 - 4.13 (m, 4 H), 2.98 (ddd, J_{HH} = 4 Hz, J_{HH} = 11 Hz, J_{PH} = 22 Hz, 1 H), 1.90 - 2 .15, (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.14 -1.40 (m, 4 H), 1.09 (t, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.3, 129.2 (d, J_{PCCC} = 7 Hz, 2 C),128.4 (2 C), 127.0, 62.5 (d, J_{POC} = 7 Hz), 61.7 (d, J_{POC} = 7 Hz), 44.6 (d, J_{PC} = 138 Hz), 29.8 (d, J_{PCCC} = 15 Hz), 28.5, 22.3, 16.4 (d, J_{POCC} = 6 Hz), 16.2 (d, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 30.3.

Ethyl (chloromethyl)pentylphosphinate (Table 4.1, entry 6). The title compound was prepared from ethyl [bis(chloromethyl)]phosphinate **59g** (4.0 mmol, 760 mg, 1.0 equiv) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded ethyl (chloromethyl)pentylphosphinate (3.12 mmol, 662 mg, 78 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.03 – 4.26 (m, 2 H), 3.54 (d, J = 8 Hz, 2 H), 1.32 - 1.93 (m, 8 H), 1.30 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.4 (d, J_{POC} = 7 Hz), 34.7 (d, J_{PC} = 91 Hz), 33.0 (d, J_{PCCC} = 15 Hz), 25.6 (d, J_{PC} = 100 Hz), 22.3, 21.1 (d, J_{PCC} = 4 Hz), 16.4 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 50.4. HRMS calcd. for $C_8H_{18}ClO_2P$, 212.0733, found 212.0730.

Diethyl pentylphosphonothioate (Table 4.1, entry 7). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonothioate **59h** (4.0 mmol, 808 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled to - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe. After the reaction mixture had been stirred for 10 min at this temperature, it was cooled to - 90^{o}C (liquid nitrogen/ethanol bath) and Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mL, 1.0 equiv) was added in one portion. The reaction solution was warmed slowly to rt and was quenched by addition of water. The resulting biphasic mixture was stirred at rt for 2 h, the layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 2:98, v/v) yielded diethyl pentylphosphonothioate (3.32 mmol, 774 mg, 83 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.99 - 4.23 (m, 4 H), 1.21 - 2.00 (m, 8 H), 1.30 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 7 Hz), 34.8 (d, J_{PC} = 111 Hz), 32.6 (d, J_{PCCC} = 18 Hz), 22.7 (d, J_{PCC} = 4 Hz), 22.4 (d, J_{PCCCC} = 1 Hz), 16.4 (d, J_{POCC} = 7 Hz), 14.1. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 100.9; HRMS calcd. for $C_9H_{21}O_2PS$, 224.1000, found 224.1000.

Diphenyl pentylphosphine-borane (Table 4.1, entry 8). The title compound was prepared from diphenyl (chloromethyl)phosphine-borane **59k** (2.1 mmol, 521 mg, 1.0 equiv) and Bu_3B (2.1 mL, 1.0 M solution in diethyl ether, 2.1 mmol, 1.0 equiv).

Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:9, v/v) yielded diphenyl pentylphosphine-borane (1.30 mmol, 352 mg, 62 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.70 (m, 10 H), 2.14 - 2.23 (m, 2 H), 1.23 – 1.56 (m, 6 H), 0.85 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 98 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 132.4 (d, J_{PCCC} = 10 Hz, 4 C), 131.3 (2 C), 129.9 (d, J_{PC} = 55 Hz, 2 C), 129.0 (d, J_{PCC} = 10 Hz, 4 C) , 33.5 (d, J_{PCCC} = 14 Hz), 25.8 (d, J_{PC} = 38 Hz) 22.9, 22.3, 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.0 (m); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ – 40.4 (m); HRMS calcd. for $C_{17}H_{28}BNP$, [M + NH_4 – H_2]: 286.1896, found 286.1899.

Diethoxy pentylphosphonite-borane (Scheme 4.10, 58i-H). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (3.2 mmol, 590 mg, 1.0 equiv) and Bu_3B (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy pentylphosphonite-borane (2.94 mmol, 607 mg, 92%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 - 4.16 (m, 4 H), 1.24 – 1.75 (m, 8 H), 1.31 (t, J = 7 Hz, 6 H), 0.91 (t, J = 7 Hz, 3 H), 0.50 (qd, J_{BH} = 94 Hz, J_{PBH} = 15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.2 (d, J_{POC} = 5 Hz), 33.0 (d, J_{PCCC} = 14 Hz), 29.9 (d, J_{PC} = 56 Hz), 22.3, 21.4, 16.7 (d, J_{POCC} = 5 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.0 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.6 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_9H_{28}BNO_2P$, $[M + NH_4]^+$ 224.1951, found 224.1944.

Monodeuterated Diethoxy pentylphosphonite-borane (Scheme 4.10, 58i-D). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **58i** (3.2 mmol, 590 mg, 1.0 equiv) and Bu_3B (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). The reaction mixture was quenched by addition of D_2O. The resulting biphasic

mixture was stirred for 2 h at rt. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy pentylphosphonite-borane (2.94 mmol, 610 mg, 92%). Deuterium incorporation 95 %.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 - 4.16 (m, 4 H), 1.21 - 1.75 (m, 7 H), 1.30 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 92 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.2 (d, J_{POC} = 4 Hz), 33.0 (d, J_{PCCC} = 14 Hz), 29.7 (dt, J_{PC} = 52 Hz, J_{DC} = 19 Hz), 22.3, 21.3, 16.8 (d, J_{POCC} = 5 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.0 (q, J_{PB} = 80 Hz). ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 43.7 (dq , J_{BP} = 80 Hz, J_{BH} = 92 Hz); HRMS calcd. for $C_9H_{27}DBNO_2P$, ($[M + NH_4]^+$) 225.2014, found 225.2010.

Diethoxy 1–methylpen tylphosphonite-borane (Scheme 4.10, 58j-H). The title compound was prepared from diethoxy 1-chloroethylphosphine-borane **59j** (3.2 mmol, 634 mg, 1.0 equiv) and Bu_3B (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy 1–methylpentylphosphonite-borane (2.75 mmol, 606 mg, 86 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 - 4.20 (m, 4H), 1.37 - 1.79 (m, 7 H), 1.31 (t, J = 7 Hz, 6 H), 1.12 (d, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 93 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.3 (d, J_{POC} = 5 Hz), 33.7 (d, J_{PC} = 57 Hz), 29.5 (d, J_{PCCC} = 12 Hz), 28.5 (d, J_{PCC} = 2 Hz) 22.5, 16.6 (d, J_{POCC} = 6 Hz), 13.9, 12.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 151.1 (q, J_{PB} = 79 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 44.1 (dq , J_{BP} = 79 Hz, J_{BH} = 93 Hz).); HRMS calcd. for $C_{10}H_{30}BNO_2P$, ($[M + NH_4]^+$): 238.2107, found 238.2105.

Diethyl cyclohexylmethylphos phonate (Table 4.2, Entry 1). [163] The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and Cy_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl cyclohexylmethylphosphonate (3.32 mmol, 777 mg, 83 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 - 4.18 (m, 4 H), 1.89 (d, J = 13 Hz, 2 H), 1.33 (t, J = 7 Hz, 6 H), 1.26 - 1.89 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.2 (d, J_{POC} = 7 Hz), 34.5 (d, J_{PCCC} = 11 Hz, 2 C), 33.2 (d, J_{PC} = 138 Hz), 32.6 (d, J_{PCC} = 4 Hz), 26.1, 26.0 (d, J_{PCCCC} = 6 Hz, 2 C), 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.0.

Diethyl 2-methyl-butylphospho nate (Table 4.2, Entry 2). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and (*sec*-Bu)$_3$B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 2-methyl-butylphosphonate (3.44 mmol, 716 mg, 86 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06 - 4.14 (m, 4 H), 1.25 - 1.95 (m, 5 H), 1.34 (t, J = 7 Hz, 6 H), 1.05 (d, J = 7 Hz, 3 H) 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.3 (t, J_{POC} = 6 Hz), 30.7 (d, J_{PC} = 139 Hz), 31.2 (d, J_{PCCC} = 14 Hz), 29.7 (d, J_{PCC} = 4 Hz), 20.3 (d, J_{PCCC} = 7 Hz) 16.4 (d, J_{POCC} = 6 Hz), 10.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.3; HRMS (EI$^+$) calcd. for $C_9H_{22}O_3P$, ([M]$^+$) 209.1307, found 209.1308.

Diphenyl propylphosphine-borane (Table 4.2, entry 3). The title compound was prepared from Diphenyl (chloromethyl)phosphine-borane **59k** (2.1 mmol, 521 mg, 1.0 equiv) and Et_3B (2.1 mL, 1.0 M solution in THF, 2.1 mmol, 1.0 equiv). Purification of

the crude product by chromatography on silica gel (EtOAc/hexanes 1:9, v/v) yielded diphenyl propylphosphine-borane (1.78 mmol, 432 mg, 85 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 - 7.70 (m, 10 H), 2.12 - 2.29 (m, 2 H), 1.48 - 1.63 (m, 2 H), 1.00 (t, J = 7 Hz, 3 H), 0.80 (q, J_{BH} = 98 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 132.4 (d, J_{PCCC} = 10 Hz, 4 C), 131.3 (2 C), 129.9 (d, J_{PC} = 55 Hz), 129.0 (d, J_{PCC} = 10 Hz, 4 C), 28.0 (d, J_{PC} = 37 Hz), 17.0, 16.1 (d, J_{PCCC} = 15 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 16.6 (q, J_{PB} = 58 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 39.7 (dq , J_{BP} = 58 Hz, J_{BH} = 98 Hz), HRMS calcd. for $C_{15}H_{22}BNP$, [M + NH_4 – H_2]: 258.1583, found 258.1579.

Diethoxy 2–methylbutylphospho nite-borane (Eq. 4.6). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (3.2 mmol, 590 mg, 1.0 equiv) and (*sec*-Bu)$_3$B (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy 2–methylbutylphosphonite-borane (2.62 mmol, 541 mg, 82 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 - 4.20 (m, 4 H), 1.26 - 1.93 (m, 5 H), 1.30 (t, J = 7 Hz, 6 H), 1.01 (d, J = 7 Hz, 3 H) 0.89 (t, J = 7 Hz, 3 H), 0.50 (qd, J_{BH} = 94 Hz, J_{PBH} = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.1 (d, J_{POC} = 4 Hz), 36.9 (d, J_{PC} = 54 Hz), 31.2 (d, J_{PCCC} = 10 Hz), 29.2, 20.8 (d, J_{PCCC} = 6 Hz), 16.7 (d, J_{POCC} = 6 Hz), 11.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.5 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 43.7 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_9H_{28}BNO_2P$, ([M + NH_4]$^+$) 224.1951, found 224.1952.

Diethoxy octylphosphonite-borane (Eq. 4.7). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (3.2 mmol, 590 mg, 1.0 equiv) and $(heptyl)_3B$ (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy octylphosphonite-borane (2.34 mmol, 580 mg, 73 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 - 4.16 (m, 4H), 1.23 – 1.76 (m, 14 H), 1.31 (t, J = 7 Hz, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.0 (d, J_{POC} = 4 Hz), 31.8, 33.0 (d, J_{PCCC} = 15 Hz), 30.3 (d, J_{PC} = 56 Hz), 29.1 (2 C), 22.6, 21.6, 16.7 (d, J_{POCC} = 5 Hz); 14.1. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.1 (q, $J_{PB=}$ 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.6 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_{12}H_{34}BNO_2P$, ($[M + NH_4]^+$) 266.2420, found 266.2413.

General Procedure for the Conversion of Phosphinite-Boranes in to *H*-Phosphinate Esters.

To a 0.2 M solution of phosphinite-borane in dry CH_2Cl_2 at 0 °C, was added tetrafluoroboric acid diethyl ether complex (3.0 equiv). An exothermic reaction ensued and gas evolved. The reaction was then warmed to rt and stirred for additional 6 h. Subsequently, the mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate solution was slowly added. The resulting biphasic mixture was stirred vigorously for 5 – 10 min and poured into separatory funnel. The organic layer was separated and aqueous layer was extracted with EtOAc (3 X). The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo to give *H*-phosphinate.

Ethyl octyl-*H*-phosphinate (Table 4.3, Entry 1).[20,22] The title compound was prepared from diethoxy octylphosphinite-borane (1.6 mmol, 400 mg, 1.0 equiv) and

tetrafluoroboric acid diethyl ether complex (4.8 mmol, 777 mg, 653 μl, 3.0 equiv) in 96 % yield (1.54 mmol, 317 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 527 Hz, 1 H), 4.03 - 4.23 (m, 2 H), 1.27 - 1.80 (m, 14 H), 1.36 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 7 Hz), 31.8, 30.4 (d, J_{PCCC} = 15 Hz), 29.1, 29.0, 28.6 (d, J_{PC} = 93 Hz), 22.6, 20.7, 16.2 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.7 (dm, J = 530 Hz).

Ethyl nonyl-*H*-phosphinate (Table 4.3, Entry 2). The title compound was prepared from diethoxy octylphosphinite-borane (1.6 mmol, 420 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (4.8 mmol, 777 mg, 653 μl, 3.0 equiv) in 94 % yield (1.50 mmol, 330 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 527 Hz, 1 H), 4.00 - 4.27 (m, 2 H), 1.27 - 1.80 (m, 16 H), 1.36 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 7 Hz), 32.0, 30.4 (d, J_{PCCC} = 16 Hz), 29.9, 29.4, 29.3, 28.9 (d, J_{PC} = 91 Hz), 22.9, 20.9, 16.5 (d, J_{POCC} = 6 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.3 (dm, J = 526 Hz).

Ethyl pentyl-*H*-phosphinate (Table 4.3, Entry 3). The title compound was prepared from diethoxy pentylphosphinite-borane (1.6 mmol, 330 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (4.8 mmol, 777 mg, 653 mL,3.0 equiv) in 96 % yield (1.54 mmol, 253 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.09 (d, J = 526 Hz, 1H), 4.01 - 4.26 (m, 2H), 1.26 - 1.83 (m, 8H), 1.37 (t, J = 7 Hz, 3H), 0.91 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.4 (d, J_{POC} = 7 Hz), 32.5 (d, J_{PCCC} = 16 Hz), 28.1 (d, J_{PC} = 94 Hz), 22.2, 20.3 (d, J_{PCCC}

= 3 Hz), 16.3 (d, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.3 (dm, J = 527 Hz); HRMS (EI^+) calcd for $C_7H_{18}O_2P$ ($[M]^+$): 165.1044, found: 165.1043.

Ethyl pentyl-*H*-phosphinate (Table 4.3, Entry 4). The title compound was prepared from diethoxy pentylphosphinite-borane (1.0 mmol, 207 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (1.0 mmol, 486 mg, 408 µl, 3.0 equiv) in 95 % yield (0.95 mmol, 157 mg), 95 % of deuterated compound.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 524 Hz, 1 H), 4.01 - 4.26 (m, 2 H), 1.26 - 1.83 (m, 7 H), 1.38 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.4(d, J_{POC} = 5 Hz), 32.6 (d, J_{PCCC} = 16 Hz), 28.3 (dt, J_{PC} = 94 Hz, J_{DC} = 19 Hz), 22.2, 20.4, 16.3 (d, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.3 (dm, J = 527 Hz); HRMS (EI^+) calcd. for $C_7H_{17}DO_2P$ ($[M]^+$) 166.1107, found 166.1109.

Ethyl 2-methylbutyl-*H*-phosphinate (Table 4.3, Entry 5). The title compound was prepared from diethoxy 2-methylbutylphosphinite-borane (1.6 mmol, 330 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (4.8 mmol, 777 mg, 653 µl, 3.0 equiv) in 96 % yield (1.54 mmol, 253 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, J = 527 Hz, 1 H), 4.01 - 4.27 (m, 2 H), 1.25 - 1.96 (m, 5 H), 1.38 (t, J = 7 Hz, 3 H), 1.10 (d, J = 15 Hz, 3 H) 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 4 Hz), 35.6 (d, J_{PC} = 93 Hz), 30.9 (d J_{PCCC} = 13 Hz), 29.0, 20.5 (d, J_{PCC} = 7 Hz), 16.4 (d, J_{POC} = 6 Hz), 11.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.5, 39.2 (dm, J = 527 Hz). HRMS (EI^+) calcd. for $C_7H_{18}O_2P$, ($[M]^+$) 165.1044, found 165.1043.

Ethyl 2-phenylethyl-*H*-phosphinate (Table 4.3, Entry 6). The title compound was prepared from diethoxy 2 - phenylethylphosphinite-borane (1.2 mmol, 288 mg, 1.0

equiv.) and tetrafluoroboric acid diethyl ether complex (3.6 mmol, 583 mg, 490 μl, 3.0 equiv.) in 98 % yield (1.18 mmol, 233 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 - 7.31 (m, 5 H), 7.11 (d, J = 532 Hz, 1 H), 4.02 - 4.26 (m, 2 H), 2.87 – 2.98 (m, 2 H), 2.05 – 2.16 (m, 2 H), 1.38 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 140.1 (d, J_{PCCC} = 15 Hz), 128.7 (2 C), 128.1 (2 C), 126.5, 62.6 (d, J_{POC} = 6 Hz), 31.3 (d, J_{PC} = 93 Hz), 26.9, 16.2 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.2 (d, J = 534 Hz), HRMS calcd. for $C_{10}H_{15}O_2P$, 198.0810, found 198.0810.

Ethyl 1-octylnonyl- *H*-phosphinate (Table 4.3, Entry 7). The title compound was prepared from diethoxy octylphosphinite-borane (1.0 mmol, 360 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (3.0 mmol, 486 mg, 408 μl, 3.0 equiv) in 93 % yield (0.93 mmol, 296 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 519 Hz, 1 H), 4.00 - 4.26 (m, 2 H), 1.27 - 1.69 (m, 27 H), 1.36 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 7 Hz), 28.6 (d, J_{PC} = 93 Hz), 31.9, 31.8, 29.7, 29.6, 29.4, 29.3, 29.1, 27.5 (d, J_{PCCC} = 9 Hz), 27.4 (d, J_{PCC} = 9 Hz), 27.0, 26.9, 22.7, 22.6, 16.3 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 45.3 (dm, J = 520 Hz).

Ethyl 1-chlorooctyl- *H*-phosphinate (Table 4.3, Entry 8). The title compound was prepared from diethoxy octylphosphinite-borane (1.2 mmol, 340 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (3.6 mmol, 583 mg, 490 μl, 3.0 equiv.) in 92 % yield (1.10 mmol, 265 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 572 Hz, 1 H), 4.11 - 4.33 (m, 2 H), 3.77 – 3.91 (m, 1 H), 1.27 - 1.80 (m, 13 H), 1.42 (t, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C

NMR ($CDCl_3$, 75.45 MHz) δ 64.2 (d, J_{POC} = 7 Hz), 63.9 (d, J_{POC} = 7 Hz), 53.8 (d, J_{PC} = 103 Hz), 53.5 (d, J_{PC} = 102 Hz), 32.0, 30.8, 30.4 (d, J_{PCCC} = 7 Hz), 29.0, 26.4, 22.9, 16.5 (d, J_{POCC} = 6 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.2 (dm, J = 573 Hz) and 34.8 (dm, J = 575 Hz).

Ethyl allyl-octylphosphinate (Scheme 4.11). Method A. A flame-dried, 50 mL, three-necked, round-bottomed flask charged with diethoxy octylphosphinite-borane (1.6 mmol, 400 mg, 1.0 equiv) *N*-methylpiperazine (12.8 mmol, 1.28 g, 1.4 mL, 8.0 equiv) and dry toluene (10 mL). The solution was heated at reflux for 24 h. After cooling to rt, the mixture was concentrated in high vacuo to remove access of *N*-methylpiperazine. The residue was diluted with dry toluene (20 mL) and allyl bromide (3.2 mmol, 387 mg, 270 μl, 2.0 equiv) was added. The reaction mixture was heated under reflux for 3 h. After cooling to rt, the mixture was washed with H_2O, the aqueous phase was extracted with EtOAc (3 X) and the combined organic fractions were dried with $MgSO_4$, concentrated in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc) yielded ethyl allyl-octylphosphinate **9** (0.94 mmol, 231 mg, 59 %).

Method B. A flame-dried, seal tube was purged with nitrogen, charged with diethoxy octylphosphonite-borane (1.6 mmol, 400 mg, 1.0 equiv) and diethylamine (40 mL). The solution was heated at 55^{o}C for 3 days. After cooling to rt, the mixture was concentrated in high vacuo. The residue was diluted with dry toluene (20 mL) and transferred *via* cannula under nitrogen to the flame-dried, 50 mL, three-necked, round-bottomed flask. Allyl bromide (8.0 mmol, 968 mg, 678 μl, 5.0 equiv) was than added and the mixture was heated under reflux for 3 h. After cooling to rt, the reaction mixture was washed with H_2O, the aqueous phase was extracted with EtOAc (3 X) and the combined organic

fractions were dried with $MgSO_4$, concentrated in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc) yielded ethyl allyl-octylphosphinate **9** (1.04 mmol, 256 mg, 65 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 - 5.90 (m, 1 H), 5.16 - 5.25 (m, 2 H), 4.02 - 4.15 (m, 2 H), 2.57 (dd, J = 8 Hz, J = 10 Hz, 2 H), 1.27 - 1.77 (m, 14 H), 1.32 (t, J = 7 Hz, 6 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 128.3 (d, J_{PCC} = 9 Hz), 120.0 (d, J_{PCCC} = 12 Hz), 60.5 (d, J_{POC} = 7 Hz), 34.6 (d, J_{PC} = 85 Hz), 32.0, 31.0 (d, J_{PCCC} = 15 Hz), 29.2, 27.6 (d, J_{PC} = 93 Hz), 22.8, 21.8 (d, J_{PCC} = 4 Hz), 16.8 (d, J_{POCC} = 6 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 54.9; HRMS calcd. for $C_{13}H_{27}O_2P$; 246.1749, found 246.1750.

Chapter IV: Section 4.2.2. Selective Migration.[142]

Diethyl (2-phenylethyl)phosphonate (Table 4.4, entry 1). [164] The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and B-benzyl-9-BBN (8.0 mL, 0.5 M solution in THF, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl (2-phenylethyl)phosphonate (2.76 mmol, 668 mg, 69 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 - 7.33 (m, 5 H), 4.05 - 4.16 (m, 4 H), 2.88 – 2.97 (m, 2 H), 2.60 (t, J = 17 Hz, 1 H), 2.06 (t, , J = 17 Hz, 1 H), 1.33 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 141.1 (d, J_{PCCC} = 17 Hz), 128.8 (2 C), 128.3 (2 C), 126.6, 61.8 (d, J_{POC} = 7 Hz), 28.3 (d, J_{PCC} = 6 Hz), 27.8 (d, J_{PC} = 139 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 31.9.

Diethyl (1,2-diphenyl)ethylphosphonate (Table 4.4, entry 2). [165] The title compound was prepared from diethyl chloro-phenyl-methylphosphonate **59f** (4.0 mmol, 1.05 g, 1.0 equiv) and B-benzyl-9-BBN (8.0 mL, 1.0 M solution in THF, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl (1,2-diphenyl)ethylphosphonate (2.36 mmol, 751 mg, 59 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 – 7.34 (m, 10 H), 3.65 - 4.12 (m, 4 H), 3.13 – 3.50 (m, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.09 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.3 (d, J_{PCCC} = 16 Hz), 135.7 (d, J_{PCC} = 6 Hz),129.7 (d, J_{PCCC} = 7 Hz, 2 C),128.8 (2 C), 128.6 (2 C), 128.4 (2 C), 127.4, 126.4, 63.0 (d, J_{POC} = 7 Hz), 62.1 (d, J_{POC} = 7 Hz), 46.8 (d, J_{PC} = 136 Hz), 36.5, 16.6 (d, J_{POCC} = 6 Hz), 16.4 (d, J_{POCC} = 6 Hz). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 29.3.

Diethyl nonylphosphonate (Table 4.4, entry 3). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and 9-octyl-BBN (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1 : 1, v/v) Diethyl nonylphosphonate (2.00 mmol, 529 mg, 50 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 - 4.18 (m, 4 H), 1.23 - 1.76 (m, 16 H), 1.30 (t, J = 7 Hz, 6 H), 0.89 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.2 (d, J_{POC} = 5 Hz) 32.1, 30.9 (d, J_{PCCC} = 14 Hz), 30.4, 30.1 (d, J_{PC} = 38 Hz), 29.6, 29.5, 29.3, 22.9, 21.8, 16.8 (d, J_{POCC} = 6 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.0 (q, J_{PB} = 81 Hz); ^{11}B ($CDCl_3$, 28.88 MHz) δ - 43.6 (dq, J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_{13}H_{36}BNO_2P$, ($[M + NH_4]^+$) 280.2577, found 280.2571.

Diethoxy 2-phenylethylphosphonite-borane (Table 4.4, Entry 4). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **4i** (3.2 mmol, 590 mg, 1.0 equiv) and B–benzyl-9-BBN (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5 : 99.5, v/v) yielded diethoxy 2-phenylethylphosphonite-borane (2.27 mmol, 545 mg, 71 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 - 7.34 (m, 5 H), 3.96 - 4.23 (m, 4 H), 2.84 - 2.92 (m, 2 H), 2.02 – 2.12 (m, 2 H), 1.30 (t, J = 7 Hz, 6 H), 0.50 (q, J_{BH} = 92 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 141.2 (d, J = 14 Hz), 128.6 (2 C), 128.3 (2 C), 126.6, 63.4 (d, J_{POC} = 5 Hz), 31.9 (d, J_{PC} = 54 Hz), 28.0, 16.8 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 147.6 (q, J_{PB} = 80 Hz); ^{11}B $CDCl_3$, 28.88 MHz) δ –43.7 (dq, J_{BP} = 80 Hz, J_{BH} = 92 Hz); HRMS calcd. for $C_{12}H_{26}BNO_2P$, ($[M + NH_4]^+$): 258.1794, found 258.1796.

Diethoxy nonylphosphonite-boran e (Table 4.4, entry 5). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (3.2 mmol, 590 mg, 1.0 equiv) and 9-octyl-BBN (3.2 mL, 1.0 M solution in diethyl ether, 3.2 mmol, 1.0 equiv). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 0.5:99.5, v/v) yielded diethoxy nonylphosphonite-borane (1.98 mmol, 520 mg, 62 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97 - 4.18 (m, 4 H), 1.23 - 1.77 (m, 16 H), 1.31 (t, J = 7 Hz, 6 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.2 (d, J_{POC} = 6 Hz) 32.1, 31.9 (d, J_{PCCC} = 17 Hz), 30.4, 25.8 (d, J_{PC} = 140 Hz), 29.6, 29.3, 22.9, 21.8, 16.8 (d, J_{POCC} = 6 Hz), 14.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.9

Diethyl (cyclooctylmethyl)phosphonate (Table 4.4, Entry 6 and 7). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and Alpine-borane (8.0 mL, 0.5 M solution in THF, 4.0 mmol, 1.0 equiv, Entry 6) or 9-Cy-BBN (4.0 mL, 1.0 M solution in THF, 4.0 mmol, 1.0 equiv, Entry 7). Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl (cyclooctylmethyl)phosphonate (3.32 mmol, 870 mg, 83 % and 3.00 mmol, 789 mg, 75 % respectively).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 – 4.18 (m, 4 H), 1.31 (t, J = 6 Hz, 6 H), 1.25– 2.05 (m, 17 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.2 (d, J_{POC} = 6 Hz), 33.5 (d, J_{PC} = 138 Hz), 33.0 (d, J_{PCCC} = 11 Hz, 2 C), 32.5, 27.3 (2 C), 26.0, 24.9 (2 C), 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.3. HRMS calcd. for $C_{13}H_{27}O_3P$, 262.1700, found 262.1698.

Chapter IV: Section 4.3.1.[166]

General Procedure for the Reaction of Halomethylphosphorus Anions with Trialkylborane and BH_3•Me_2S

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b**, **59e**, **59f**, **59h**, or **59i** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by trialkylborane (2.50 mmol, 1.0 M in THF or Et_2O, 2.5 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0

mL, 1.0 equiv) was added slowly followed by chlorophosphine (3.75 mmol, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, BH_3•Me_2S (3.80 mmol, 2.0 M in THF, 1.90 mL, 1.5 equiv) was added and stirring was continued for 15 min. The solvent was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl 1-(diethoxyphosphanyl-borane)pentylphosphonate 66 (Scheme 4.16). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in THF, 2.5 mL, 1.0 equiv), and diethyl chlorophosphite (3.75 mmol, 587 mg, 540 μl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) yielded **66** (684 mg, 2.00 mmol, 80 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03 – 4.22 (m, 8 H), 2.12 – 2.29 (tt, J_{HP} = 20 Hz, J_{HH} = 6 Hz, 1H), 2.18 – 1.78 (m, 2 H), 1.62 – 1.41 (m, 4 H), 1.34 (t, J = 7 Hz, 6 H), 1.32 (t, J = 7 Hz, 6 H), 0.91 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.2 (d, J_{POC} = 4 Hz), 64.4 (d, J_{POC} = 4 Hz), 62.6 (t, J_{POC} = 6 Hz), 40.0 (dd, $J_{P(O)C}$ = 134 Hz, $J_{P(BH3)C}$ = 42 Hz), 31.5 (t, J_{PCCC} = 5 Hz), 24.5 (d, J_{PCC} = 5 Hz), 22.5, 16.5 (d, J_{POCC} = 5 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 145.7 & 24.9 (d, J_{PP} = 7 Hz).

Diethyl 1-(diethoxyphosphanyl-borane)propylphosphonate (Table 4.5, entry 1). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv), Et_3B (2.50 mmol, 1.0 M solution in THF, 2.5 mL, 1.0 equiv), and

diethyl chlorophosphite (3.75 mmol, 540 μl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexane 4:6, v/v) yielded diethyl 1-(diethoxyphosphanyl-borane)propylphosphonate (722 mg, 2.30 mmol, 92 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04 – 4.22 (m, 8 H), 2.08 – 2.24 (tt, J_{HP} = 20 Hz, J_{HH} = 6 Hz, 1H), 1.87 – 2.02 (m, 2 H), 1.35 (t, J = 6 Hz, 6 H), 1.33 (t, J = 6 Hz, 6 H), 1.15 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.2 (d, J_{POC} = 4 Hz), 63.7 (d, J_{POC} = 4 Hz), 62.3 (t, J_{POC} = 6 Hz), 42.5 (dd, $J_{P(O)C}$ = 134 Hz, $J_{P(BH3)C}$ = 42 Hz), 18.4 (d, J_{PCC} = 4 Hz), 16.5 (d, J_{POCC} = 5 Hz), 16.3 (d, J_{POCC} = 5 Hz), 14.4 (dd, J_{PCCC} = 6 Hz, J_{PCCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 145.5 & 24.7 (d, J_{PP} = 7 Hz); HRMS (EI^+) calcd. for $C_{11}H_{28}BO_5P_2$ ($[M]^+$) 313.1505, found 313.1500.

Diethyl 1-(diphenylphosphanyl-borane)propylphosphonate (Table 4.5, en try 2). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv), Et_3B (2.50 mmol, 1.0 M solution in THF, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 693 μl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)propylphosphonate (586 mg, 1.55 mmol, 62 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 – 7.98 (m, 2 H), 7.76 – 7.82 (m, 2 H), 7.39 – 7.21 (m, 6 H), 3.75 – 4.03 (m, 4 H), 2.72 – 2.89 (m, 1H), 1.62 – 2.01 (m, 2 H), 1.13 (t, J = 7 Hz, 3 H), 1.08 (t, J = 7 Hz, 3 H), 1.07 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.5 (d, J_{PCCC} = 10 Hz, 2 C,), 132.8 (d, J_{PCCC} = 10 Hz, 2 C), 131.4 (d, J_{PCCCC} = 2 Hz), 131.3 (d, J_{PCCCC} = 2 Hz), 128.8 (d, J_{PCC} = 10 Hz, 2 C), 128.7 (d, J_{PC} = 28 Hz, 2 C), 128.5 (d, J_{PCC} = 10 Hz, 2 C), 62.2 (d, J_{POC} = 6 Hz), 62.3 (d, J_{POC} = 6 Hz), 36.1 (dd, $J_{P(O)C}$ = 138 Hz, $J_{P(BH3)C}$ = 24 Hz), 20.4 (d, J_{PCC} = 3 Hz), 16.1 (d, J_{POCC} = 6

Hz), 16.0 (d, J_{POCC} = 6 Hz), 15.2 (dd, J_{PCCC} = 7 Hz, J_{PCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.9 & 23.3; HRMS (EI$^+$) calcd. for $C_{19}H_{28}BO_3P_2$ ([M]$^+$) 377.1607, found 377.1603.

Diethyl 1-(diphenylphosphanyl-borane)pentylphosphonate (Table 4.5, entry 3). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 673 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)pentylphosphonate (904 mg, 2.22 mmol, 89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 – 7.99 (m, 2 H), 7.76 – 7.82 (m, 2 H), 7.42 – 7.49 (m, 6 H), 3.75 – 4.00 (m, 4 H), 2.78 – 2.94 (m, 1H), 1.56 – 2.01 (m, 6 H), 1.12 (t, J = 7 Hz, 3 H), 1.08 (t, J = 7 Hz, 3 H), 0.78 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.3 (d, J_{PCCC} = 10 Hz, 2 C), 132.7 (d, J_{PCCC} = 10 Hz, 2 C), 131.2 (d, J_{PCCCC} = 2.0 Hz), 131.1 (d, J_{PCCCC} = 2.0 Hz), 128.6 (d, J_{PCC} = 4 Hz, 2 C), 128.5 (d, J_{PCCC} = 10 Hz, 2 C), 128.5 (d, J_{PCCC} = 10 Hz, 2 C), 62.4 (d, J_{POC} = 6 Hz), 62.3 (d, J_{POC} = 6 Hz), 34.3 (dd, $J_{P(O)C}$ = 138 Hz, $J_{P(BH3)C}$ = 24 Hz), 32.1 (dd, J_{PCCC} = 7 Hz, J_{PCCC} = 3 Hz) 26.0 (d, J_{PCC} = 3 Hz), 22.3, 16.1 (d, J_{POCC} = 6 Hz), 13.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.8 & 26.0; HRMS (EI$^+$) calcd. for $C_{21}H_{32}BO_5P_2$ ([M]$^+$) 405.1920, found 405.1922.

Diethyl 1-(diphenylphosphanyl- borane)-2-methyl-butylphosphonate (Table 4.5, entry 4). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv), (*sec*-Bu)$_3$B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 673 µl, 1.5 equiv). Purification of

the crude product by flash chromatography on silica gel (EtOAc/hexanes 1:1, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)-2-methyl-butylphosphonate (700 mg, 1.72 mmol, 69 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 – 7.98 (m, 10 H), 3.64 – 4.12 (m, 4 H), 3.05 (m, 1H), 1.37– 2.05 (m, 3 H), 1.13 (t, J = 7 Hz, 6 H), 0.99 (t, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.1 (d, J_{PCC} = 9 Hz, 2 C), 132.6 (d, J_{PCC} = 9 Hz, 2 C), 131.2 (2 C), 128.6 (d, J_{PCCC} = 10 Hz, 2 C), 128.5 (d, J_{PC} = 38 Hz, 2 C), 128.0 (d, J_{PCCC} = 10 Hz, 2 C), 61.9 (d, J_{POC} = 7 Hz), 61.2 (d, J_{POC} = 7 Hz), 40.3 (dd, $J_{P(O)C}$ = 137 Hz, $J_{P(BH3)C}$ = 20 Hz), 39.0 (dd, $J_{P(O)C}$ = 137 Hz, $J_{P(BH3)C}$ = 20 Hz), 34.6, 31.9 (d, J_{PCCC} = 10 Hz), 20.4 (t, J_{PCC} = 3 Hz), 16.9 (d, J_{PCCC} = 7 Hz), Hz), 16.1 (d, J_{POCC} = 6 Hz), 15.9 (d, J_{POCC} = 6 Hz), 12.7, 12.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.1, 25.0 & 21.9; HRMS (EI$^+$) calcd. for $C_{21}H_{32}BO_5P_2$ ([M]$^+$) 405.1920, found 405.1925.

Diethyl 1-(diphenylphosphanyl-borane)-1 -methyl-pentylphosphonate (Table 4.5, entry 6). The title compound was prepared from diethyl (1-chloroethyl)phosphonate **59e** (2.50 mmol, 500 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 673 μl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexane 1:1, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)-1-methyl-pentylphosphonate (798 mg, 1.90 mmol, 76 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (t, J = 10 Hz, 2 H), 8.09 (t, J = 10 Hz, 2H), 7.37 – 7.50 (m, 6 H), 3.44 – 4.16 (m, 4 H), 1.23 – 1.97 (m, 6 H), 1.46 (dd, J = 16 Hz, 3 H), 1.08 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 0.73 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H);

^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.6 (d, J_{PCC} = 9 Hz, 2 C), 135.1 (d, J_{PCC} = 9 Hz, 2 C), 131.4, 131.1, 126.5 (d, J_{PC} = 54 Hz, 2 C), 128.3 (d, J_{PCCC} = 10 Hz, 2 C), 128.1 (d, J_{PCCC} = 10 Hz, 2 C), 126.5 (d, J_{PC} = 54 Hz, 2 C), 62.5 (d, J_{POC} = 7 Hz), 62.0 (d, J_{POC} = 7 Hz), 39.5 (dd, $J_{P(O)C}$ = 118 Hz, $J_{P(BH3)C}$ = 20 Hz), 34.2, 26.5, 23.3, 18.6, 16.4 (t, J_{POCC} = 6 Hz), 16.2 (t, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 29.8 (d, J_{PP} = 14 Hz) & 23.2 (m); HRMS (EI^+) calcd. for $C_{22}H_{34}BO_3P_2$ ($[M]^+$) 419.2076, found 419.2082.

Diethyl 1-(diethoxyph osphanyl-borane)-1-phenyl-pentylphosphonate (Table 4.5, entry 7). The title compound was prepared from diethyl 1-chloro-benzylphosphonate **59f** (2.50 mmol, 655 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and diethyl chlorophosphite (3.75 mmol, 540 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) yielded diethyl 1-(diethoxyphosphanyl-borane)-1-phenyl-pentylphosphonate (565 mg, 1.35 mmol, 54 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 – 7.64 (m, 5 H), 4.03 – 4.22 (m, 4 H), 3.72 – 4.00 (m, 4 H), 2.33 – 2.54 (m, 2 H), 1.34 – 1.50 (m, 4 H), 1.30 (t, J = 7 Hz, 6 H), 1.15 (t, J = 7 Hz, 6 H), 0.94 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 131.3, 130.8 (2 C), 127.7 (2 C), 127.4, 65.3 (d, J_{POC} = 3 Hz), 64.7 (d, J_{POC} = 3 Hz), 63.2 (d, J_{POC} = 7 Hz), 62.5 (d, J_{POC} = 7 Hz), 55.1 (dd, $J_{P(O)C}$ = 133 Hz, $J_{P(BH3)C}$ = 36 Hz), 29.2, 26.6 (dd, J_{PCCC} = 10 Hz), 23.7, 16.4, 14.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.2 (d, J_{PP} = 4 Hz) & 144.9; HRMS (EI^+) calcd. for $C_{19}H_{36}BO_5P_2$ ($[M]^+$) 417.2131, found 417.2138.

Diethyl 1-(diethoxyphosphanyl-borane)pentylphosphonothioate (Table 4.6, entry 1). The title compound was prepared from diethyl (chloromethyl)phosphonothioate **59h**

(2.50 mmol, 505 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and diethyl chlorophosphite (3.75 mmol, 540 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 1:9, v/v) yielded diethyl 1-(diethoxyphosphanyl-borane)pentylphosphonothioate (618 mg, 1.72 mmol, 69 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97– 4.22 (m, 8 H), 2.27 – 2.41 (m, 1H), 1.37 – 2.05 (m, 6 H), 1.34 (t, J = 7 Hz, 12 H), 0.91 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.9 (d, J_{POC} = 7 Hz), 62.9 (d, J_{POC} = 7 Hz), 46.5 (dd, $J_{P(O)C}$ = 102 Hz, $J_{P(BH3)C}$ = 41 Hz), 32.0 (d, J_{PCCC} = 5 Hz), 24.9, 22.5, 16.5, 16.2, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 145.7 & 92.9 (d, J_{PP} = 10 Hz).); HRMS (EI^+) calcd. for $C_{13}H_{32}BO_4P_2S$ ($[M]^+$) 357.1590, found 357.1591.

Diethyl 1-(diphenylphosphanyl-borane)pentylphosphonothioate (Table 4.6, entry 2). The title compound was prepared from diethyl (chloromethyl)phosphonothioate **59h** (2.50 mmol, 505 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 673 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 2:8, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)pentylphosphonothioate (939 mg, 2.22 mmol, 89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 – 7.95 (m, 2 H), 7.74 – 7.88 (m, 2 H), 7.39 – 7.48 (m, 6 H), 3.74 – 4.06 (m, 4 H), 3.09 (tt, J_{HP} = 13 Hz, J_{HH} = 3.7 Hz, 1H), 1.00 – 2.13 (m, 6 H), 1.08 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 0.73 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.5 (d, J_{PCC} = 9 Hz, 2 C), 132.6 (d, J_{PCC} = 9 Hz, 2 C), 131.1 (2 C), 129.4 (d, J_{PC} = 54 Hz, 2 C), 128.5 (d, J_{PCCC} = 10 Hz, 2 C), 128.2

(d, J_{PCCC} = 10 Hz, 2 C), 63.1 (d, J_{POC} = 7 Hz), 62.3 (d, J_{POC} = 7 Hz), 40.1 (dd, $J_{P(O)C}$ = 107 Hz, $J_{P(BH3)C}$ = 21 Hz), 32.2 (dd, J_{PCCC} = 6 Hz), 26.4, 22.2, 15.7 (d, J_{POCC} = 4 Hz), 15.6 (d, J_{POCC} = 4 Hz), 13.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.2 & 93.6 (d, J_{PP} = 20 Hz).); HRMS (EI^+) calcd. for $C_{21}H_{32}BO_5P_2S$ ($[M]^+$) 421.1691, found 421.1689.

Diethyl 1-(diphenylphosphanyl-borane)-2-methyl-butylphosphonothioate (Table 4.6, entry 3). The title compound was prepared from diethyl (chloromethyl)phosphonothioate **59h** (2.50 mmol, 505 mg, 1.0 equiv), (*sec*-Bu)$_3$B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and chlorodiphenylphosphine (3.75 mmol, 673 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 2:8, v/v) yielded diethyl 1-(diphenylphosphanyl-borane)-2-methyl-butylphosphonothioate (654 mg, 1.55 mmol, 62 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 – 7.94 (m, 10 H), 3.67 – 4.03 (m, 4 H), 3.25 – 3.40 (m, 1H), 1.47– 2.06 (m, 3 H), 1.28 (t, J = 7 Hz, 6 H), 1.20 (t, J = 7 Hz, 3 H), 0.92 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.9 (d, J_{PCC} = 10 Hz, 2 C), 132.6 (d, J_{PCC} = 10 Hz, 2 C), 131.0 (2 C), 129.3 (d, J_{PC} = 50 Hz, 2 C), 128.6 (d, J_{PCCC} = 10 Hz, 2 C), 127.9 (d, J_{PCCC} = 10 Hz, 2 C), 62.4 (d, J_{POC} = 7 Hz), 62.6 (d, J_{POC} = 7 Hz), 45.8 (dd, $J_{P(S)C}$ = 108 Hz, $J_{P(BH3)C}$ = 15 Hz), 45.1 (dd, $J_{P(S)C}$ = 108 Hz, $J_{P(BH3)C}$ = 15 Hz), 35.8, 35.4, 30.6 (d, J_{PCCC} = 9 Hz), 26.2 (d, J_{PCC} = 9 Hz), 19.5 (d, J_{PCCC} = 9 Hz) 16.7 (d, J_{PCCC} = 8 Hz), 15.9 (d, J_{POCC} = 7 Hz), 15.6 (d, J_{POCC} = 7 Hz), 12.7, 12.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.2 & 90.6, 89.5; HRMS (EI^+) calcd. for $C_{21}H_{32}BO_5P_2S$ ($[M]^+$) 421.1691, found 421.1700.

Tetraethyl pentyl-1,1-bisphosphonite-diborane (Table 4.6, entry 4). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (2.50 mmol,

461 mg, 1.0 equiv), Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv), and diethyl chlorophosphite (3.75 mmol, 540 µl, 1.5 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 5:95, v/v) yielded tetraethyl pentyl-1,1-bisphosphonite-diborane (697 mg, 2.05 mmol, 82 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.01 – 4.18 (m, 8 H), 2.15 (tt, J_{HP} = 14 Hz, J_{HH} = 5 Hz, 1H), 1.80 – 1.95 (m, 2 H), 1.26 – 1.59 (m, 4 H), 1.32 (t, J = 7 Hz, 12 H), 0.91 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.3 (d, J_{POC} = 3 Hz), 64.0 (d, J_{POC} = 3 Hz), 43.2 (t, J_{PCP} = 43 Hz), 32.3 (dd, J_{PCCC} = 5 Hz), 23.4, 22.5, 16.6 (d, J_{POCC} = 6 Hz), 13.9 (d, J = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 146.5 (q, J_{PB} = 67 Hz); HRMS calcd. for $C_{13}H_{40}B_2NO_4P_2$, ($[M + NH_4]^+$) 358.2619, found 358.2625.

1,1–bis(Diphenylphosphino-borane)pentane (Table 4.6, entry 6) . A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with (chloromethyl)diphenylphosphine-borane **59k** (2.80 mmol 695 mg, 1.0 equiv) and dry THF (10 mL). The solution was cooled below – 90 ^{o}C (liquid nitrogen/ethanol bath) and *sec*-butyllitium (2.80 mmol, 1.4 M solution in cyclohexane, 2.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (2.80 mmol, 1.0 M in Et_2O, 2.8 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 78 ^{o}C (dry ice/acetone bath) and *n*-butyllithium (2.80 mmol, 2.5 M solution in hexane, 1.12 mL, 1.0 equiv) was added slowly followed by diphenylchlorophosphine (4.20 mmol, 753 µl, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, BH_3•Me_2S (4.20 mmol, 2.0 M in THF, 2.1 mL, 1.5 equiv) was added and stirring was continued for 15 min. The solvent was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with

EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. The residue was recrystallized from EtOAc/hexanes to give 1,1–bis(diphenylphosphino-borane)pentane as a white solid (2.16 mmol, 1.01 g, 77 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 – 7.83 (m, 20 H), 3.41 – 3.54 (m, 1H), 1.87 – 1.94 (m, 2 H), 0.83 – 1.80 (m, 4 H), 0.50 – 1.50 (m, 6 H), 0.45 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.6 (dd, J_{PCCC} = 10 Hz), 131.5 (d, J_{PCCCC} = 7 Hz), 128.6 (d, J_{PCCC} = 10 Hz), 133.6 (d, J_{PCCCCC} = 4 Hz), 127.5 d, J_{PC} = 55 Hz), 33.1, 32.8 (dd, J_{PCP} = 21 Hz), 28.3, 22.3, 13.3. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24 (br s); HRMS (EI^+) calcd. for $C_{29}H_{30}P_2$ [M- 2(BH_3)] 440.1823, found 440.1819; HRMS (EI^+) calcd. for $C_{29}H_{32}P_2B$ [M- BH_3 - H] 453.2072, found 453.2076.

General Procedure fo r the Reaction of Halomethylphosphorus Anions (59b, 59f) with Benz yl-9-BBN. A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** or **59f** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below – 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by benzyl-9-BBN (2.50 mmol, 0.5 M in THF, 5.0 ml 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to – 70 ^{o}C (dry ice/acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by diethyl chlorophosphite (9.75 mmol, 1.52 g, 1.40 µl, 3.9 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt BH_3•Me_2S (10.0 mmol, 2.0 M in THF, 5.0 mL, 4.0 equiv) was added and stirring was continued for 15 min. The solvent was removed in vacuo, the

residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded described compounds.

Diethyl 1-(diethoxyphosphanyl-borane)-2-phenyl-ethanephosphonat e (Table 4.5, entry 5). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) yielded diethyl 1-(diethoxyphosphanyl-borane)-2-phenyl-ethanephosphonate (686 mg, 1.82 mmol, 73 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 – 7.28 (m, 5 H), 3.90 – 4.20 (m, 8 H), 3.10 – 3.55 (m, 2 H), 2.56 – 2.73 (m, 1 H), 1.29 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.6, 128.9 (2 C), 128.2 (2 C), 126.4, 64.3, 63.7, 62.3 (d, J_{POC} = 6 Hz), 62.2 (d, J_{POC} = 6 Hz), 40.1 (dd, $J_{P(O)C}$ = 130 Hz, $J_{P(BH3)C}$ = 42 Hz), 30.2, 16.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.6 (d, J_{PP} = 11 Hz) & 144.3; HRMS (EI^+) calcd. for $C_{16}H_{30}BO_5P_2$ ($[M]^+$) 375.1662, found 375.1660.

Diethyl 1-(diethoxyphosphanyl-borane)-1,2-diphenyl-ethanephosphonate (Table 4.5, entry 8). The title compound was prepared from diethyl 1-chloro- benzylphosphonate **59f** (2.50 mmol, 655 mg, 1.0 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 4:6, v/v) yielded diethyl 1-(diethoxyphosphanyl-borane)-1,2-diphenyl-ethanephosphonate (723 mg, 1.60 mmol, 64 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 – 7.05 (m, 10 H), 4.02 – 4.24 (m, 4 H), 3.84 – 3.93 (m, 4 H), 3.75 – 3.55 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.13 (t, J = 7 Hz, 6 H), 1.02 (t, J

= 7 Hz, 3 H), 0.00 – 1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.3 (dd, J_{PCCC} = 14 Hz, J_{PCCC} = 4 Hz), 131.6 (q, J_{PCC} = 4 Hz), 131.2 (4 C), 127.8 (d, J_{PCCCCC} = 1 Hz), 127.6 (d, J_{PCCCC} = 2 Hz) 127.5 (2 C), 126.6 (2 C), 65.4 (d, J_{POC} = 4 Hz), 65.0 (d, J_{POC} = 4 Hz), 62.7 (d, J_{POC} = 8 Hz), 62.5 (d, J_{POC} = 8 Hz), 56.5 (dd, $J_{P(O)C}$ = 136 Hz, $J_{P(BH3)C}$ = 33 Hz), 35.2 (dd, J_{PCC} = 5 Hz), 16.4 (t, J_{POCC} = 12 Hz), 16.3 (t, J_{POCC} = 12 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.9 (d, J_{PP} = 4 Hz) & 144.0 (m); HRMS calcd. for $C_{22}H_{35}BO_5P_2$ 452.2053, found 452.2044.

General Procedure fo r the Reaction of Halomethylphosphorus Anions (59b, 59i) with Trialkylborane then HCl. A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** or **59i** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below – 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by trialkylborane (2.5 mmol, 1.0 M in THF or Et_2O, 2.5 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to – 70 ^{o}C (dry ice/acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by diethyl chlorophosphite (3.75 mmol, 587 mg, 540 µl, 1.5 equiv). The resulting mixture was then refluxed for 2 h under nitrogen. After cooling to rt, HCl (7.5 mmol, 0.5 M, 15 ml, 3.0 equiv) and the biphasic reaction mixture was gently refluxing for 20 min. The layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes) yielded described compounds.

Diethyl 1-(Ethoxyphosphinyl)pentylphosphonate 63 (Scheme 4.16). The title compound was prepared from diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 465 mg, 1.0 equiv) and Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc) yielded **63** (510 mg, 1.70 mmol, 68 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, J = 575 Hz, 1 H), 4.07 – 4.23 (m, 6 H), 2.17 – 2.37 (m, 1H), 1.47 – 2.06 (m, 6 H), 1.36 (t, J = 6 Hz, 9 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.2 (d, J_{POC} = 7 Hz), 63.1 (d, J_{POC} = 7 Hz), 62.8 (d, J_{POC} = 7 Hz), 62.7 (d, J_{POC} = 7 Hz), 62.5 (d, J_{POC} = 7 Hz), 38.6 (dd, J_{PC} = 131 Hz, J_{PC} = 83 Hz), 38.5 (dd, J_{PC} = 131 Hz, J_{PC} = 83 Hz), 31.1 (dt, J_{PCCC} = 6 Hz), 22.9 (dd, J_{PCC} = 3 Hz), 22.5, 16.4 (d, J_{POCC} = 6 Hz), 16.2 (d, J_{POCC} = 6 Hz), 13.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.9 (s), 24.2 (d, J_{PP} = 4 Hz) & 36.7 (d, J_{PP} = 4 Hz; d, J_{PH} = 581 Hz), 33.5 (d, J_{PH} = 581 Hz); HRMS (EI^+) calcd. for $C_{11}H_{25}O_5P_2$ ($[M]^+$) 299.1177, found 299.1169.

Diethyl 1-(ethoxyphosphinyl)pentylphosphonite-borane (Table 4.6, entry 5). The title compound was prepared from diethoxy (chloromethyl)phosphine-borane **59i** (2.50 mmol, 461 mg, 1.0 equiv) and Bu_3B (2.50 mmol, 1.0 M solution in Et_2O, 2.5 mL, 1.0 equiv). Purification of the crude product by flash chromatography on silica gel (EtOAc/hexane 1:1, v/v) yielded diethyl 1-(ethoxyphosphinyl)pentylphosphonite-borane (507 mg, 1.70 mmol, 68 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J = 571 Hz, 1 H), 4.07 – 4.24 (m, 6 H), 2.10 – 2.31 (m, 1H), 1.49 – 2.03 (m, 6 H), 1.38 (t, J = 6 Hz, 3 H), 1.34 (t, J = 6 Hz, 6 H), 0.91 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.6 (d, J_{POC} = 4 Hz), 64.5 (d, J_{POC} = 4 Hz), 64.3 (t, J_{POC} = 4 Hz), 63.4 (d, J_{POC} = 7 Hz), 63.3 (d, J_{POC} = 7

Hz), 41.9 (dd, J_{PC} = 83 Hz, J_{PC} = 30 Hz), 41.3 (dd, J_{PC} = 83 Hz, J_{PC} = 30 Hz), 31.7 (t, J_{PCCC} = 6 Hz), 22.6 (dd, J_{PCC} = 3 Hz), 22.1, 16.6 (d, J_{POCC} = 6 Hz), 16.4 (d, J_{POCC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 32.4 (d, J_{PP} = 10 Hz; d, J_{PH} = 571 Hz), 32.2 (d, J_{PP} = 12 Hz J_{PH} = 571 Hz) & 145.6 (m); HRMS (EI^+) calcd. for $C_{11}H_{27}BO_4P_2$ ($[M]^+$) 297.1556, found 297.1552.

Procedure for The reaction of Diethyl (Chloromethyl)phosphonate 59b w ith Tributylborane and Cumene Hydroperoxide.

Tetraethyl pentyl-1,1-bis phosphonate 64 (Scheme 4.16) .[167] A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below –90 ^oC (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by tributylborane (2.50 mmol, 1.0 M in Et_2O, 2.5 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to – 70 ^oC (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by diethyl chlorophosphine (3.75 mmol, 0.54 mL, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to 0 ^oC cumene hydroperoxide (10.0 mmol, 1.52 g, 1.48 ml, 4.0 equiv) was added and stirring was continued for 1 h at rt. The reaction was partitioned between water and EtOAc. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/MeOH, 95:5, v/v) yielded **64** (447 mg, 1.30 mmol, 52 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 – 4.20 (m, 8 H), 2.35 (tt, J_{HP} = 22 Hz, J_{HH} = 6 Hz, 1H), 1.85 – 2.60 (m, 2 H), 1.18 – 1.60 (m, 4 H), 1.34 (t, J = 7 Hz, 6 H) 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.4 (t, J_{POC} = 7 Hz), 39.0 (d, $J_{P(O)C}$ = 133 Hz), 31.8 (t, J_{PCCC} = 5 Hz), 24.6 (d, J_{PCC} = 5 Hz), 22.4, 16.5 (d, J_{POCC} = 6 Hz), 13.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.0.

Procedure for the Reaction of Diethyl (Chloromethyl)phosphonate 59b with Tributylborane and S_8.

Diethyl 1-(diethoxy-thiophosphoryl)pentylphosphonate 65 (Scheme 4.16) . A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate **59b** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below –90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by tributylborane (2.50 mmol, 1.0 M in Et_2O, 2.5 ml, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to –70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by diethyl chlorophosphine (3.75 mmol, 587 mg, 540 µl, 1.5 equiv). The resulting mixture was refluxed for 2 h under nitrogen. After cooling to rt, S_8 (7.50 mmol, 240 mg, 3.0 equiv) was added and stirring was continued for 1 h at rt and next for 30 min under gentle reflux. The reaction mixture was cooling to rt and was partitioned between water and EtOAc. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography (EtOAc/hexanes 1:1 v/v) on silica gel yielded **65 (**622 mg, 1.72 mmol, 69 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07 – 4.23 (m, 8 H), 2.44 (tt, J_{HP} = 23 Hz, J_{HH} = 6 Hz, 1H), 1.88 – 2.10 (m, 2 H), 1.20 – 1.62 (m, 4 H), 1.35 (t, J = 7 Hz, 6 H), 1.33 (t, J = 7 Hz, 6 H) 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.8 (d, J_{POC} = 7 Hz), 62.7 (d, J_{POC} = 7 Hz), 43.2 (dd, $J_{P(O)C}$ = 138 Hz, $J_{P(S)C}$ = 104 Hz), 31.5 (dt, J_{PCCC} = 5 Hz), 26.1, 22.5, 16.4 (m), 13.9 (d, J = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 93.2 (d, J_{PP} = 3 Hz) & 24.3 (d, J_{PP} = 3 Hz); HRMS calcd. for $C_{13}H_{30}O_5P_2S$ [M] 360.1289, found 360.1298.

Decomplexation Procedures for 1,1-Bisphosphonite-borane 67 (Scheme 4.17).

Diethyl 1-(ethoxyphosphinyl)pentylphosphonite-borane 68 (Scheme 4.17) . To a 0.1 M solution of **67** (0.88 mmol, 300 mg, 1.0 equiv.) in dry CH_2Cl_2 at 0 °C, was added tetrafluoroboric acid diethyl ether complex (4.4 mmol, 0.60 mL, 5.0 equiv). An exothermic reaction ensued and gas evolved. The reaction was then warmed to rt and stirred for additional 12 h. Subsequently, the mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate solution was slowly added. The resulting biphasic mixture was stirred vigorously for 5 – 10 min and poured into separatory funnel. The organic layer was separated and aqueous layer was extracted with EtOAc (3 X). The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo to give **68** (247 mg, 0.83 mmol, 94 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J = 571 Hz, 1 H), 4.07 – 4.24 (m, 6 H), 2.10 – 2.31 (m, 1H), 1.49 – 2.03 (m, 6 H), 1.38 (t, J = 6 Hz, 3 H), 1.34 (t, J = 6 Hz, 6 H), 0.91 (t, J = 7 Hz, 3 H), 0.00 – 1.00 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 64.6 (d, J_{POC} = 4 Hz), 64.5 (d, J_{POC} = 4 Hz), 64.3 (t, J_{POC} = 4 Hz), 63.4 (d, J_{POC} = 7 Hz), 63.3 (d, J_{POC} = 7 Hz), 41.9 (dd, J_{PC} = 83 Hz, J_{PC} = 30 Hz), 41.3 (dd, J_{PC} = 83 Hz, J_{PC} = 30 Hz), 31.7 (t, J_{PCCC} = 6 Hz), 22.6 (dd, J_{PCC} = 3 Hz), 22.1, 16.6 (d, J_{POCC} = 6 Hz), 16.4 (d, J_{POCC} = 6 Hz),

16.3 (d, J_{POCC} = 6 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 32.4 (d, J_{PP} = 10 Hz; d, J_{PH} = 571 Hz), 32.2 (d, J_{PP} = 12 Hz J_{PH} = 571 Hz) & 145.6 (m); HRMS (EI$^+$) calcd. for $C_{11}H_{27}BO_4P_2$ ([M]$^+$) 297.1556, found 297.1552.

Diethyl pentyl-1,1-bis-*H*-phosphinate 69 (Scheme 4.17). A flame-dried, 50 mL, three-necked, round-bottomed flask charged with **67** (0.88 mmol, 300 mg, 1.0 equiv) *N*-methylpiperazine (17.6 mmol, 1.77 g, 1.96 mL, 20 equiv) and dry toluene (15 mL). The solution was heated at reflux for 16 h. After cooling to rt, the mixture was concentrated in high vacuo to remove access of *N*-methylpiperazine. The residue was diluted with dry THF (20 mL) and HCl (4.4 mmol, 0.5 M, 8.8 ml, 5 equiv) was added. The reaction mixture was gently refluxing for 20 min. After cooling to rt, the residue was diluted with EtOAc, layers were separated, the aqueous phase was extracted with EtOAc (3 X), the combined organic layers were dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/MeOH 9:1; v/v) yielded **68** (167 mg, 0.65 mmol, 74 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 570 Hz, 2 H), 4.09 – 4.32 (m, 4 H), 2.15 – 2.33 (m, 1H), 1.51 – 2.04 (m, 6 H), 1.41 (t, J = 6 Hz, 3 H), 1.40 (t, J = 6 Hz, 3 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.7 (t, J_{POC} = 6 Hz), 63.6 (t, J_{POC} = 7 Hz), 40.3 (J_{PC} = 83 Hz), 40.1 (t, J_{PC} = 83 Hz), 39.7 (t, J_{PC} = 83 Hz), 31.1 (t, J_{PCCC} = 6 Hz), 22.7 (dd, J_{PCC} = 2 Hz), 21.5, 21.3, 20.7 16.4 (d, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 32.8, 32.6, 32.4 (d, J_{PH} = 570 Hz); HRMS (EI$^+$) calcd. for $C_9H_{23}O_4P_2$ ([M]$^+$) 257.1072, found 257.1074.

Chapter IV: Section 4.3.2. Transformation P-C-B complex into P-C-C *via* acylation, alkylation, aldol, conjugate adition.

Transformation P-C-B Complex into P-C-C *via* Acylation (Table 4.7 and 4.8).

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b**, **59e**, **59h** or **59i** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by organoboranes (2.50 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to -70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by acyl choride (see Table 4.7 and 4.8 for number of equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl 1-(2,2 – dimethyl-propionyl)pentylphosphonate (Table 4.7, Entry 1).

Yield: 92 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 - 4.21 (m, 4 H), 3.64 (dm, J_{PH} = 21 Hz, 1H), 1.78 - 2.00 (m, 2 H), 1.24 - 1.36 (m, 4 H), 1.33 (t, J = 7 Hz, 6 H), 1.20 (s, 9 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 212.5 (d, J = 6 Hz), 64.7 (t, J_{POC} = 7 Hz), 46.5 (d, J_{PC} = 130 Hz), 45.5 (d, J = 2 Hz), 31.1 (d, J_{PCCC} = 13 Hz), 29.2 (d, J_{PCC} = 6 Hz), 26.8, 22.8, 16.6 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.9.

Diethyl 1-(2,2 – dimethyl-propion yl)-1-methylpentylphosphonate (Table 4.7, E ntry 2).

Yield: 78 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 - 4.22 (m, 4 H), 1.77 – 1.95 (m, 2 H), 1.40 (d, J = 17 Hz, 3 H), 1.24 - 1.37 (m, 4 H), 1.33 (t, J = 7 Hz, 6 H), 1.20 (s, 9 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 212.4 (d, J = 6 Hz), 64.7 (d, J_{POC} = 7 Hz), 64.1(d, J_{POC} = 7 Hz), 46.5 (d, J_{PC} = 125 Hz), 45.4 (d, J = 2 Hz), 31.3 (d, J_{PCCC} = 13 Hz), 29.4 (d, J_{PCC} = 6 Hz), 26.8, 22.8, 16.6 (d, J_{POCC} = 6 Hz), 15.2, 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.6.

Diethyl 1-(2,2 – dimethylpropionyl)pentylphosphonothioate (Table 4.7, Entry 3).

Yield: 86 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 - 4.25 (m, 4 H), 3.64 (dt, J_{PH} = 17 Hz, J_{HH} = 6 Hz, 1H), 1.84 - 1.98 (m, 2 H), 1.25 - 1.37 (m, 4 H), 1.30 (t, J = 7 Hz, 6 H), 1.19 (s, 9 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 212.0, 63.5 (d, J_{POC} = 7 Hz), 62.8 (d, J_{POC} = 7 Hz), 52.9 (d, J_{PC} = 100 Hz), 45.3, 30.8 (d, J_{PCCC} = 14 Hz), 29.6 (d, J_{PCC} = 4 Hz), 26.9, 22.6, 16.1 (d, J_{POCC} = 6 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 93.5.

Diethyl 1-(2,2 – dimethylpropionyl)pentylphosphonite-borane (Table 4.7, Entry 4).

Yield: 65 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 - 4.21 (m, 4 H), 3.64 (dt, J_{PH} = 18 Hz, J_{HH} = 6 Hz, 1H), 1.85 - 1.98 (m, 2 H), 1.24 - 1.35 (m, 4 H), 1.32 (t, J = 7 Hz, 6 H), 1.19 (s, 9 H), 0.90 (t, J = 7 Hz, 3 H), 0.5 (dq, J_{BH} = 94 Hz, J_{PH} = 15 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 212.0, 63.6 (d, J_{POC} = 6 Hz), 63.0 (d, J_{POC} = 6 Hz), 46.1 (d, J_{PC} = 42 Hz), 45.3, 30.8 (d, J_{PCCC} = 10 Hz), 29.6 (d, J_{PCC} = 4 Hz), 26.8, 22.4, 16.2 (d, J_{POCC} = 5 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 144.1 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -42.9 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz).

Diethyl 1-(2,2 – dimethyl-propionyl)-2-m ethylbutylphosphonate (Table 4.7, Entry 5).

Yield: 86 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03 - 4.22 (m, 4 H), 3.60 (dd, J_{PH} = 21 Hz, J_{HH} = 9 Hz, 0.25 H), 3.56 (dd, J_{PH} = 20 Hz, J_{HH} = 9 Hz, 0.75 H), 2.05 - 2.23 (m, 2 H), 1.78 – 1.86 (m, 1 H), 1.30 (t, J = 7 Hz, 6 H), 1.20 (s, 9 H), 1.13 (d, J = 7 Hz, 2 H), 0.89 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.2 (75 %) & 25.1 (25 %).

Diethyl 1-(2,2 – dimethylpropionyl)-2-phenylethylphosphonate (Table 4.7, Entry 6).

Yield: 63 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 – 7.23, 4.12 - 4.22 (m, 4 H), 3.90 (ddd, J_{PH} = 20 Hz, J_{HH} = 10 Hz, J_{HH} = 4.5 Hz, 1H), 3.10 - 3.27 (m, 2 H), 1.24 - 1.36 (m, 4 H), 1.35 (dt, J = 7 Hz, J = 2 Hz, 6 H), 0.83 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 211.5 (d, J = 5 Hz), 139.2 (d, J = 16 Hz), 129.5, 128.7, 127.0, 63.1 (d, J_{POC} = 7 Hz), 62.7 (d, J_{POC} = 7 Hz), 49.2 (d, J_{PC} = 127 Hz), 45.4 (d, J = 2 Hz), 35.2 (t, J_{PCC} = 5 Hz), 26.2, 16.6 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.5.

Diethyl 1-benzoylpentylphosphonate 73 (Table 4.8, Entry 3).

Yield: 62 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 - 8.01, 3.96 - 4.26 (m, 5 H), 2.00 - 2.33 (m, 2 H), 1.23 - 1.32 (m, 4 H), 1.28 (t, J = 7 Hz, 3 H), 1.17 (t, J = 7 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 196.5 (d, J = 6 Hz), 137.9, 133.5, 128.8 (d, J = 8 Hz), 63.4 (d, J_{POC} = 7 Hz), 62.7 (d, J_{POC} = 7 Hz), 47.5 (d, J_{PC} = 128 Hz), 31.4 (d, J_{PCCC} = 15 Hz), 27.5 (d, J_{PCC} = 5 Hz), 22.7, 16.5 (d, J_{POCC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.7.

Benzoic acid 2-(diethoxy-phosphoryl)-pheny l-hex-1-enyl ester 74 (T able 4.8, Entry 1).

Yield: 30 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 - 8.13 (m, 2 H), 7.26 - 7.86 (m, 8 H), 4.05 - 4.15 (m, 4 H), 2.38 (dt, J = 20 Hz, J = 8 Hz, 2 H), 1.33 – 1.63 (m, 4 H), 1.24 (t, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 164.5, 156.8, 134.8 (d, J = 14 Hz), 133.7, 130.3, 129.7, 128.7, 128.5, 120.4 (d, J_{PC} = 173 Hz), 62.1 (d, J_{POC} = 7 Hz), 32.4, 29.6 (d, J_{PCCC} = 7 Hz), 22.7, 16.4 (d, J_{POCC} = 7 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 18.9.

Transformation P-C-B Complex into P-C-C *via* Alkylation (Table 4.9).

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b**, or **59i** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by organoboranes (2.50 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by electrophile (3.75 mmol, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl 1-methylpentylphosphonate. (Table 4.9, entry 1).

Yield: 74 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04 - 4.16 (m, 4 H), 1.36 – 1.79 (m, 7 H) 1.30 (t, J = 7 Hz, 6 H), 1.17 (dd, J_{HH} = 7 Hz, J_{HP} = 18 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.6 (t, J_{POC} = 6 Hz), 30.9 (d, J_{PC} = 140 Hz), 29.8 (2 C), 29.7, 29.6, 22.7, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 13.3 (d, J_{PCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.7.

Diethyl (2-phenylmethyl)pentylphosphonate. (Table 4.9, entry 2).

Yield: 60 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 - 7.31 (m, 5 H), 4.00 - 4.11 (m, 4 H), 3.10 (td, J = 13 Hz, J = 5, 1 H), 2.66 (td, J = 13 Hz, J = 9 Hz, 1 H), 2.06 (m, 1 H), 1.17 - 1.69 (m, 6 H) 1.29 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 140.4 (d, J = 13 Hz), 129.2, 128.5,126.5, 61.8 (t, J_{POC} = 7 Hz), 38.0 (d, J_{PC} = 138 Hz), 34.8 (d, J_{PCC} = 3 Hz), 29.8 (d, J_{PCCC} = 7 Hz), 27.7 (d, J_{PCC} = 3 Hz), 22.8, 16.6 (d, J_{POCC} = 5 Hz), 14.0, (d, J_{PCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.7.

Diethoxy 1-allyloctylphosphonite-borane (Table 4.9, Entry 3).

Yield: 72 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 – 5.86 (m, 1 H), 5.02 – 5.11 (m, 2 H), 3.96 - 4.17 (m, 4H), 2.15 (m, 1 H), 2.55 (m, 1 H), 1.26 - 1.79 (m, 13 H), 1.30 (t, J = 7 Hz, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.4 (d, J = 10 Hz), 116.7, 63.5 (t, J_{POC} = 4 Hz), 39.5 (d, J_{PC} = 56 Hz), 32.2 (d, J_{PCC} = 3 Hz), 32.0, 29.7, 29.3, 27.7 (d, J_{PCCC} = 8 Hz), 27.1 (d, J_{PCC} = 3 Hz), 22.8, 16.7 (d, J_{POCC} = 6 Hz); 14.3. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 152.4 (q, $J_{PB=}$ 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.6 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz);

Diethoxy 1-octylnonylphosphonite-borane (Table 4.9, Entry 4).

Yield: 76 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 - 4.17 (m, 4 H), 1.27 - 1.69 (m, 27 H), 1.32 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 6 H), 0.50 (qd, J_{BH} = 94 Hz, J_{PBH} = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.4 (d, J_{POC} = 5 Hz), 39.3 (d, J_{PC} = 55 Hz), 32.1, 32.0,

29.9, 29.8, 29.6 (d, J_{PCCC} = 9 Hz), 29.3, 28.1 (d, J_{PCCC} = 9 Hz), 27.7, 27.6, 22.7, 23.0, 23.9, 16.7 (d, J_{POCC} = 5 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 152.7 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.7 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz).

Transformation P-C-B complex into P-C-C *via* Aldol Reaction.

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b**, or **59i** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by organoboranes (2.50 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by benzaldehyde (292 mg, 2.75 mmol, 280 µl, 1.1 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded the described compound.

Diethyl (1-hydroxy-phenyl-methyl-pentyl)phosphonate 75 (Scheme 4.24).

Yield: 70 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 - 7.40 (m, 5 H), 5.45 - 5.42 (m, 1 H), 4.10 - 4.21 (m, 4 H), 2.60 - 2.78 (m, 1 H), 2.00 - 2.15 (m, 2 H), 1.17 - 1.69 (m, 4 H) 1.35 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.5. & 34.6 (*syn*:*anti*, 50:50)

Diethoxy (1-hydroxy-phenyl-methyl-pentyl)phosphonite-borane 76 (Scheme 4.25).

Yield: 78 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 - 7.44 (m, 5 H), 5.39 - 5.42 (m, 1 H), 4.09 - 4.18 (m, 4 H), 2.68 - 2.76 (m, 1 H), 1.96 - 2.10 (m, 2 H), 1.18 - 1.65 (m, 4 H) 1.33 (t, J = 7 Hz, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.5 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.4 (d, J = 13 Hz), 128.3, 127.3, 125.7, 70.1, 64.4 (d, J_{POC} = 5 Hz), 62.2 (d, J_{POC} = 5 Hz), 48.1 (d, J_{PC} = 53 Hz), 31.7 (d, J_{PCCC} = 5 Hz), 22.5, 20.9, 16.8 (d, J_{POCC} = 5 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 151.6 (q, J_{PB} = 82 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.8 (dq , J_{BP} = 82 Hz, J_{BH} = 94 Hz).

Ethyl (1-hydroxy-phenyl-methyl-pentyl)phosphinate 77 (Scheme 4.25).

Yield: 94 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 - 7.33 (m, 5 H), 6.96 (d, J_{PH} = 530 Hz), 5.39 - 5.42 (m, 1 H), 4.00 - 4.24 (m, 2 H), 3.02 (qd, J = 14 Hz, J = 7 Hz, 1 H), 1.23 – 2.03 (m, 6 H) 1.35 (t, J = 7 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.9 (d, J = 13 Hz), 129.3 (d, J = 2 Hz), 128.7 (d, J = 13 Hz), 126.7, 69.8, 62.9 (d, J_{POC} = 7 Hz), 46.1 (d, J_{PC} = 94 Hz), 46.0 (d, J_{PC} = 94 Hz), 29.7 (d, J_{PCC} = 7 Hz), 26.4 (d, J_{PCCC} = 11 Hz), 22.8, 16.4 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.90 & 42.87 (dm, J_{PH} = 533 Hz), *syn*:*anti*, 50:50.

Diethyl (1-dimethylaminomethylpent yl)phosphonate 80 (Scheme 4.27). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** (466 mg, 2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (2.50 mmol, 2.5 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was

added slowly followed by the solution of dimethyl(methylene)ammonium iodide (694 mg, 3.75 mmol, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/Hexanes 7:3, v/v) gave compound **80** in 70 % (464 mg, 1.75 mmol) isolated yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ fgvv/4.04 - 4.16 (m, 4 H), 2.35 - 2.53 (m, 2 H), 2.12 (s, 6 H), 1.86 - 1.98 (dm, J = 19 Hz, 1 H), 1.26 - 1.70 (m, 6 H), 1.32 (t, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.7.

Transformation P-C-B Complex into P-C-C *via* Conjugate Addition.

Diethyl [1-(3-Oxo-cyclohexyl)pen tyl]phosphonate 81 (Sch eme 4.28). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** (466 mg, 2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below -90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by organoboranes (2.50 mmol, 2.5 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by solution of cyclohexenone (288 mg, 3.00 mmol, 290 µl, 1.2 equiv) and TMSCl (327 mg, 3.00 mmol, 382 µl, 1.2 equiv) in 5 mL of THF. The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF

was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/Hexanes 7:3, v/v) gave compound **81** in 60 % (456 mg, 1.50 mmol) isolated yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 - 4.17 (m, 2 H), 1.28 – 2.61 (m, 16 H) 1.32 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 61.7 (d, J_{POC} = 7 Hz), 61.5 (d, J_{POC} = 7 Hz), 46.3, 46.1 (d, J_{PC} = 138 Hz), 41.4, 46.0 (d, J_{PC} = 94 Hz), 38.7, 30.9 (d, J_{PCCC} = 8 Hz), 29.1 (d, J_{PCCC} = 10 Hz), 26.0 (d, J_{PCC} = 3 Hz), 25.6, 22.9, 16.7 (d, J_{POCC} = 5 Hz), 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 33.4.

Chapter IV: Section 4.3.3. Transforma tion P-C-B Complex into P-C-X functionalities (X = Si, Se, O, I,).

Diethyl 1-trimethylsilylpentyl phosphonate 87 (Scheme 4.34). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** (466 mg, 2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by organoboranes (2.50 mmol, 2.5 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by *N*-trimethylsilylimidazole (421 mg, 3.00 mmol, 1.3 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was

removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/Hexanes 7:3, v/v) gave compound **87** in 71 % (496 mg, 1.77 mmol) isolated yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 - 4.14 (m, 4 H), 1.25 - 1.84 (m, 6 H) 1.30 (t, J = 7 Hz, 6 H), 1.03 (dq, J = 24 Hz, J = 4 Hz), 0.90 (t, J = 7 Hz, 3 H), 0.14 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.2 (d, J_{POC} = 7 Hz), 34.5 (d, J_{PCC} = 5 Hz), 26.6 (d, J_{PC} = 125 Hz), 25.9 (d, J_{PCCC} = 6 Hz), 23.9, 17.7 (d, J_{POCC} = 6 Hz), 15.1, 0.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.4

Diethyl pentyl-1(*Z*)-enylphosphonate 88 (Scheme 3.35). [168] A flame-dried, 100 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** (933 mg, 5.0 mmol, 1.0 equiv) and dry THF (20 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (5.0 mmol, 2.5 M solution in hexane, 2.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (5.0 mmol, 5.0 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 70 ^{o}C (dry ice / acetone bath) and a red-brown solution of phenylselenyl chloride (5.75 mmol, 1.10 g, 1.15 equiv) in 5 mL of dry THF was added slowly. The addition of each drop is accompanied by the instantaneous discharge of color. After addition is complete, the resulting yellow reaction mixture is allowed to warm to rt and ^{31}P NMR indicated the formation of α-selenophosphonate **87**, which was converted into diethyl pentyl-1(*Z*)-enylphosphonate **88** by the addition of pyridine (2.37 mg, 30 mmol, 2.40 mL, 6.0 equiv) at - 78 ^{o}C (dry ice / acetone bath) followed by 30 %

H_2O_2 (30 mmol, 6.0 equiv) and H_2O (1:1 by volume) at 0 ^oC and. After warming to rt, the organic layer was separated and aqueous layer was extracted with EtOAc (3 X). The combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc/Hexanes 5:5, v/v) gave compound **87** in 71 % (496 mg, 1.77 mmol) isolated yield.

^1H NMR ($CDCl_3$, 300 MHz) δ 6.40 (ddt, J = 53 Hz, J = 13 Hz, J = 7 Hz, 1 H), 5.52 (ddt, J = 20 Hz, J = 13 Hz, J = 2 Hz, 1 H), 3.95 - 4.11 (m, 4 H), 2.43 – 2.50 (m, 2 H), 1.28 - 1.80 (m, 2 H) 1.23 (t, J = 7 Hz, 6 H), 0.84 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 153. 7 (d, J_{PCC} = 5 Hz), 116 (d, J_{PC} = 183 Hz), 61.1 (d, J_{POC} = 6 Hz), 32.4 (d, J_{PCCC} = 8 Hz), 21.9 (d, J_{PCCCC} = 2 Hz), 16.7 (d, J_{POCC} = 6 Hz), 13.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.7.

Diethyl 1-hydroxypentylphosphonate 87 (Scheme 4.34). A flame-dried, 100 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59b** (933 mg, 5.0 mmol, 1.0 equiv) and dry THF (15 mL). The solution was cooled below - 90 ^oC (liquid nitrogen/ethanol bath) and *n*-butyllitium (5.0 mmol, 2.5 M solution in hexane, 2.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (5.0 mmol, 5.0 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and the solution of PCC (6.47 g, 30 mmol, 6.0 equiv) in 45 mL of dry CH_2Cl_2 was added. The resulting mixture was heated at reflux for 10 h under nitrogen. After cooling to rt, the reaction mixture was filtered and the filtrate washed with water. The aqueous phase was then extracted with EtOAc (3 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash

chromatography on silica gel (EtOAc/Hexanes 7:3, v/v) gave compound **87** in 71 % (496 mg, 1.77 mmol) isolated yield.

Yield: 50 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.13 - 4.13 (m, 4 H), 3.84 - 3.87 (m, 1 H), 1.58 – 1.74 (m, 6 H), 1.35 (t, J = 7 Hz, 6 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 68.8 (d, J_{PC} = 161 Hz), 62.9 (t, J_{POC} = 7 Hz), 62.7 (t, J_{POC} = 7 Hz), 31.2, 28.0 (d, J_{PCC} = 13 Hz), 22.6, 16.7 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.4

Procedure for the synthesis of α-iodo phosphonates.[47]

Diethyl 1-iodopentylphosphonate 92 (Scheme 4.43). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled below - 90 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe followed by Bu_3B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and I_2 (4.8 mmol, 1.2 g, 1.2 equiv) was added in one portion. The resulting mixture was stirred at reflux for 2 h, after cooling to rt, was diluted with EtOAc washed with aqueous solution of sodium thiosulfate (1 X) and water (1 X). Organic layer was dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexanes 3:7, v/v) yielded diethyl pentylphosphonate (3.05 mmol, 1.02 g, 76 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.14 - 4.25 (m, 4 H), 3.69 - 3.79 (m, 1 H), 1.31 - 2.04 (m, 7 H), 1.35 (t, J = 7 Hz, 6 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.7 (q, J_{POC} = 7 Hz), 32.9 (d, J_{PCC} = 2 Hz), 32.3 (d, J_{PCCC} = 13 Hz), 21.7, 18.2 (d, J_{PC} = 154 Hz), 16.6 (d, J_{POCC} = 6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 23.2; HRMS (EI^+) calcd. for $C_9H_{20}IO_3P$, ($[M]^+$) 334.0195, found 334.0201.

Diethyl 1–iodo–2-meth ylbutylphosphonate 93 (Scheme 6). A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with diethyl (chloromethyl)phosphonate **59b** (4.0 mmol, 746 mg, 1.0 equiv) and dry THF (20 mL). The solution was cooled below – 90^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.5 mL, 1.6 M solution in hexane, 4.0 mmol, 1.0 equiv) was added slowly *via* syringe followed by (*sec*-Bu)$_3$B (4.0 mL, 1.0 M solution in diethyl ether, 4.0 mmol, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and I_2 (4.8 mmol, 1.2 g, 1.2 equiv) was added in one portion. The resulting mixture was stirred at reflux for 2 h, after cooling to rt, was diluted with EtOAc washed with aqueous. solution of sodium thiosulfate (1 X) and water (1 X). Organic layer was dried with $MgSO_4$, and solvents removed in vacuo. Purification of the crude product by chromatography on silica gel (EtOAc/hexane 3:7 v/v) yielded diethyl pentylphosphonate (2.88 mmol, 962 mg, 72%), mixture of diastereoisomers (50/50)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.15 - 4.26 (m, 4 H), 3.95 (2dd, J = 13 Hz, J = 2 Hz, 1 H), 1.70 - 1.91 (m, 1 H), 1.36 (t, J = 7 Hz, 6 H), 1.15 - 1.26 (m, 2 H), 1.02 (t, J = 6 Hz, 3 H) 0.91 (2t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 63.7 (dd, J_{POC} = 7 Hz, J = 3 Hz,), 63.3 (q, J_{POC} = 7 Hz), 36.4, 35.2, 30.7 (d, J_{PCCC} = 16 Hz), 29.4 (d, J_{PC} = 150 Hz), 28.7 (d, J_{PC} = 150 Hz), 28.1, 19.7 (d, J_{PCCC} = 15 Hz), 18.9, 16.4 (d, J_{POCC} = 6 Hz), 11.6,

11.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.5, 22.2; HRMS (EI^+) calcd. for $C_9H_{20}IO_3P$, ($[M]^+$) 334.0195, found 334.0197.

Chapter IV: Section 4.4. Asymmetric Synthesis of Functionaliz ed Organophosphorus Compounds *via* Organoboranes.

(*R,R*)-*N,N'*-Dimethyl-*N,N'*-(1,2-cyclohexanedily)-chlomethylphosphonic diamine 59l (Eq. 4.16). [138] Anhydrous Et_3N (5.62 g, 7.75 mL, 55.6 mmol, 2.02 equiv) was added dropwise to the solution of (*R,R*)-*N,N'*-dimethyl-1,2-diaminocyclohexane **104** of (3.91 g, 27.5 mmol, 1.0 equiv) in dry THF (60 mL) at rt. A solution of (chloromethyl)phosphonic dichloride (4.60 g, 27.5 mmol, 1.0 equiv) in 30 mL of THF was added dropwise over a period of 20 min, and the mixture stirred for an additional 2 h at rt,. The resulting precipitate was filtered and the filtrate evaporated. Purification of the crude product by silica gel chromatography (EtOAc/hexanes, 95:5, v/v) gave compound **59l** (5.54 g, 23.4 mmol, 85 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (2 X dd, J = 15 Hz, J = 13 Hz 2 H), 2.72 – 2.80 (m, 1 H), 2.73 (d, J = 10 Hz, 3 H), 2.62 (d, J = 10 Hz, 3 H), 2.53 - 2.61 (m, 1 H), 2.01 - 2.05 (m, 2 H), 1.73 - 1.99 (m, 2 H), 1.10 - 1.36 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.9 (d, J = 7 Hz), 63.5 (d, J = 6 Hz), 52.7 (d, J_{PC} = 160 Hz), 31.0, 28.9, 28.7, 28.3, 25.0 (2 C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.3; $[\alpha]^{22}_D$ = -110.1 (c 1.0, $CHCl_3$), $[\alpha]^{25}_D$ = -109.8 (c 1.0, $CHCl_3$).

(*R,R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate s alt 102 (Scheme 4.49) was synthesized according to the procedure of Jacobsen.[139b]

(*R,R*)-1,2-Diaminocyclohexane-*N,N'*-diethyl d icarbamate 103 (Scheme 4.49). [169,138a] To a solution of (*R,R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **102** (30.0 g, 0.11 mol) at 0 ^{o}C in 250 mL three-necked, round-bottomed flask were added ethyl chloroformate (25.0 g, 0.23 mol, 2.1 equiv) and a solution of NaOH (35.2 g, 0.88 mol, 8.0 equiv) in H_2O (40 mL) through two addition funnels. During the addition, the temperature was maintained between 0 and 10 ^{o}C. When the addition was complete, the mixture was stirred at rt for 5 h and the precipitate was filtered off and rinsed with CH_2Cl_2. the filtrate was dried ($MgSO_4$). The residue was recrystallised from a solution of CH_2Cl_2 containing the minimum amount of hexanes, providing **103** as a white solid in 70 % (19.9 g, 77 mmol) yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.98 - 5.07 (m, 2 H), 4.17 (q, J = 7 Hz, 4 H), 3.28 - 3.34 (m, 2 H), 1.40 - 2.20 (m, 8 H), 1.21 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 157.0, 60.7, 55.4, 32.8 (2 C), 24.8, 14.6; $[\alpha]^{20}_{D}$ = +45.5 (c 1.0, $CHCl_3$).

(*R,R*)-*N,N'*-Dimethyl-1,2-diaminocyclohexane 104 (Scheme 4.49).[138a] To a flame-dried 1 L three-necked, round-bottomed flask, equipped with a reflux condenser and purged with nitrogen, was added LAH (11.0 g; 290 mmol, 7.5 equiv) and 400 mL of dry THF. The suspension was cooled to 0 ^{o}C and solid (*R,R*)-1,2-Diaminocyclohexane-*N,N'*-diethyl dicarbamate **103** (10.0 g, 38.9 mmol) was added portionwise. The mixture was stirred at rt for 1 h then refluxed for 14 h. The resulting gray suspension was cooled to 0 ^{o}C and water (11.0 mL), 15 % NaOH (11.0 mL) and H_2O (33.0 mL) were sequentially added. The mixture was stirred for 1 h at rt to give a white precipitate which was filtered and rinsed with THF (2 X 100 mL). The solvent was evaporated and the residue acidified (10 % HCl) (pH ~ 2) then extracted with CH_2Cl_2 (3 X 100 mL). The aqueous layer was

treared with NaOH (10 %) until basic pH, then extracted with CH_2Cl_2 (3 X 200 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a yellowish residue which solidified to give 3.96 g (27.9 mmol, 70 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 6 H), 2.06 - 1.56 (m, 4 H, ring), 1.69 (s, 2 H), 080 – 1.20 (m, 4 H, ring); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 63.0, 33.4, 30.6, 42.8; $[\alpha]^{22}_D$ = -144.3 (c 1.15, $CHCl_3$), lit. $[\alpha]_D$ = -144.2 (c 1.15, $CHCl_3$)).

(*R,R*)-*N,N'*-Dibenzyl-*N,N'*-(1,2-cyclohexanedily)-chlomethylphosphonic diamine 59m (Scheme 4.52). Anhydrous Et_3N (2.47 g, 3.40 mL, 24.4 mmol, 2.03 equiv) was added dropwise to the solution of (*R,R*)-*N,N'*-dibenzyl-1,2-diaminocyclohexane **107** of (3.5 g, 12.0 mmol, 1.0 equiv) in dry THF (25 mL) at rt. A solution of (chloromethyl)phosphonic dichloride (2.00 g, 12.0 mmol, 1.0 equiv) in 10 mL of THF was added dropwise over a period of 20 min, and the mixture stirred for an additional 2 h at rt. The resulting precipitate was filtered and the filtrate evaporated. Purification of the crude product by silica gel chromatography (EtOAc/hexanes, 95:5, v/v) gave compound **59m** (3.59 g, 9.24 mmol, 77 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 - 7.51 (m, 10 H), 4.40 - 4.52 (m, 2 H), 4.20 (dd, J = 15 Hz, J = 12 Hz, 2 H), 4.11 (dd, J = 15 Hz, J = 12 Hz, 2 H), 3.90 - 3.98 (m, 2 H), 2.87 - 2.99 (m, 2 H), 1.95 - 2.01 (m, 2 H), 1.69 - 1.94 (m, 2 H), 1.10 - 1.36 (m, 4 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.5.

(*R,R*)-*N,N'*-Dibenzylidene-1,2-diaminocyclohexane (Scheme 4.52). Benzaldehyde (5.70 g, 53.7 mmol) was added to a solution of (*R,R*)-1,2-diaminocyclohexane **101** (3.12 g, 27.4 mmol) in toluene (60 mL) and the mixture was stirred at rt for 45 min. The

solvent and H_2O was evaporated and residue was recrystallized from petroleum ether to give 70 % (5.57 g, 19.2 mmol) of desired product.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 2H), 7.31 - 7.58 (m, 10 H), 3.42 (m, 2 H), 1.86 (m, 6 H), 1.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 160.9, 136.2, 130.0, 128.2, 127.7, 73.6, 55.7, 32.8, 24.3; $[\alpha]^{24}_D$ = -211.4 (c 1.20, $CHCl_3$).

(*R,R*)-*N,N'*-Dibenzyl-1,2-diaminocyclohexane 107 (Scheme 4.52). To a 250 mL flask purged with nitrogen, was added (*R,R*)-*N,N'*-dibenzylidene-1,2-diaminocyclohexane (5.0 g, 17.2 mmol), methanol (100 mL) and the mixture was cooled to 0 ^{o}C. $NaBH_4$ (1.50 g, 39.6 mmol, 2.3 equiv) was added portionwise and the reaction mixture was stirred for 4 h at rt. The solvent was evaporated, the residue acidified (10 % HCl) then extracted with 3 X 100 mL of CH_2Cl_2. The aq. layer was treated with NaOH (10 %) until pH ~ 12 and extracted with 3 X 200 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give 3.5 g (12.0 mmol, 70 %) of product **107** as a colorless oil residue which solidified.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 - 7.35 (m, 10 H), 3.91 (d, J = 13 Hz, 2 H), 3.67 (d, J = 13 Hz, 2 H), 2.27 (m, 2 H), 2.18 (m, 2 H), 2.01 (s br., 2 H), 1.73 (m, 2 H), 1.25 (m, 2 H), 1.15 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 140.8, 128.2, 127.9, 126.6, 60.7, 55.7, 31.4, 24.9; $[\alpha]^{24}_D$ = - 67.0 (c 1.15, $CHCl_3$).

(*R,R*)-*N,N'*-Bis(2,2-dimethylpropyl)-*N,N'*(1,2cyclohexanedily)chlomethylphosphonic diamine 59n (Scheme 4.52). Anhydrous Et_3N (2.09 g, 2.90 mL, 20.7 mmol, 2.03 equiv) was added dropwise to the solution of (*R,R*)-*N,N'*-dibenzyl-1,2-diaminocyclohexane **108** of (1.70 g, 10.2 mmol, 1.0 equiv) in dry THF (20 mL) at rt. A solution of (chloromethyl)phosphonic dichloride (2.00 g, 10.2 mmol, 1.0 equiv) in 10 mL of THF

was added dropwise over a period of 20 min, and the mixture stirred for an additional 2 h at rt,. The resulting precipitate was filtered and the filtrate evaporated. Purification of the crude product by silica gel chromatography (EtOAc/hexanes, 95:5, v/v) gave compound **59n** (2.28 g, 7.14 mmol, 70 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (dd, J = 15 Hz, J = 11 Hz, 2 H), 3.75 (dd, J = 15 Hz, J = 12 Hz, 2 H), 3.34 - 3.47 (m, 1 H), 2.92 - 3.09 (m, 1 H), 2.58 - 2.82 (m, 4 H), 1.80 – 2.15 (m, 4 H), 1.26 - 1.30 (m, 4 H), 0.97 (s, 18 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.8.

(*R,R*)-*N,N'*-Bis(2,2-dimethylproplidene)-1,2-diaminocyclohexane (Scheme 4.52). pivaldehyde (5.00 g, 58.0 mmol) was added to a solution of (*R,R*)-1,2-diaminocyclohexane **101** (3.31 g, 29.0 mmol) in toluene (60 mL) and the mixture was stirred at rt for 45 min. The solvent and H_2O was evaporated and residue was recrystallized from petroleum ether to give 62 % (4.51 g, 18.0 mmol)of (*R,R*)-*N,N'*-Bis(2,2-dimethylproplidene)-1,2-diaminocyclohexane.

(*R,R*)-*N,N'*- Bis(2,2-dimethylpropyl)-1,2-diaminocyclohexane 108 (Scheme 4.52). To a 250 mL flask purged with nitrogen, was added (*R,R*)-*N,N'*-Bis(2,2-dimethylproplidene)-1,2-diaminocyclohexane (4.50 g, 18.0 mmol), methanol (100 mL) and the mixture was cooled to 0 ^{o}C. $NaBH_4$ (1.57 g, 41.4 mmol, 2.3 equiv) was added portionwise and the reaction mixture was stirred for 4 h at rt. The solvent was evaporated, the residue acidified (10 % HCl) then extracted with 3 X 100 mL of CH_2Cl_2. The aq. layer was treated with NaOH (10 %) until pH ~ 12 and extracted with 3 X 200 mL of CH_2Cl_2. The organic layer was dried over MgSO4 and evaporated to give 2.66 g (10.4 mmol, 58 %) of product **108** as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56 (d, J = 11 Hz, 2 H), 2.16 (d, J = 11 Hz, 2 H), 2.11 (d, J = 11 Hz, 2 H), 2.05 (s br., 2 H) 2.27 - 1.15 (m, 8 H), 0.91 (s, 18 H).

Procedure for the Reaction of 59l-n with Bu_3B and Electrophiles.

A flame-dried, 50 mL, three-necked, round-bottomed flask was purged with nitrogen, charged with **59l-n** (2.50 mmol, 1.0 equiv) and dry THF (10 mL). The solution was cooled below - 100 ^{o}C (liquid nitrogen/ethanol bath) and *n*-butyllitium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly by syringe followed by Bu_3B (2.50 mmol, 2.5 mL, 1.0 M solution in Et_2O, 1.0 equiv) in one portion. The reaction mixture was warmed slowly to rt and then was cooled down to - 78 ^{o}C (dry ice / acetone bath) and *n*-butyllithium (2.50 mmol, 2.5 M solution in hexane, 1.0 mL, 1.0 equiv) was added slowly followed by electrophile (3.75 mmol, 1.5 equiv). The resulting mixture was heated at reflux for 2 h under nitrogen. After cooling to rt, THF was removed in vacuo, the residue was diluted with EtOAc and washed with water. The aqueous phase was then extracted with EtOAc (2 X), the combined organic fractions were dried with $MgSO_4$ and solvent removed in vacuo. Purification of the crude product by flash chromatography on silica gel yielded the described compound.

***R,R*)-*N,N'*-Dimethyl-*N,N'*-(1,2-cyclohexanedily)-1-trimethylsilylpentylphosphonic phosphonic diamine 105a (Scheme 4.50).**

48 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 - 2.70 (m, 2 H), 2.60 (d, J = 10 Hz, 3 H), 2.56 (d, J = 10 Hz, 3 H), 1.97 - 2.05 (m, 2 H), 1.80 - 1.87 (m, 2 H), 1.20 - 1.71 (m, 11 H), 0.91 (t, J = 7 Hz, 3 H), 0.14 (s, 9 H); ; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 49.7 (70 %) & 50.0 (30 %)

***(R,R)*-*N,N'*-Dimethyl-*N,N'*-(1,2-cyclohexanedily)-1-methylpentylphosphonic diamine 105b (Scheme 4.50).**

90 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.61 - 2.70 (m, 2 H), 2.62 (d, J = 10 Hz, 3 H), 2.56 (d, J = 11 Hz, 3 H), 1.95 - 2.04 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.28 - 1.68 (m, 11 H), 1.21 (dd, J = 18 Hz, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 48.8 (67 %) & 49.1(33 %).

***(R,R)*-*N,N'*-Dibenzyl-*N,N'*-(1,2-cyclohexanedily)-1-ethylpentylphosphonic diamine 109 (Scheme 4.53).**

73 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.45 (m, 4 H), 7.40 - 7.43 (m, 6 H), 4.42 - 4.56 (m, 2 H), 3.96 (dd, J = 16 Hz, J = 8 Hz, 2 H), 2.89 - 3.01 (m, 2 H), 1.24 - 1.93 (m, 17 H), 0.98 (t, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 140.9 (J = 3 Hz), 139.7 J = 6 Hz), 128.5, 127.9, 127.6, 127.2, 65.5 (d, J = 7 Hz), 65.3 (d, J = 7 Hz), 49.0, 46.6 (d, J = 6 Hz), 41.0 (d, J_{PC} = 112 Hz), 31.2 (d, J = 11 Hz), 30.3 (d, J_{PCCC} = 10 Hz), 30.1 (d, J = 5 Hz), 28.7, 24.4, 23.1, 22.3, 14.2, 13.7 (d, J = 11 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 48.4 (80 %) & 48.5(20 %).

(*R,R*)-*N,N'*-Bis(2,2-dimethylpropyl)-*N,N'*(1,2cyclohexanedily)-1-ethylpentyl phosphonic diamine 110 (Scheme 4.53).

70 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20 - 3.31 (m, 1 H), 2.85 - 3.16 (m, 1 H), 2.58 - 2.82 (m, 4 H), 1.30 - 2.10 (m, 17 H), 0.98 (s, 18 H), 0.96 (t, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 48.7 (50 %) & 49.2 (50 %).

Chapter V: Section 5.2. Borane Complexes of the H_3PO_2 P(III) Tautomer[147]

Diethoxyphosphine-borane 116 (Eq. 5.6). In a flame-dried three-neck round-bottomed flask was placed diethyl chlorophosphite (10 g, 63.9 mmol) in THF (100 mL) under N_2 and this was cooled to -78 ^oC. $LiBH_4$ (1.67 g, 76.7 mmol, 1.20 equiv) was then added (quickly in air) at -78 ^oC and the reaction mixture was stirred at this temperature for 10 min, then allowed to warm up to rt and stirred for 1 h. The reaction mixture was poured directly into a beaker containing a mixture of concentrated HCl (12 N, 28 mL) and ice (200 g). The resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes/EtOAc, 80 : 20, v/v) afforded **116** (8.65 g, 63.3 mmol, 99%) as a colorless oil.

^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, J_{PH} = 444 Hz, 1H), 4.25 - 4.01 (m, 4H), 1.37 (dt, J = 7 Hz, 6 H), 1.18 - 0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 65.1 (d, J_{POC} = 7 Hz), 16.4 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 128.3 (dq, J_{PB} = 74 Hz, J_{PH} = 450 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 41.0 (dq, J_{BP} = 75 Hz, J_{BH} = 97 Hz); HRMS (EI) calcd for $C_4H_{14}BO_2P$ $(M + NH_4)^+$: 154.1168, found: 154.1165.

Typical alkylation P rocedure for the Al kylation of Diethoxyphosphine-borane (Table 5.1). Neat diethoxyphosphine-borane **116** (3.68 mmol, 500 mg, 1.0 equiv) was placed under vacuum in a flame-dried two-neck flask, during 5 min before use. Anhydrous THF (6 mL or 10 mL, respectively) was then added under N_2. The flask was then placed at -78 ^oC and deoxygenated under high vacuum for 5 min. The reaction flask was back-filled with N_2 and LiHMDS (1.0 M in THF, 1 equiv) was added at -78 ^oC. After 15 min, the electrophile (1.0 equiv) was added under N_2 as a neat liquid or as a THF solution (0.5 M) for solids. After the addition of the electrophile, the reaction mixture

was allowed to slowly reach rt then stirring was continued (see Table 5.1 for reaction times). The reaction mixture was quenched with a saturated solution of NH_4Cl/brine and extracted with EtOAc (3 X). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude mixturewas purified by column chromatography over silica gel.

Diethoxy methylphosphonite-borane (Table 5.1, entry 1).

Yield: 80 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.13 - 3.96 (m, 4H), 1.50 (d, J = 8 Hz, 3H), 1.32 (t, J = 7 Hz, 6H), 0.90–0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.1 (d, J_{POC} = 5 Hz), 16.71 (d, J_{POCC} = 6 Hz), 15.7 (d, J_{PC} = 56 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.7 (q, J_{PB} = 83 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 41.8 (dq, J_{BP} = 83 Hz, J_{BH} = 91 Hz); HRMS (EI) calcd for $C_5H_{16}BO_2P$ $(M + NH_4)^+$: 168.1325, found: 168.1321.

Diethoxy octylphosphonite-borane (Table 5.1, entry 2).

Yield: 74–77%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 - 4.16 (m, 4H), 1.23 – 1.76 (m, 14 H), 1.31 (t, J = 7 Hz, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.50 (q, J_{BH} = 94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.0 (d, J_{POC} = 4 Hz), 31.8, 33.0 (d, J_{PCCC} = 15 Hz), 30.3 (d, J_{PC} = 56 Hz), 29.1 (2 C), 22.6, 21.6, 16.7 (d, J_{POCC} = 5 Hz); 14.1. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 149.1 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -43.6 (dq , J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS calcd. for $C_{12}H_{34}BNO_2P$, $([M + NH_4]^+)$ 266.2420, found 266.2418.

Diethoxy-1-methylethylphosphonite-borane (Table 5.1, entry 3).

Yield: 48 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.15 - 3.99 (m, 4H), 1.96 - 1.86 (m, 1H), 1.39 (t, J = 7 Hz, 6H), 1.14 (dd, J = 17, 7 Hz, 6H), 1.00 - 0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.5 (d, J_{POC} = 5 Hz), 28.9 (t, J_{PC} = 59 Hz), 16.8 (d, J_{POCC} = 5

Hz), 15.4; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 154.8 (q, J_{PB} = 75 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 45.0 (dq, J_{BP} = 74 Hz, J_{BH} = 94 Hz); HRMS (EI) calcd for $C_7H_{20}BO_2P$ $(M + NH_4)^+$: 196.1638, found: 196.1629.

Diethoxy allylphosphonite-borane (Table 5.1, entry 4).

Yield: 69 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 - 5.72 (m, 1H), 5.24 - 5.23 (m, 1H), 5.21 - 5.17 (m, 1H), 4.18 - 4.11 (m, 4H), 2.62 (dd, J = 17, 8 Hz, 2H), 1.31 (t, J = 7 Hz, 6H), 1.05 - 0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 127.3 (d, J_{PCC} = 5 Hz), 120.2 (d, J_{PCCC} = 11 Hz), 63.3 (d, J_{POC} = 4 Hz), 35.9 (d, J_{PC} = 54 Hz), 16.6 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 144.0 (q, J_{PB} = 81 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 42.9 (dq, J_{BP} = 86 Hz, J_{BH} = 95 Hz); HRMS (EI) calcd for $C_7H_{18}BO_2P$ $(M + NH_4)^+$: 194.1481, found: 194.1483.

Benzyl diethoxyphosphinylacetate-borane (Table 5.1, entry 5).

Yield: 25 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.33 (m, 5H), 5.17 (s, 2H), 4.11 - 4.03 (m, 4H), 3.01 (d, J = 10.3 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H), 0.95–0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 165.7, 128.9, 128.8, 67.6, 64.3 (d, J_{POC} = 4 Hz), 38.6 (d, J_{PCC} = 44 Hz), 16.6 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 139.1 (q, J_{PB} = 72 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 42.2 (dq, J_{BP} = 76 Hz, J_{BH} = 95 Hz); HRMS (EI) calcd for $C_{15}H_{22}BO_4P$ $(M + NH_4)^+$: 302.1693, found: 302.1695.

Diethoxy(diethoxyphosphinoylmethyl)phosphonite-borane (Table 5.1, entry 6).

Yield: 52 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.22 - 4.08 (m, 8H), 2.46 (dd, J = 20.8, 10.6 Hz, 2H), 1.38 - 1.31 (m, 12H), 1.20 - 0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.9 (d, J_{POC} = 4 Hz), 62.5 (d, J_{POC} = 6 Hz), 29.3 (dd, $J_{P(O)C}$ = 137 Hz, $J_{P(BH3)C}$ = 43 Hz), 16.4

(d, J_{POCC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 138.8 (q, J_{PB} = 80 Hz), 19.9 (s); ^{11}B NMR (CDCl3, 28.88 MHz) δ - 41.4 (dq, J_{BP} = 80 Hz, J_{BH} = 95 Hz); HRMS (EI) calcd for $C_9H_{25}BO_5P_2$ (M_H): 285.1192, found: 285.1191.

Diethoxy benzyloxymethylphosphonite-borane (Table 5.1,entry 7).

Yield: 89 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 - 7.24 (m, 5H), 4.66 (s, 2H), 4.20 - 4.04 (m, 4H), 3.77 (s, 2H), 1.32 (dt, J = 7 Hz, 6H), 1.10–0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.3,128.7, 128.2, 75.4 (d, J_{PCOC} = 8 Hz), 67.7 (d, J_{PC} = 70 Hz), 63.9 (d, J_{POC} = 5 Hz), 16.8 (d, J_{POCC} = 5 Hz); ^{31}P NMR (CDCl3, 121.47 MHz) δ 138.0 (q, J_{PB} = 83 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 43.0 (dq, J_{BP} = 81 Hz, J_{BH} = 94 Hz); HRMS (EI) calcd for $C_{12}H_{22}BO_3P$ $(M + NH_4)^+$: 274.1743, found: 274.1749.

Diethoxy 3-pyridylmethylphosphonite-borane (Table 5.1, entry 8)

Yield: 69 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 - 8.47 (m, 2H), 7.63 - 7.60 (m, 1H), 7.28 - 7.25 (m, 1H), 4.08 - 3.90 (m, 4H), 3.14 (d, J = 11 Hz, 2H), 1.25 (t, J = 7.2 Hz, 6H), 1.00–0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 150.9 (d, J_{PCC} = 5 Hz), 148.3 (d, J_{PCCCNC} = 3 Hz), 138.0 (d, J_{PCCC} = 4 Hz), 123.5 (d, J_{PCCCC} = 3 Hz), 64.2 (d, J_{POC} = 4 Hz), 35.8 (d, J_{PC} = 53 Hz), 16.7 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 143.0 (q, J_{PB} = 76 Hz); ^{11}B NMR (CDCl3, 28.88 MHz) δ - 43.0 (dq, J_{BP} = 76 Hz, J_{BH} = 87 Hz); HRMS (EI) calcd for $C_{10}H_{19}BNO_2P$ (M + H): 228.1325, found: 228.1325.

Diethoxy (2-hydroxy-hex-5-enyl)phosphonite-borane (Table 5.1, entry 9).

Yield: 36 - 50%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85 - 5.74 (m, 1H), 5.10 - 4.92 (m, 2H), 4.22 - 3.90 (m, 4H), 2.57 (s, 1H), 2.39 - 2.10 (m, 2H), 2.04 - 1.94 (m, 2H), 1.74 - 1.58 (m,

2H), 1.33 (t, J = 7.0 Hz, 6H), 1.20–0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.1, 115.1 (d, $J_{PCCCCCC}$ = 2 Hz), 65.8, 63.5, 38.4 (d, J_{PC} = 54 Hz), 37.5(d, J_{PCCC} = 9 Hz), 29.8,16.7 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$,121.47 MHz) δ 146.8 (q, J_{PB} = 86 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 42.2 (dq, J_{BP} = 81 Hz, J_{BH} = 90 Hz); HRMS (EI) calcd for $C_{10}H_{24}BO_3P$ $(M + NH_4)^+$: 252.1900, found: 252.1907.

Reaction of 116 with carbonyl compounds.

Diethoxy (hydroxymethyl)phosphonite-borane (Eq. 5.7).

To diethoxyphosphine-borane **116** (0.408 g, 3 mmol, 1.0 equiv.) in CH_3CN (5 mL) were added diisopropylethylamine (1.05 mL, 6 mmol, 2.0 equiv.) and paraformaldehyde (0.184 g, 6 mmol, 2.0 equiv.) at rt. The solution was stirred at reflux for 6 h. The reaction mixture was then concentrated in vacuo, and the resulting residue was partitioned between H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3 X 20 mL) and the combined organic layers washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes / EtOAc, 100:0 to 80:20, v/v) produced the expected compound 23 (2.01 mmol, 334 mg, 67%) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.22 - 4.08 (m, 4H), 3.91 (s, 2H), 2.54 (s, 1H), 1.34 (dt, J = 7.2 Hz, 6H), 1.10 - 0.00 (m, 3H); ^{13}C NMR (CDCl3, 75.45 MHz) δ 64.0 (d, J_{POC} = 5 Hz), 60.8 (d, J_{PC} = 67 Hz), 16.7 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 138.8 (q, J_{PB} = 80 Hz); ^{11}B NMR (CDCl3, 28.88 MHz) δ - 43.8 (dq, J_{BP} = 80 Hz, J_{BH} = 94 Hz); HRMS (EI) calcd for $C_{10}H_{24}BO_3P$ $(M + NH_4)^+$: 184.1274, found: 184.1271.

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VITA

Monika Iwona Antczak was born January 29, 1978, in Hajnowka, Poland. She is the daughter of Lidia and Henryk Antczak. She received a Master of Science – Engineer degree with a major in Biotechnology from Wroclaw University of Technology, Poland, in September 2002.

In February 2002, she received the Erasmus/Socrates Fellowship and joined Dr. Jean-Luc Pirat's group at Ecole Nationale Superieure de Chimie de Montpellier, UMR – CNRS 5076, France as a research assistant.

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In August 2003, she enrolled in the chemistry Ph.D. program at Texas Christian University, Fort Worth, TX, to pursuit research in Organic Chemistry. While working on her doctorate in Chemistry, she worked as a Graduate Teaching Assistant for four semesters. In September 2005, she was awarded with the Outstanding Student Seminar Award. She has currently five publications.

ABSTRACT

NEW METHODOLOGIES FOR THE SYNTHESIS OF

ORGANOPHOSPHORUS COMPOUNDS

by Monika I. Antczak, Ph.D., 2008

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The work presented in this dissertation focus on the development of new methodologies for the preparation of organophosphorus compounds. A review of the most relevant literature in terms of the preparative methodologies and reactivity of *H*-phosphinic acid, phosphonic acids and phosphine-borane derivatives is provided in Chapter I. The following chapter describes the addition of hypophosphorous compounds to unsaturated substrates in the presence of metal-catalysts or radical initiators. A novel alkyne hydrophosphinylation catalyzed by nickel chloride or its hydrate, in the absence of added ligand, was discovered and explored in the synthesis of various important organophosphorus compounds. The AIBN-initiated radical addition of alkyl phosphinates to alkenes and alkynes provides alkyl-*H*-phosphinates in good yield and more importantly offers one of the best synthetic approach for the preparation of *trans*-alkenyl-phosphinates. Straightforward application to the synthesis of biologically active GABA

(γ-aminobutyric acid) analogs using AIBN-initiated radical hydrophosphinylation is also demonstrated. The synthesis of novel GABA analogs using methods developed in the Montchamp group and their biological evaluation is discussed in Chapter III. In Chapter IV the synthesis of a various functionalized organophosphorus compounds *via* organoboranes is reported. In some cases, selective migration of one group attached to boron can be observed. Phosphonite-borane complexes are introduced as novel synthons for the synthesis of phosphinic esters. The synthesis and the reactivity of these novel complexes are expanded in Chapter V.