CARBON-PHOSPHORUS BOND FORMATION

NEW METHODOLOGIES FOR THE PREPARATION OF ORGANOPHOSPHORUS COMPOUNDS OF BIOLOGICAL INTEREST

by

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LIST OF ABBREVIATIONS

Ac	Acetyl
AHP	Anilinium hypophosphite
AIBN	Azobisisobutyronitrile
Alk	Alkyl
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BOC	*tert*-Butyl carbamate
BSA	*N,O*-Bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
Cbz	Benzyloxycarbonyl
conc.	Concentrated
Cy	Cyclohexyl
dba	Dibenzylideneacetone
de	Diasteromeric excess
DEA	N,N-Diethylamine
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide

DMSO	Dimethylsulfoxide
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
GABA	γ-Aminobutyric acid
Hex	Hexyl
HMDS	Hexamethyldisilazane
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazane
M. P.	Melting point
Me	Methyl
Men	Menthyl
MS	Mass spectroscopy
MW	Microwaves
Nu	Nucleophile
Oct	Octyl
Pent	Pentyl
Ph	Phenyl
Pht	Phthalimide
Piv	Pivaloyl

Pr	Propyl
PTC	Phase Transfer Catalysis
Pyr	Pyridine
RCM	Ring-closing metathesis
r.t.	Room temperature
TBAF	Tetrabutylammonium fluoride Xantphos 9,9-Dimethyl-4,5 bis(diphenylphosphino)xanthene
TBDMS	tert-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosylate
Z (CBZ)	Benzyl carbamate

Chapter One: Background, Preparation and Reactivity of Organophosphorus compounds.

Over the last few decades, interest in the synthesis of organophosphorus compounds has grown tremendously.[1] This attention is a direct outcome of developing applications for phosphorus compounds, as well as a comprehension of their role in biological systems.[1] Organophosphorus compounds are important in a variety of applications, from medicines to pesticides, from ligands in catalysis, to extractants and flame-retardants.[1] Phosphorus is very abundant in nature, and its organic chemistry is based on the existence of a wide range of stable functional groups that contain a carbon-phosphorus bond or that are organic derivatives of inorganic phosphorus acids (esters). Phosphorus-containing compounds can be arbitrarily classified in eight major classes (Table 1.1).

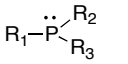
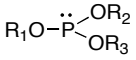
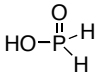
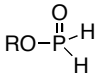
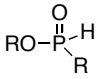
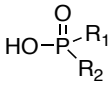
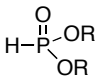
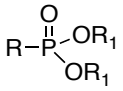
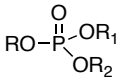
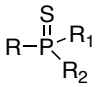
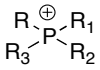
Table 1.1 Classification of phosphorus compounds

Phosphorus Compounds	Linkages
Oxyphosphorus	P-O
Carbophosphorus	P-C
Azaphosphorus	P-N
Metallophosphorus	P-Metal
Boranophosphorus	P-B
Silaphosphorus	P-Si
Thiaphosphorus	P-S
Halophosphorus	P-Halogen

Organophosphorus compounds are identified in a more descriptive nomenclature by their coordination number, σ (the number of directly attached atoms, i.e., the number of σ bonds), and their valency, λ (used to describe the total number of bonds, including "π-bonds", and thus represents the valence of phosphorus) (Chart 1.1). For example, while common phosphines will be described as σ^3,λ^3, an alkyl ester of phosphoric acid $(RO)(OH)_2P(=O)$ will be described as

σ^4,λ^5 (since four atoms are attached to P and is four-coordinate with a formal double bond to oxygen).

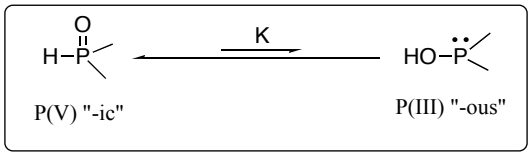
Chart 1.1 Nomenclature of some common organophosphorus species

R_1= R_2= H; R_3=alkyl, aryl R_1=H; R_2= R_3=alkyl, aryl R_1= R_2= R_3=alkyl, aryl	Primary phosphine Secondary phosphine Tertiary phosphine		σ^3,λ^3
Phosphites			σ^3,λ^3
Hypophosphorous acid			σ^4,λ^5
R= cation R= alkyl	Hypophosphite Alkyl phosphinate or alkyl hypophosphite		σ^4,λ^5
R= H R= alkyl	*H*-phosphinic acid *H*-phosphinate		σ^4,λ^5
Phosphonic acid or Disubstituted phosphinic acid			σ^4,λ^5
R= H R= alkyl	Phosphorous acid *H*-phosphonate or Dialkyl phosphite		σ^4,λ^5
R= H R= alkyl	Phosphonic acid Phosphonate		σ^4,λ^5
Phosphate R= R_1= R_2= H	Phosphoric acid		σ^4,λ^5
Phosphine Sulfides			σ^4,λ^5
Phosphonium			σ^4,λ^4

Phosphorus-containing compounds play a pivotal role in living organisms as carriers of genetic information and as important signaling, regulatory, energy transfer, and structural compounds.[2] Due to these key roles, biologically important phosphorus compounds have become therapeutic targets in modern medicinal research.[1,2] A particular class of organophosphorus compounds is constituted by phosphorus containing acids, [P(O)(OH)].

Specific members of this group are characterized by the presence of a phosphinylidene [P(O)(H)] moiety that acts as a bridge between the P(V) and the P(III) forms via a tautomeric equilibrium (Scheme 1.1).

Scheme 1.1 Phosphinylidene moiety (P(=O)H) and P-H tautomerism

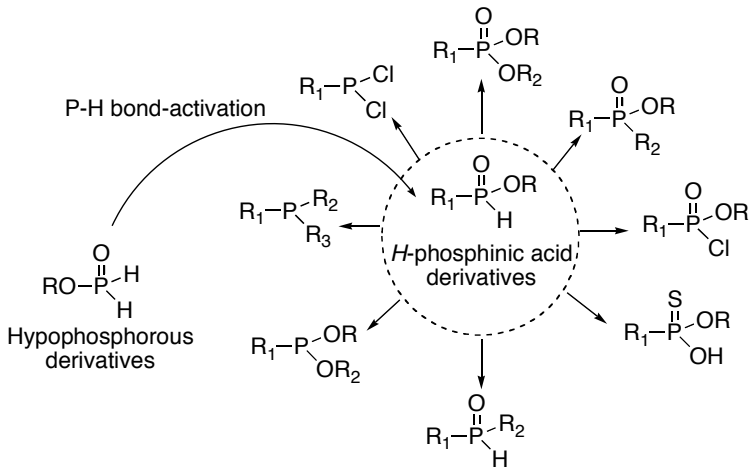


H_3PO_2 K~ 10^{-12}
$(RO)_2P(O)(H)$ K~ 10^{-6}

1.1 *H*-phosphinic acid derivatives, versatile synthetic precursors of organophosphorus compounds

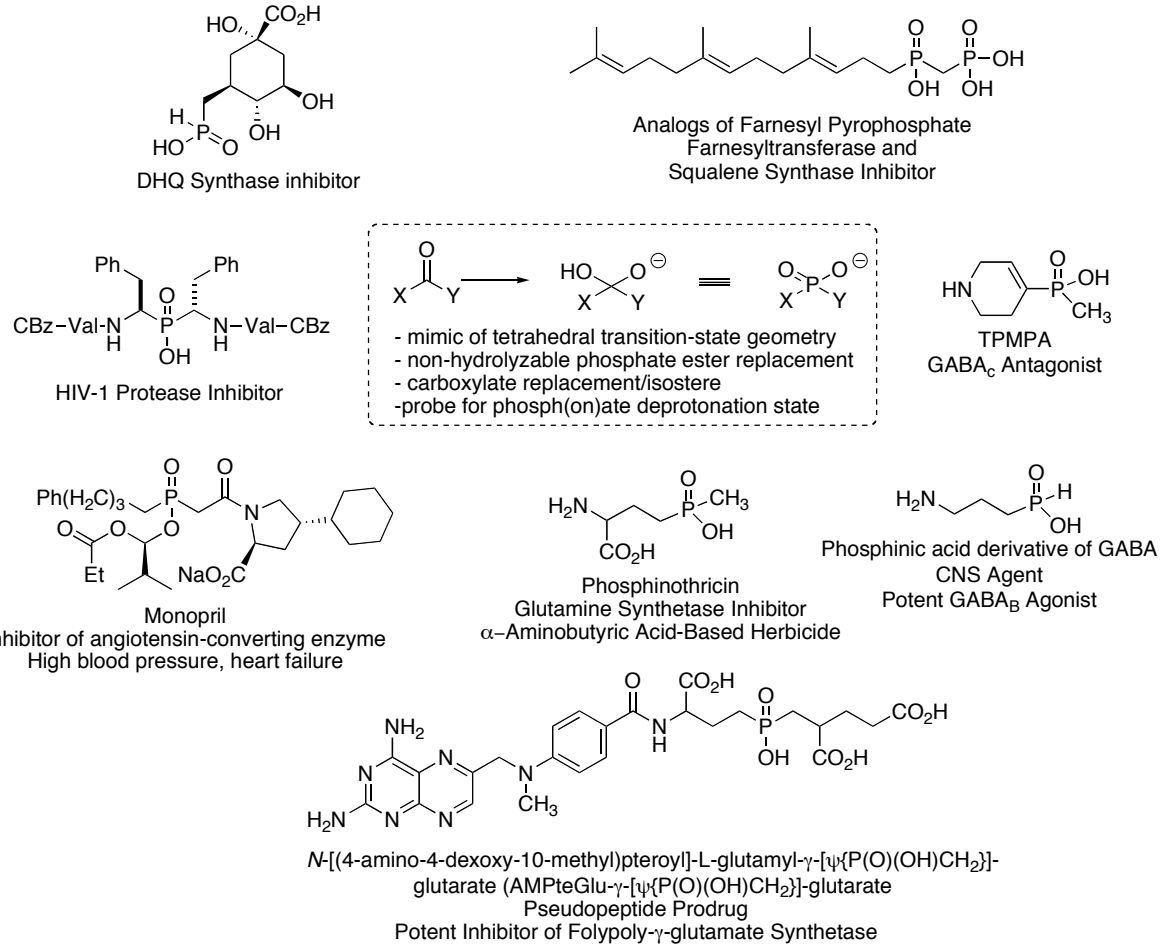
Still underexploited, this particular class of compounds contains valuable synthetic intermediates for the preparation of other more common phosphorus functionalities, including phosphinates, phosphonates, secondary phosphine oxides, as well as primary phosphines, to name a few examples (Scheme 1.2).[3]

Scheme 1.2 Transformation of *H*-phosphinic acid derivatives



Specifically, they are useful intermediates in the synthesis of disubstituted phosphinic acids, which can mimic tetrahedral transition states in enzyme-catalyzed reactions (e.g., proteases and esterases).[4k,4l] Phosphinic acids are extensively studied to achieve pharmaceutical activity through the potent inhibition of these enzymes.[4] Chart 1.2 summarizes some representative examples of biologically active phosphinic acids.[1,5]

Chart 1.2 Examples of biologically active phosphonic acids[1,5]



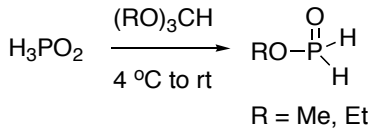
Phosphinic acids are used to replace labile phosphate groups with a non-hydrolyzable equivalent.[6] Phosphinic acids are also employed to probe the deprotonation states in some enzymes,[7] although this has generally not been exploited systematically since, until recently,

highly functionalized *H*-phosphinic acids were not readily available. Additionally, because of the tetrahedral phosphorus (Chart 1.2), they can replace the carboxylic acid moiety in important biological compounds, allowing an extra site of functionalization which can impart some selectivity for a particular receptor.[8] The human immunodeficiency virus type-1 proteinase (HIV-1 proteinase) (EC 3.4.23.16) is a member of the family of aspartyl retroviral proteinases.[9] This proteinase plays an important role in viral replication. Therefore, it is widely recognized as a potential target for chemotherapy of the acquired immunodeficiency syndrome (AIDS).[10] Inhibition of HIV-1 proteinase by phosphinic acid analogs of the heptapeptide substrate of the enzyme was introduced by Dreyer.[11] The scissile bond was replaced with the phosphinic acid moiety mimicking a hydrolytic transition state (Chart 1.2). Lastly, *H*-phosphinic acids can act as synthetic precursors via chemical oxidation,[12] or possibly as pro-drugs of biologically-active phosphonates (i.e. bisphosphonates)[13] through *in vivo* oxidation.[4a]

1.1.1 Preparation of *H*-phosphinic acid derivatives via P-C bond formation

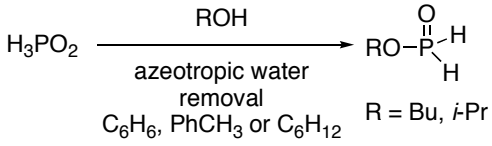
1.1.1.1 Preparation of alkyl phosphinate precursors

Hypophosphite esters (alkyl phosphinates, $(RO)P(O)H_2$) are important precursors of *H*-phosphinic acid derivatives.[1,14] These organophosphorus compounds are relatively sensitive to moisture, air, and heat (by undergoing hydrolysis, decomposition and disproportionation), which complicates handling. Several methods have been described for the preparation of alkyl phosphinates, however, only a few are commonly used.[14] In the early sixties, Fitch described the preparation of methyl and ethyl phosphinates by esterification of crystalline hypophosphorous acid (H_3PO_2) with orthoformates (Eq 1.1).[15] This method has two main drawbacks which are the use of hazardous crystalline H_3PO_2 and the formation of side products.[16]



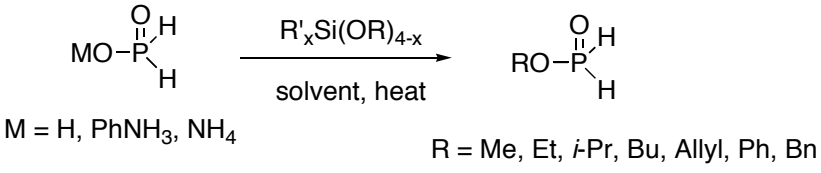
(Eq. 1.1)

A direct esterification of H_3PO_2 with alcohols under azeotropic water removal was discovered by Nifant'ev (Eq. 1.2).[17] This method suffers from the thermal decomposition of the starting materials that competes with formation of the product, which consequently lowers the reaction yield. More recently, the preparation of alkyl phosphinates derived from certain alcohols via transesterification reactions with $MeOP(O)H_2$ have also been described.[18]



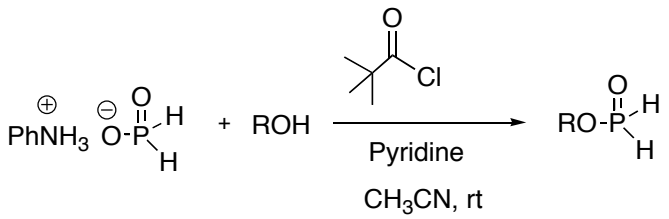
(Eq. 1.2)

The two most general methods for the preparation of alkyl phosphinates have been discovered by Montchamp and coworkers.[19,20] H_3PO_2 and its anilinium or ammonium salts are esterified with alkoxysilanes, yielding alkyl phosphinates in good yields (Eq. 1.3).[20]



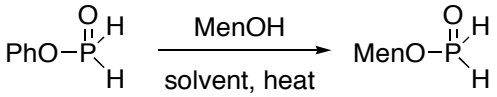
(Eq. 1.3)

Hypophosphite amine salts react with alcohols in the presence of pivaloyl chloride (Eq. 1.4).[19,20]



(Eq. 1.4)

Alkyl phosphinates for which the corresponding alkoxysilane is not commercially available can be prepared by transesterification of $PhOP(O)H_2$ (Eq. 1.5), affording the desired products in excellent yields. This reaction can be performed in a variety of solvents, and unlike other methods, the resulting alkylphosphinates are more thermally robust.



(Eq. 1.5)

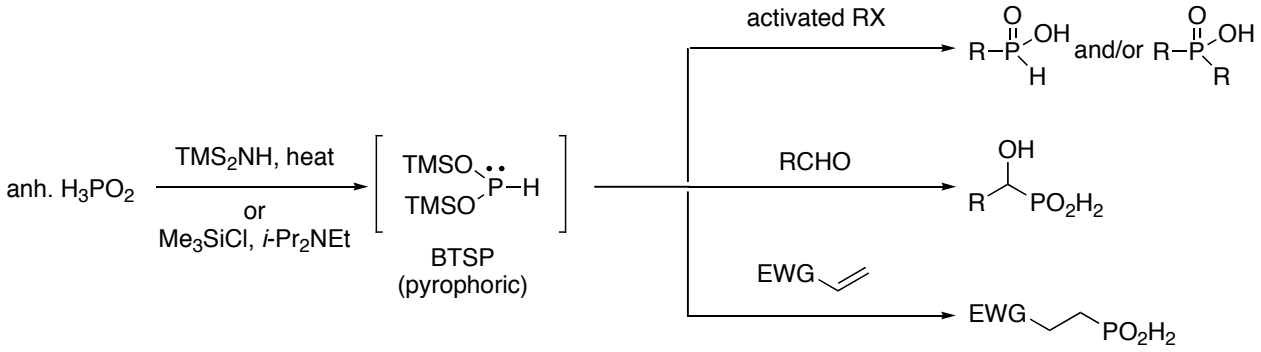
At 80 °C, methyl phosphinate prepared by the alkoxysilane method decomposes only slightly after 20 h (Eq. 1.3), whereas total decomposition is observed after 1 h when the Fitch method (Eq. 1.1) is used at the same temperature. Such unprecedented thermal stability opened up a number of possibilities for synthetic applications, provided that the organosilicon by-products do not interfere. Stock solutions of alkylphosphinates can be stored at room temperature under nitrogen for over a month, with less than 10% decomposition.

1.1.1.2 Nucleophilic addition and substitution reactions of silyl phosphonites

Initially introduced by Voronkov in 1970,[22a] bis(trimethylsiloxy)phosphine ($(TMSO)_2PH$, BTSP) has been described by Boyd and Regan as a useful synthon for the synthesis of *H*-phosphinic acids.[22b-22d] BTSP is prepared *in situ* from phosphinate amine salts and an excess of $TMSCl/Et_3N$ (0 °C to rt) or HMDS (110 °C) (Scheme 1.3). Due to its extreme pyrophoric nature, the isolation and the use of BTSP is normally avoided.[23] The preparation of *H*-

phosphinic acids is performed by addition of highly reactive alkyl halides or α,β-unsaturated esters (Scheme 1.3).

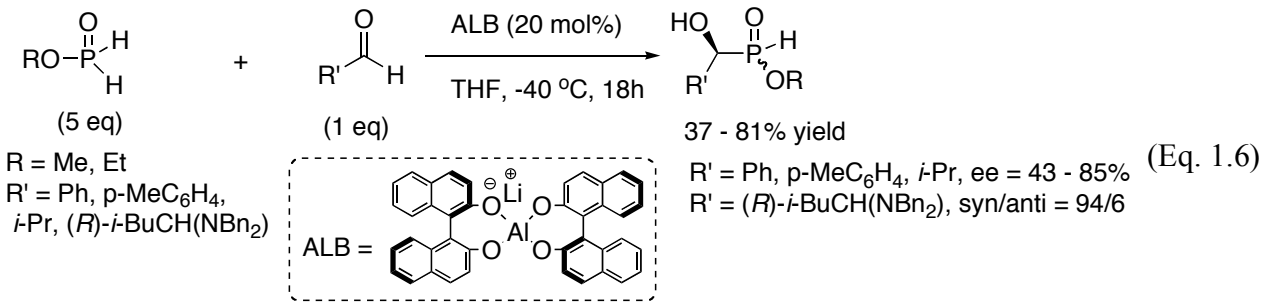
Scheme 1.3 Synthesis of *H*-phosphinic acids from silyl phosphonites



This methodology has found some practical application,[24] however several problems in terms of reactivity[4e] and selectivity towards formation of monosubstituted phosphinic acids were encountered. The reaction requires the use of a large excess of BTSP in order to avoid the formation of symmetrical disubstituted phosphinates.

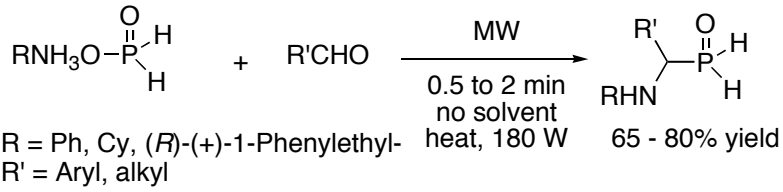
1.1.1.3 Nucleophilic addition reactions of hypophosphorous derivatives

Hypophosphorous compounds add to carbonyl groups and to Michael acceptors.[20] This transformation was first reported following a thermal hydrophosphinylation of aldehydes with the highly unstable methyl phosphinate, generated *in situ* from anhydrous H_3PO_2 and methyl orthoformate.[15,18a] An elegant asymmetric version of this transformation catalyzed by Al-Li-BINOL complexes was recently reported by Shibuya (Eq. 1.6).[25]



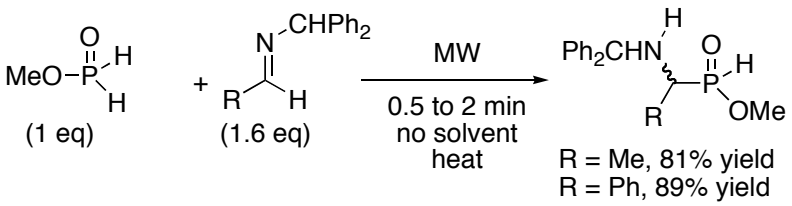
(Eq. 1.6)

The preparation of α-amino-*H*-phosphinic acids usually consists of heating anhydrous hypophosphorus acid with a Schiff base.[26] These methods involve harsh reaction conditions, long reaction times, which leads to side reactions.[18a] In 2003, Kaboudin reported an efficient and general method for the synthesis of α-aminophosphinic acids from hypophosphorous salts with aldehydes under solvent-free conditions and microwave irradiation (Eq. 1.7).[27] The use of hypophosphorous salts (anilinium hypophosphite), introduced by Montchamp,[28] prevents the problems associated with handling anhydrous H_3PO_2. The application of hypophosphorous salts is advantageous since these are highly crystalline, high-melting, inexpensive, and non hygroscopic solids.



(Eq. 1.7)

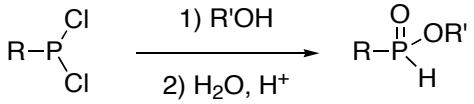
Cristau and coworkers employed a similar reaction for the preparation of phosphinodipeptide analogs (Eq. 1.8).[29]



(Eq. 1.8)

1.1.1.4 Hydrolysis or alcoholysis of dichlorophosphines

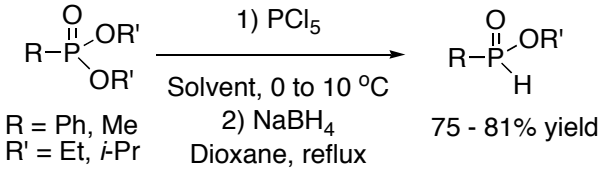
Inexpensive and available, phenyl-*H*-phosphinic acid PhP(O)(OH)H is prepared by hydrolysis of $PhPCl_2$,[30] a compound itself obtained by the Friedel-Crafts reaction of benzene with PCl_3.[30] Also, the addition of $PhPCl_2$ to some alcohols has been described to prepare *H*-phosphinate esters.[31] Other $RPCl_2$ compounds are available but they are expensive, hazardous and very reactive, making this method impractical (Eq. 1.9).



(Eq. 1.9)

1.1.1.5 Reduction of chlorophosphonates

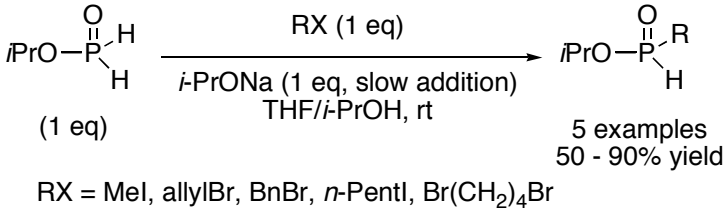
The direct selective reduction of phosphonate diesters $RP(O)(OR')_2$ is another possible approach.[32] It is a stepwise process in which phosphonates must first be converted into chlorophosphonate RP(O)(OR)Cl,[33] followed by the reduction with sodium borohydride.[34] This methodology suffers from some limitations in terms of functional group tolerance (Eq 1.10).



(Eq. 1.10)

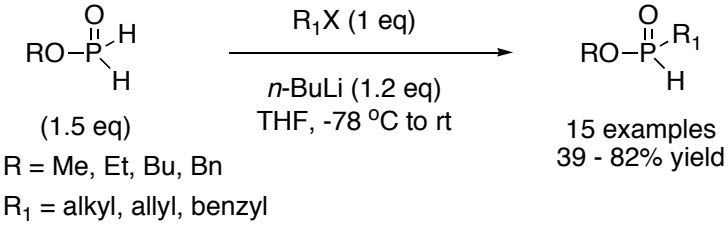
1.1.1.6 Direct alkylation of alkyl phosphinates

The alkylation of isopropyl phosphinate using alkyl halides and sodium isopropoxide as base (Eq. 1.11) was reported by Gallagher and coworkers.[35] However, this method has not found a widespread use, due to the fact that under these conditions, less hindered alkyl phosphinates cannot be alkylated because of rapid decomposition of the anion formed upon deprotonation of unhindered alkyl phosphinates.[36]



(Eq. 1.11)

Recently, Montchamp et al. established a butyllithium-promoted alkylation of primary alkyl phosphinates with reactive electrophiles, such as alkyl iodides and allylic/benzylic bromides (Eq. 1.12).[37] This direct alkylation is also promoted by DBU in refluxing acetonitrile with the most reactive alkyl halides.



(Eq. 1.12)

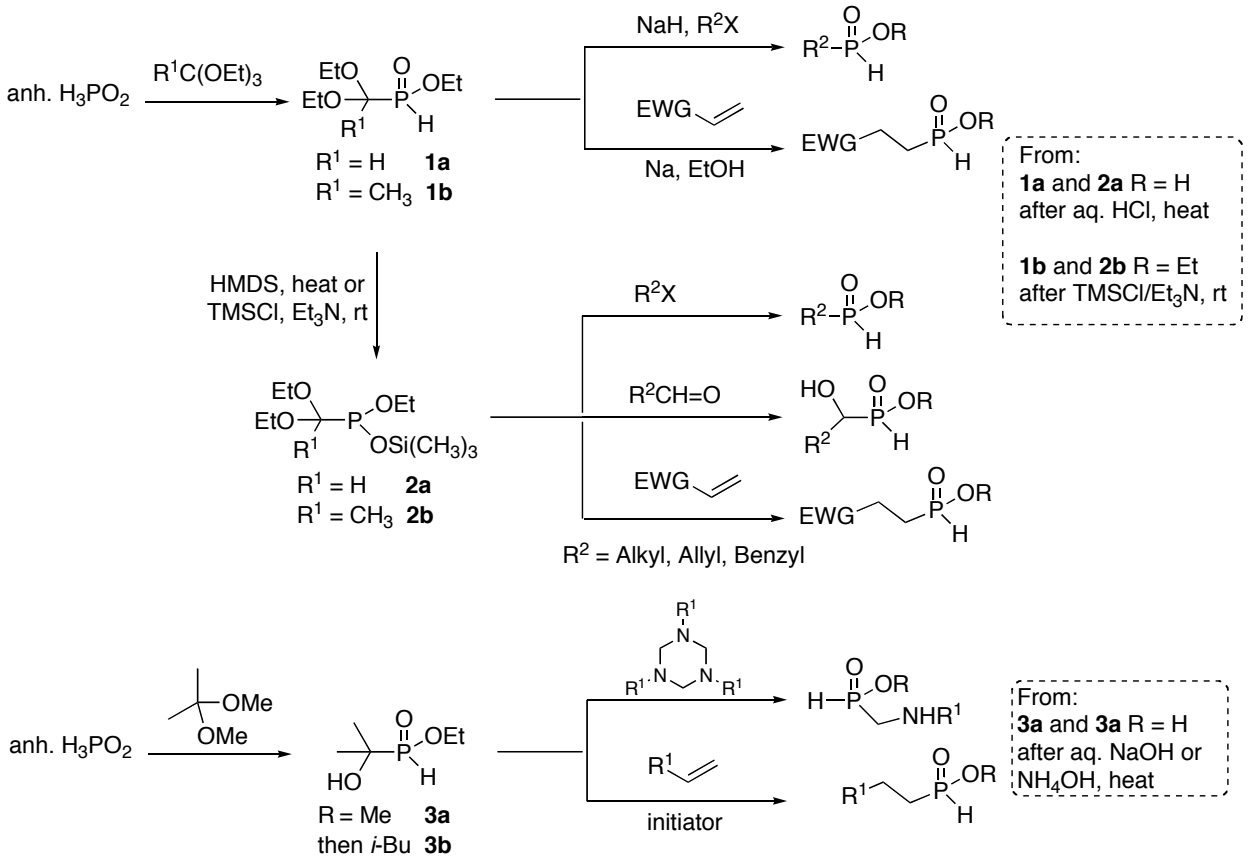
1.1.1.7 Ciba-Geigy methodology

For the preparation of α-, β-, and γ-amino-*H*-phosphinic acids, chemists at Ciba-Geigy introduced the masked hypophosphorous acid synthons **1**, **2**, **3** (Scheme 1.4).[4a-b,38]

The so-called "Ciba-Geigy" reagents exhibit a protected form of hydrogen connected to phosphorus, which solves certain limitations but must rely on a protection-deprotection strategy.

Additionally, the acidic deprotection of the acetal is not always compatible with functionalized compounds.

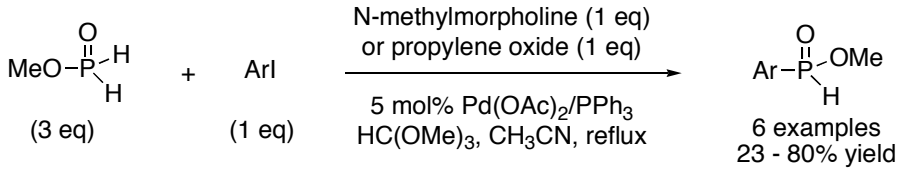
Scheme 1.4 Preparation of *H*-phosphinic acids from Ciba-Geigy synthons



The first generation of reagents uses 1,1-diethoxymethyl as protecting group **1a** and **2a** (Scheme 1.4), which requires vigorous acidic conditions for its removal (aq. HCl, 100 °C).[38a-c] The second generation of reagents uses a slightly modified ketal protecting group (1,1-diethoxyethyl) **1b** and **2b** (Scheme 1.4), cleavable under milder conditions (excess TMSCl in chloroform, at room temperature)[38d] while reagent **3** employs a 1-hydroxyalkyl protecting group, stable to acid but sensitive to basic conditions (aq. NH_4OH or NaOH, 50-80°C).[38e]

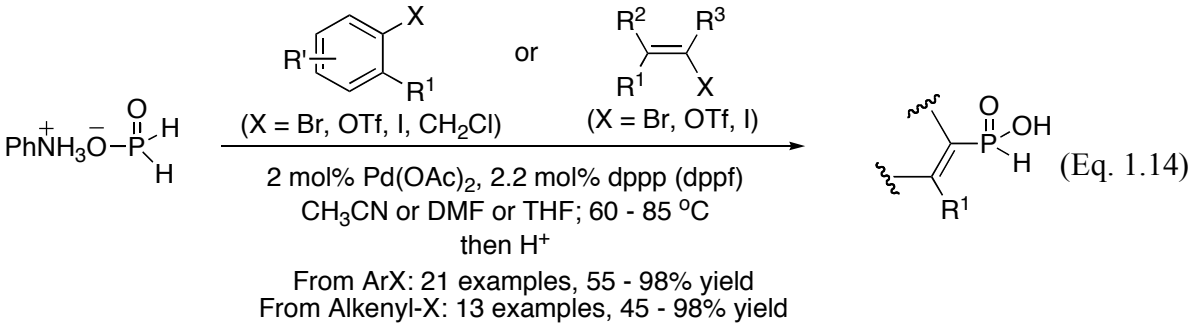
1.1.1.8 Cross-coupling reactions of aryl, alkenyl, benzylic, and allylic electrophiles

Holt reported one example of cross-coupling between triethylammonium hypophosphite and a steroid-derived dienyl triflate, but the generality of the reaction was not established.[39] Schwabacher and coworkers developed a few years later a palladium-catalyzed cross-coupling of aryl iodides with methyl- or *tert*-butyl-phosphinates prepared *in situ*, using Fitch's orthoformate method (Eq. 1.13).[18a,40]



(Eq. 1.13)

The Montchamp group made a significant contribution in this field with the development of Pd-catalyzed cross-coupling reactions of hypophosphite salts with aryl halides and alkenyl bromides and triflates (Eq. 1.14).[28,41]

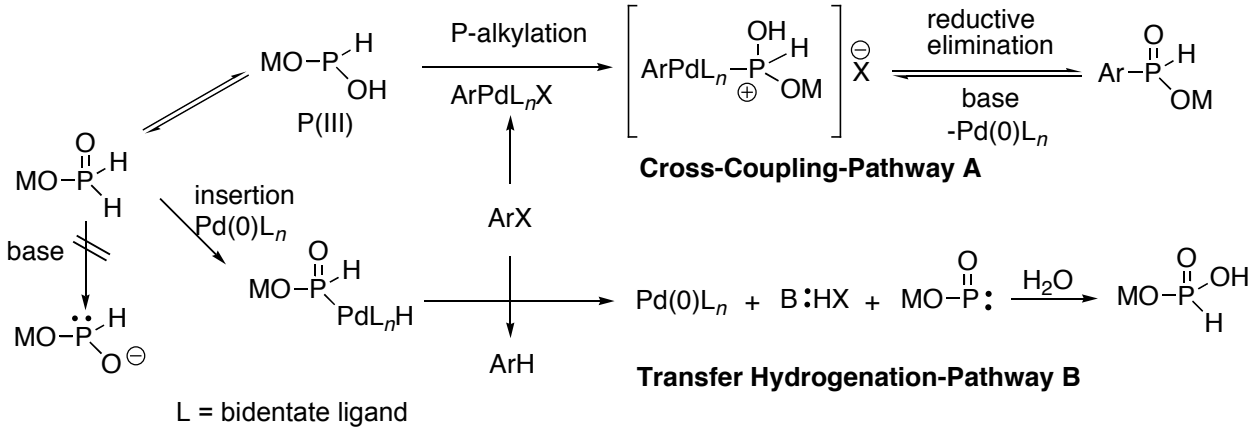


(Eq. 1.14)

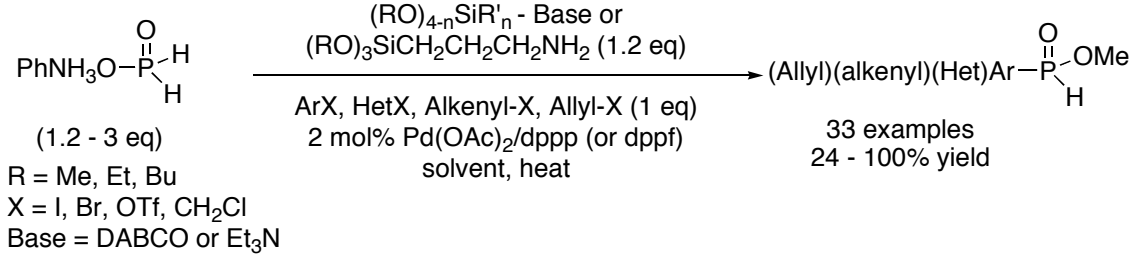
The proposed mechanism indicated that oxidative addition of the metal into the C-X and P-H bonds are two competitive processes. Also, the ligand around the metal controls the partition between them (Scheme 1.5). The competitive reduction was found to decrease significantly when $Pd(OAc)_2$/dppp (2 mol% or less) is used as the catalyst in place of $Pd(PPh_3)_4$.

Moreover, the coupling of an activated aryl chloride was reported for the first time.[28] Cross-coupling with alkenyl electrophiles sometimes required the use of dppf[42] instead of dppp as ligand because of the steric hindrance due to a *syn* substituent.[41]

Scheme 1.5 Cross-coupling and transfer hydrogenation competing pathways



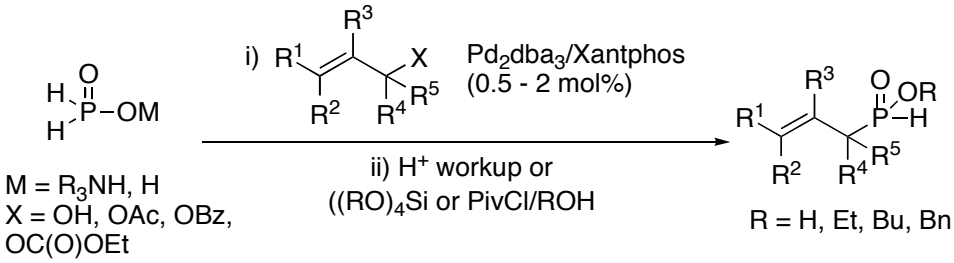
A direct cross-coupling of alkyl phosphinates with a wide range of aryl, heteroaryl, and alkenyl, as well as some allylic electrophiles was developed by Montchamp and coworkers, using the alkoxysilane method (Eq 1.15).[43,44]



(Eq. 1.15)

In terms of cross-coupling reactions of hypophosphorous acid derivatives with allylic electrophiles, the first reports have been published by the Montchamp group, yielding allylic *H*-phosphinates (Eq. 1.16 and Scheme 1.6).[44,45] Based on mechanistic studies, a general catalytic system for the cross-coupling of hypophosphorous compounds with activated allylic

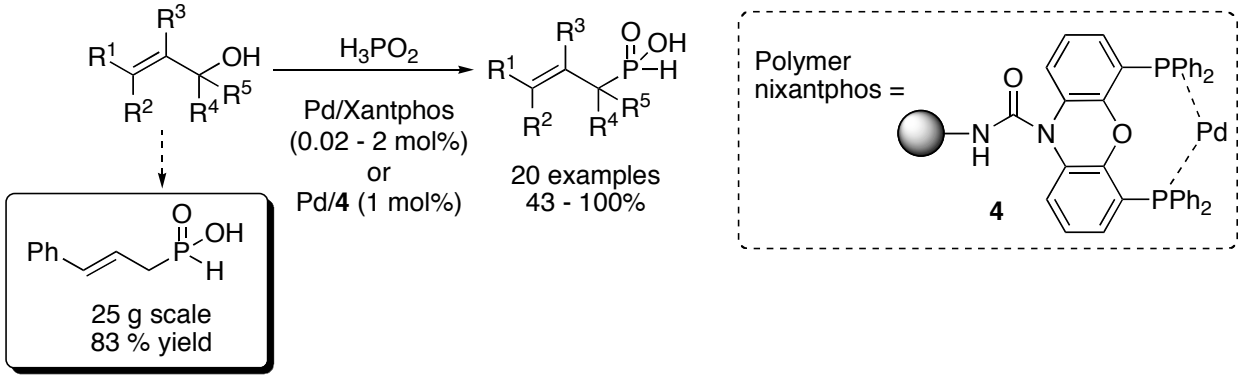
electrophiles (acetates, benzoates, and carbonates) was elucidated, leading to the development of an effective and practical synthesis of allylic *H*-phosphinic acids (Eq. 1.16).[45c] The acid products can be isolated in good yields by a simple extractive workup, esterified *in situ* to the corresponding *H*-phosphinate esters, or oxidized *in situ* to allylic phosphonates.



(Eq. 1.16)

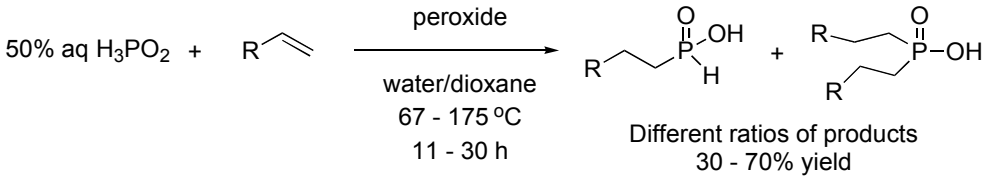
Further investigation into the allylation mechanism provided access to a Pd-catalyzed rearrangement of preformed allylic phosphinates esters,[45c] and ultimately, to a catalytic dehydrative allylation of hypophosphorous acid with allylic alcohols, which proceeds in the absence of any additives.[45a-45d] This process constitutes an environmentally benign and highly atom-economical approach to *H*-phosphinic acids (Scheme 1.6). The reaction also works using a polystyrene supported catalyst **4**, allowing the recovery (by filtration) and recycling of the palladium catalyst.[45a]

Scheme 1.6 Pd-Catalyzed dehydrative allylation of hypophosphorous acid with allylic alcohols



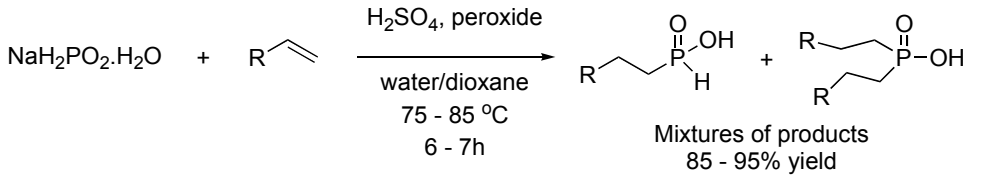
1.1.1.9 Free-radical hydrophosphinylation reactions of alkenes and alkynes

Additions of phosphorus-centered radicals as P-C bond-forming reactions are well documented.[46] Williams and Hamilton reported the addition of aqueous H_3PO_2 to olefins initiated by organic peroxides at high temperatures (Eq. 1.17).[47] The use of hazardous crystalline H_3PO_2 increased the reaction yields.[48,49] Formation of *H*-phosphinic acids and disubstituted phosphinic acids mixture was usually observed.

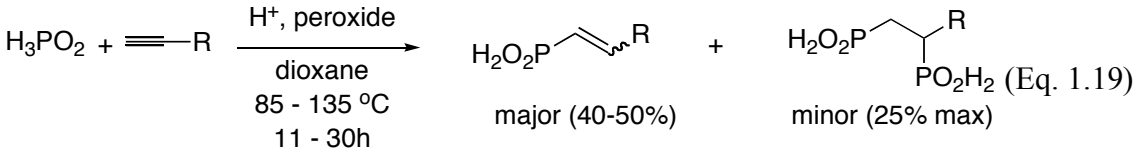


(Eq. 1.17)

Nifant'ev and coworkers contributed significantly to the development of this methodology.[50] Addition of H_3PO_2 or sodium or potassium hypophosphite salts to alkenes (Eq. 1.18) and alkynes (Eq. 1.19) is performed in the presence of peroxides and mineral or organic acids. Although the use of acid enables lowering the temperature of the reaction by also helping the breakdown of the peroxide initiator, these conditions are not compatible with acid-sensitive functionalities. Karanewsky found that the use of AIBN in refluxing ethanol provided the desired products,[51] however the conditions were strongly acidic and therefore incompatible with acid-sensitive functional groups.



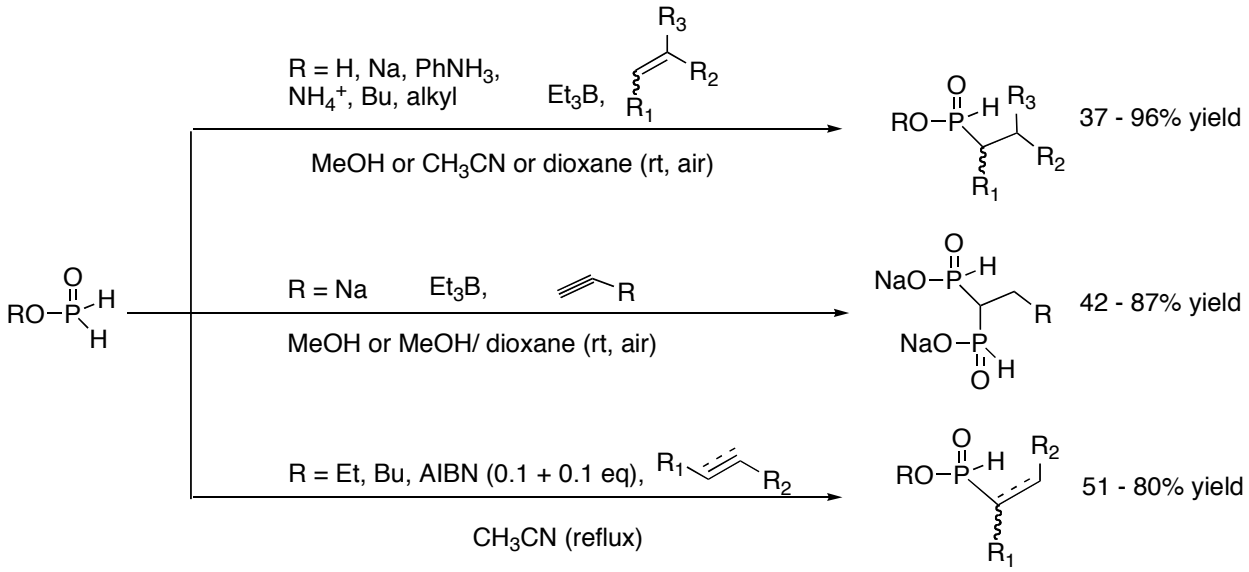
(Eq. 1.18)



(Eq. 1.19)

Montchamp et al. developed a highly efficient approach for the free-radical addition of hypophosphorous compounds to unsaturated substrates (Scheme 1.7).[52]

Scheme 1.7 Montchamp's free radical reactions of hypophosphorous compounds

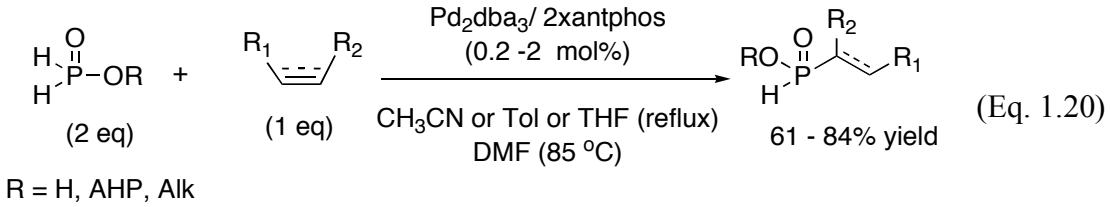


In a flask open to air, the addition of H_3PO_2 [its salts (AHP and $NaOP(O)H_2$), as well as alkyl phosphinates] to alkenes occurs at room temperature, using Et_3B/O_2 as initiator.[52] Additionally, the room temperature radical addition of $NaOP(O)H_2$ to terminal alkynes affords the previously unknown 1-alkyl-1,1-bis-*H*-phosphinates,[12,54] novel precursors of the biologically important 1,1-bisphosphonates.[13] This new radical-based methodology has found significant applications by various research groups, such as the synthesis of an intermediate of an inhibitor of Folypoly-γ-Glutamate Synthetase via hydrophosphinylation of vinylglycine.[55] Notably, the preparation of this intermediate previously failed with other conventional approaches.[4e]

At 80 °C, the AIBN-initiated hydrophosphinylations of alkenes and alkynes with alkyl phosphinates also proceeds successfully.[53]

1.1.1.10 Metal-catalyzed hydrophosphinylation

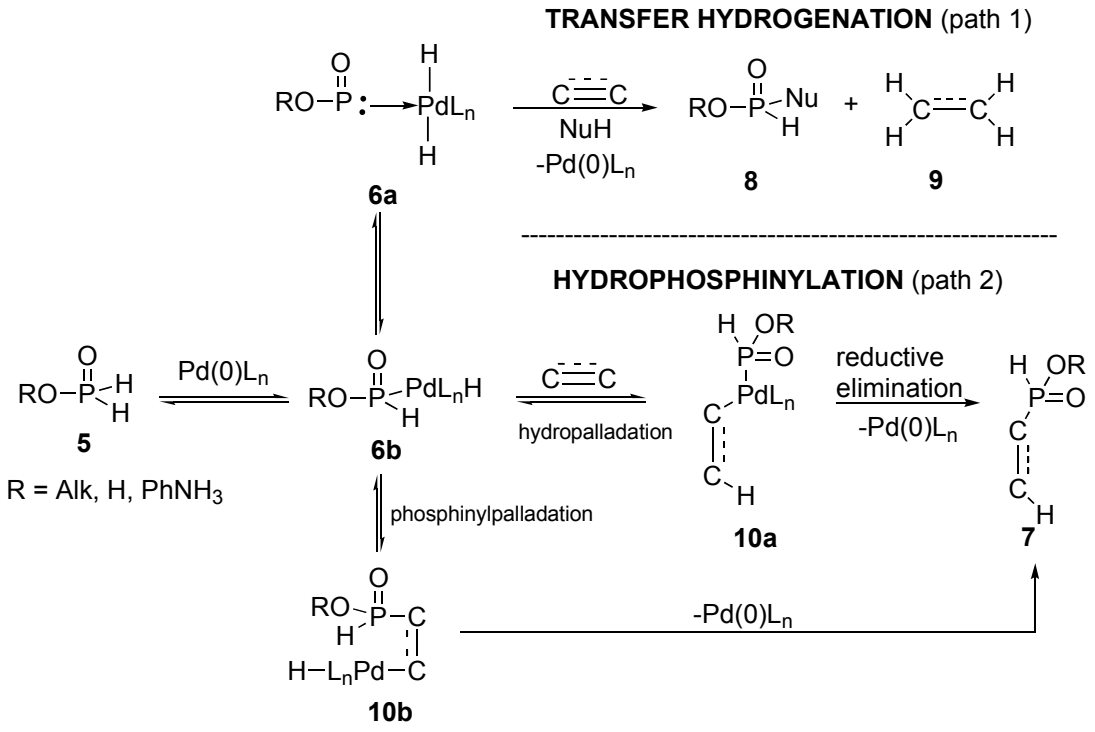
Montchamp and coworkers invented the metal-catalyzed hydrophosphinylation of hypophosphorous derivatives with unsaturated substrates.[19] A remarkably general Pd-catalyzed addition of H_3PO_2, AHP and alkyl phosphinates to alkenes and alkynes under homogeneous catalytic conditions was initially developed, yielding *H*-phosphinic acid derivatives in high yields (Eq. 1.20).[56] Noteworthy is the fact that this reaction does not require strictly anhydrous conditions.



(Eq. 1.20)

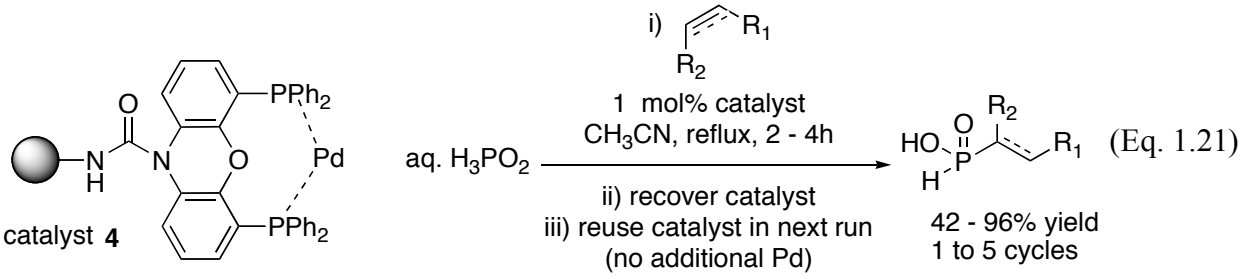
The competing transfer hydrogenation could be minimized, depending on the choice of ligand complexed to the Pd (Scheme 1.8).

Scheme 1.8 Postulated mechanistic pathways in the Pd-catalyzed hydrophosphinylation reaction



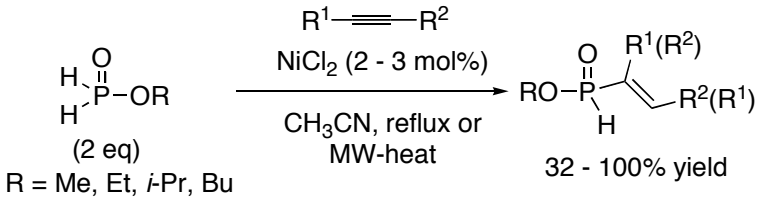
The proposed mechanism involves oxidative addition of Pd(0) into the P-H bond to form **6b** and then the reactive species palladium hydride **6a**, which can lead to undesired **8** or **9** via transfer hydrogenation. It was proposed to trap species **6b** through hydropalladation to form **10a** or through phosphinylpalladation to form **10b**, which would then undergo reductive elimination to form the desired *H*-phosphinate product. This method would require a ligand that slows down the β-hydrogen elimination from **6b** to **6a**. The most useful catalytic system was found to be Pd_2dba_3/xantphos, where loadings as low as 0.02 mol% Pd gave good conversions. [56]

An environmentally friendly variant of this method was developed, using the water-tolerant, recyclable polymer-supported catalyst **4** (Eq. 1.21).[57] The ligand can even be used with Pd/C to furnish a doubly-heterogeneous reusable catalyst.



(Eq. 1.21)

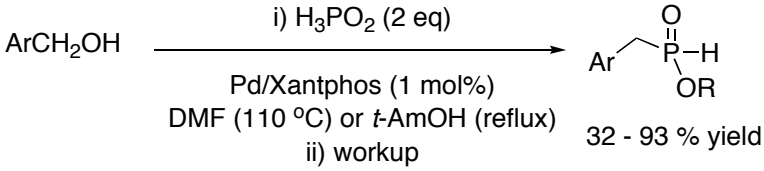
The Montchamp group also discovered a nickel-catalyzed hydrophosphinylation of internal and terminal alkynes with alkyl phosphinates (Eq. 1.22).[58] Syntheses of various important organophosphorus compounds were performed using nickel chloride or its hydrate. The reaction also proved to work efficiently under microwave heating, reducing considerably the reaction times. Current developments in phosphorus–carbon bond formation by hydrophosphinylation have been recently reviewed.[45e]



(Eq. 1.22)

1.1.1.11 Metal-catalyzed benzylation of hypophosphorous acid

The first cross-coupling of benzylic alcohols was discovered by Montchamp and coworkers (Eq 1.23).[59] The benzylic alcohols are employed without prior activation (as esters, carbonates, or halides). When DMF gave poor results, *tert*-amyl alcohol (*t*-AmOH) was used as a solvent. This methodology provides a green, PCl_3-free route to benzylic-*H*-phosphinic acids.



(Eq. 1.23)

1.1.2 Brief examples in the reactivity of *H*-phosphinic acid derivatives

Much has been published about the reactivity of *H*-phosphinic acids and esters. Some of them are listed below and selected examples will be discussed in this section:

(a) Arbuzov-like reactions

(b) Base-promoted alkylation

(c) Nucleophilic addition reactions

(d) Oxidation and oxidative esterification reactions (see Section 1.2.2.2)

(e) Displacement reactions with organometallic reagents

(f) Reduction to primary and secondary phosphines

(g) Preparation of phosphonothioic and boranophosphonic acids (Chapter II)

(h) Halogenation and reductive halogenation reactions

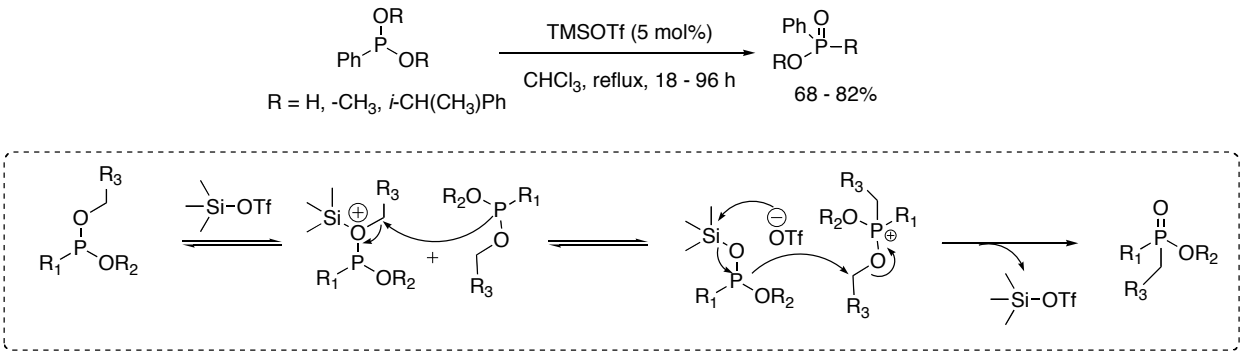
(i) Metal-catalyzed and free radical hydrophosphinylation reactions

(j) Cross-coupling reactions

1.1.2.1 Arbuzov-like reactions of *H*-phosphinic acid derivatives

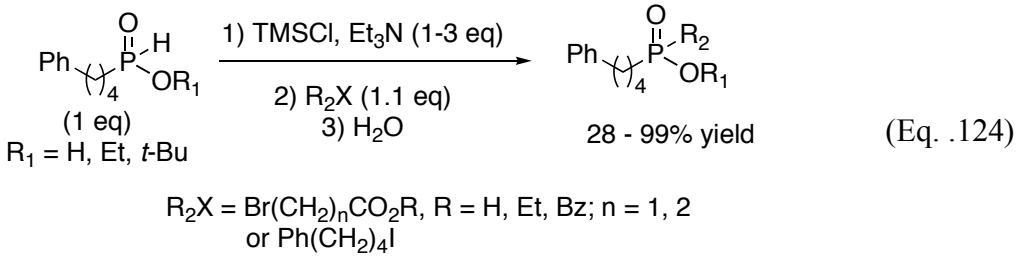
The Michaelis-Arbuzov rearrangement is a classical approach for the synthesis of disubstituted phosphinates.[60] This methodology involves the reaction of a phosphonite $R^1P(OR^2)(OR^3)$ with an alkyl halide (Scheme 1.9).[60a-d]

Scheme 1.9 Lewis acid catalyzed Michaelis-Arbuzov rearrangement of phosphonites



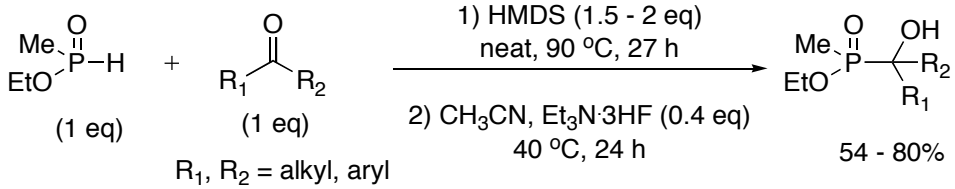
This rearrangement was shown to be catalyzed by Lewis acids (5 mol% of TMSOTf or BF_3•OEt_2) only in the case of primary or activated secondary alkyl groups, under milder conditions.[60e,60f]

Thottathil initially reported the stepwise silylation, then alkylation of *H*-phosphinates (silyl-Arbuzov reaction) with the use of reactive bromoacetates as electrophiles (Eq. 1.24).[61]



(Eq. .124)

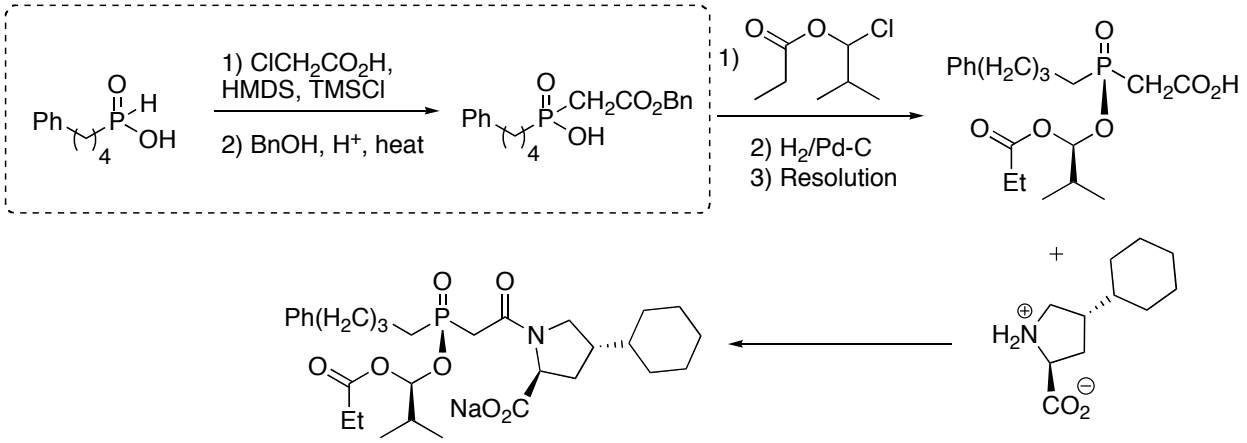
Hansen has reported an efficient reaction involving the use of trimethylsilyloxy derivatives of *H*-phosphinates with aldehydes and ketones (Eq. 1.25).[62]



(Eq. 1.25)

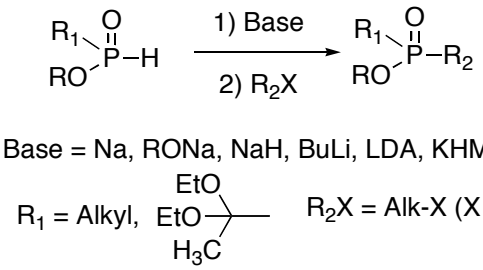
While Boyd and Regan prepared both symmetrical and unsymmetrical disubstituted phosphinic acids using highly reactive halides,[22a] Majewsky reported the formation of symmetrical disubstituted phosphinates by reaction BTSP with highly reactive halides (benzyl, allyl and α-carbonyl).[63] This methodology has found extensive applications in the synthesis of relevant biologically active molecules, such as γ-aminopropyl-*H*-phosphinic acids (GABA analogs),[4a-b] phosphasugars,[64] the commercial heart drug Monopril® (fosinopril sodium) (Scheme 1.10),[3h] MMP's inhibitors,[65] or pseudopeptides as some inhibitors of the human cyclophilin hCyp-19,[66] to name a few.

Scheme 1.10 Preparation of Monopril®



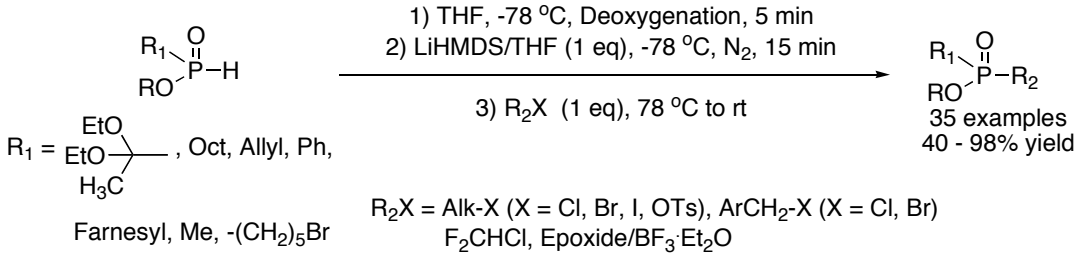
1.1.2.2 Base-promoted alkylation

Numerous examples of base-promoted *H*-phosphinate alkylation (Michaelis-Becker type reactions) have been reported, employing various bases (Na, RONa, NaH, BuLi, LDA, KHMDS) (Eq. 1.26).[4a-b,38,67]



(Eq. 1.26)

Recently, Montchamp and coworkers developed a general protocol for the direct alkylation of *H*-phosphinates using LiHMDS as the base (Eq. 1.27).[68] The phosphorus nucleophile, base, and electrophile were used in equimolar quantities. The reaction works with alkyl halides, including primary alkyl chlorides. Several GABA analogs or their precursors were synthesized.

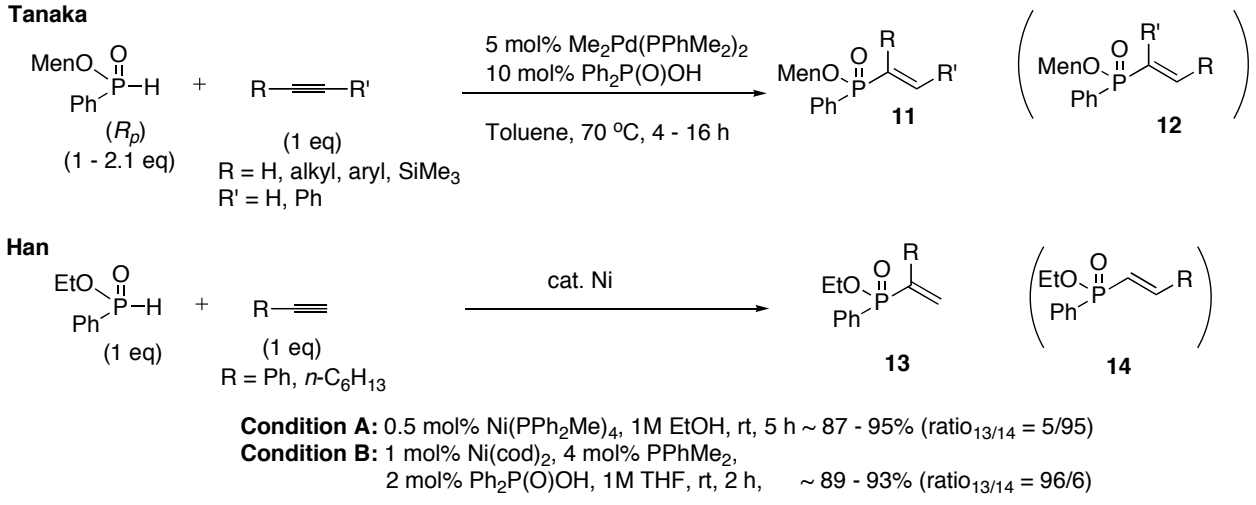


(Eq. 1.27)

1.1.2.3 Metal-catalyzed hydrophosphinylation

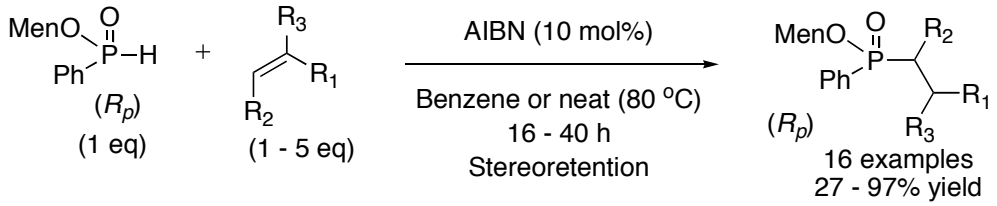
As discussed in section 1.1.1.10, the metal-catalyzed hydrophosphinylation of unsaturated compounds is directed by the oxidative addition of the metal into the P-H bond (Scheme 1.8). Only two papers reported the insertion of metals into the P-H bond of *H*-phosphinates (Scheme 1.11).[69,70] Tanaka developed a highly regioselective Pd-catalyzed hydrophosphinylation of (R_p)-menthyl phenyl-*H*-phosphinate with alkynes.[69] Han developed a regioselective Ni-catalyzed hydrophosphinylation where ethyl phenyl-*H*-phosphinate adds to terminal alkynes.[70]

Scheme 1.11 Metal-catalyzed hydrophosphinylation reactions of *H*-phosphinates



1.1.2.4 Free radical and microwave-assisted hydrophosphinylation

Addition of *H*-phosphinates to unsaturated substrates was initially promoted by the use of radical initiators such as benzoyl peroxide and AIBN.[47] This methodology has shown some drawbacks, such as the requirement of specialized radical initiators, harsh reaction conditions, use of large excess of one of the reagents.[71] On the other hand, Montchamp described that phenyl(aryl)-*H*-phosphinates undergo addition to olefins in the presence of Et_3B/air, at room temperature.[52] A few years later, Han and coworkers developed a stereospecific addition of (R_p)-menthyl phenyl phosphinate to alkenes which is promoted by AIBN in refluxing benzene (Eq. 1.28).[72]

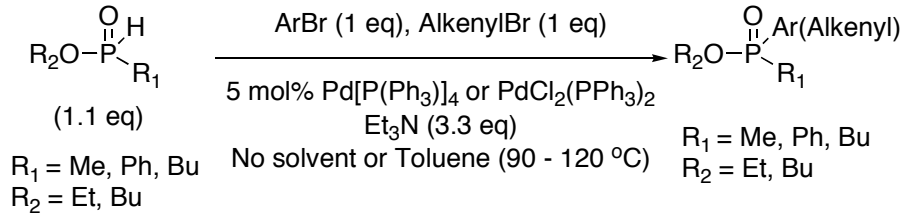


(Eq. 1.28)

R_1 = Alk, OR, SR, PR_2, $Si(OR)_3$, SnR_3,
$P(O)(OR)_2$, $P(O)R_2$, OAc, $-(CH_2)n$
R_2 = H, $-(CH_2)n$
R_3 = H, Me

1.1.2.5 Cross-coupling reactions

Xu *et al.* first discovered the cross-coupling reaction of *H*-phosphinates with aryl and alkenyl bromides.[73,74] In the presence of Pd-catalysts and a base, the halides cross-coupled efficiently with phenyl-*H*-phosphinate,[73a] and alkyl-*H*-phosphinate esters (Eq. 1.29).[73b] The same group reported that cross-coupling with enantiomerically pure (*S*)- and (*R*)-isopropyl methyl-*H*-phosphinates occurred with complete retention of configuration.[74]



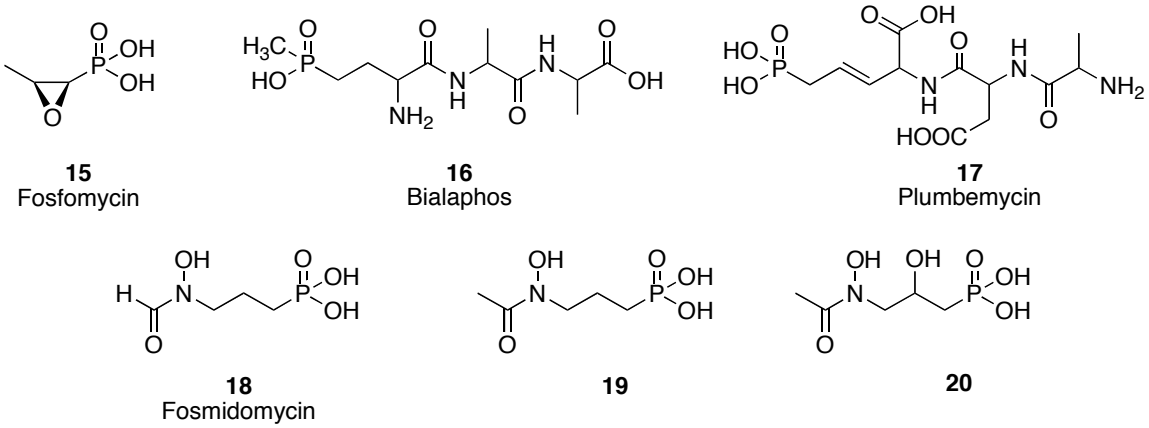
(Eq. 1.29)

1.2 Phosphonic acid derivatives and pyrophosphate analogs

1.2.1 Phosphonic acid derivatives as biologically important compounds

Most of the characterized organophosphorus compounds with substantial antibiotic activity are aminophosphonic acids (**16-20**, Chart 1.3).[78]

Chart 1.3 Examples of organophosphorus compounds with antibiotic activity



15
Fosfomycin

16
Bialaphos

17
Plumbemycin

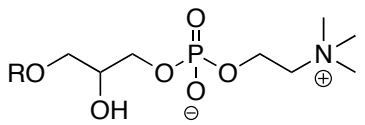
18
Fosmidomycin

19

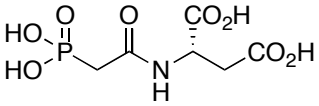
20

Anti-tumor properties[79] were found in a wide range of organophosphorus compounds (Chart 1.4) ranging from esters (**21**) to amino acid derivatives (**22**), as well as antiviral properties[80] with the clinically used Foscarnet (**23**) as an example.[1] The latter is known to inhibit viral DNA polymerase and is found to be active against HIV and the Epstein-Barr virus.[1]

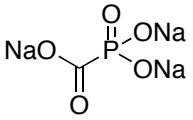
Chart 1.4 Examples of organophosphorus compounds with anti-tumor and anti-viral activities



21
phosphate ester



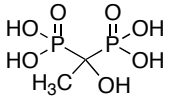
22
N-phosphonacetyl-L-aspartate
(PALA)



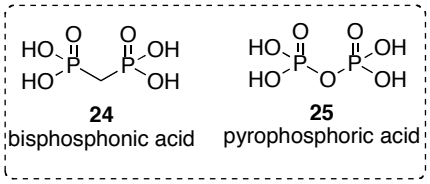
23
trisodium phosphonoformate
(Foscarnet)

The principle of replacing oxygen by a methylene has resulted in a major breakthrough in the treatment of bone diseases such as osteoporosis and Paget's disease.[1b,81,82] The formation and dissolution (resorption) of hydroxyapatite in bone have been found to be inhibited by inorganic pyrophosphate. Bisphosphonic acids **24** (Chart 1.5) are isosteric with pyrophosphoric acid **25** but are hydrolytically stable and, if attracted to bone, might prevent the resorption process.[1,81,82]

Chart 1.5 Biologically active analogues of pyrophosphates

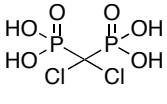


26
Etidronate

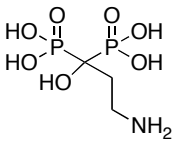


24
bisphosphonic acid

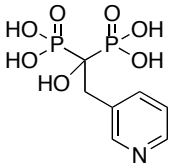
25
pyrophosphoric acid



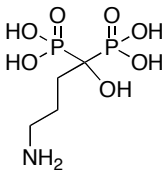
27
Clodronate



28
Pamidronate



29
Risedronate



30
Alendronate
(Fosamax)

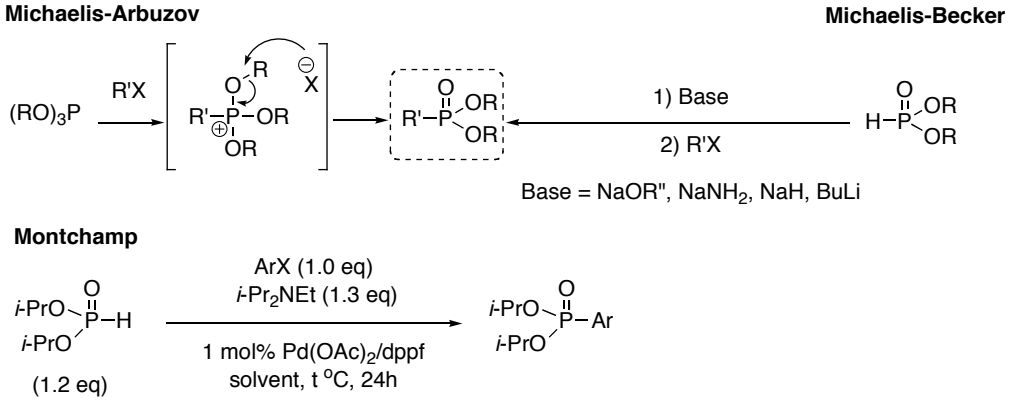
Assorted bisphosphonic acid derivatives containing substitutents on the methylene carbon have been found to exhibit the desired effect on bone diseases (Chart 1.5) and currently, many bisphosphonates are being investigated as a means to deliver a drug to the bone.[1,81,82] Montchamp and coworkers recently developed synthetic methodologies for the preparation of bisphosphorus-containing molecules and the work will be discussed in Chapter V.[12,54]

1.2.2 Preparation of phosphonic acid derivatives via phosphorus-carbon bond formation

1.2.2.1 Preparation of phosphonic acid derivatives using *H*-phosphonate chemistry

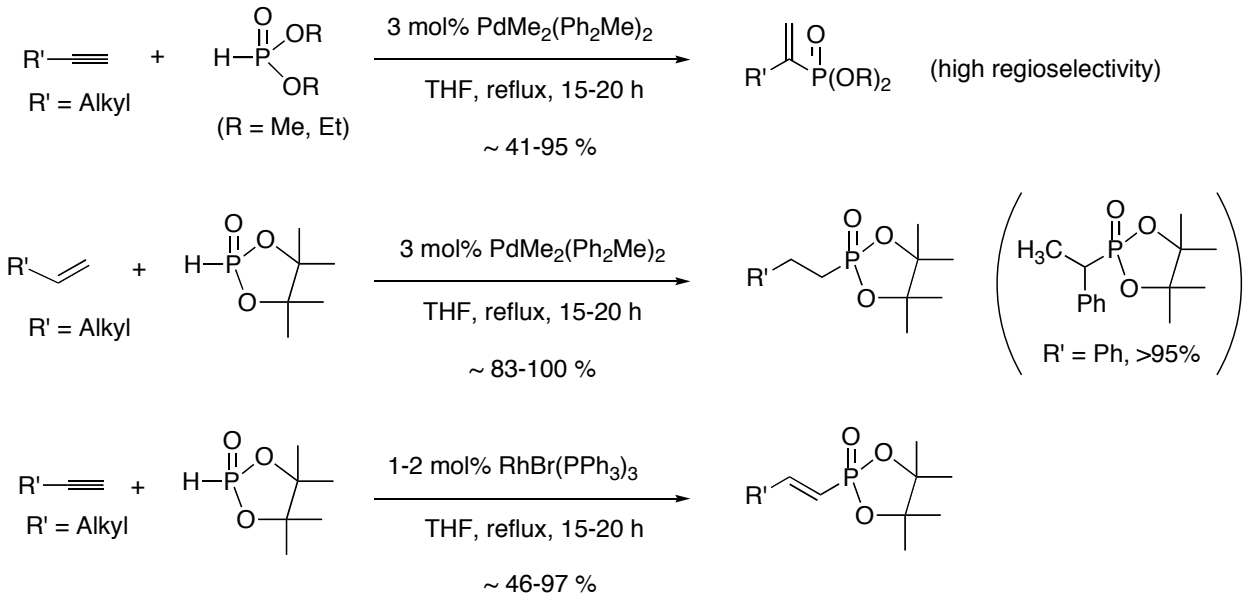
Phosphonate diesters $RP(O)(OR')_2$ are useful precursors of phosphonic acids (Chapter IV),[83] and their hydrolysis can be conveniently conducted following McKenna's protocol,[84] which uses bromotrimethysilane, at room temperature. These precursors are accessible from the corresponding *H*-phosphonate diesters via P-C bond formation. The phosphorus-carbon bonds are usually formed via the Arbuzov[60,85] or Michaelis-Becker[86] reactions, but these methods are not applicable to the synthesis of arylphosphonates (Scheme 1.12). Hirao[87] discovered in the early eighties that metal-catalyzed cross-coupling of *H*-phosphonate diesters with aryl halides provides arylphosphonates, and this methodology was recently improved by Montchamp (Scheme 1.12).[83] The work will be discussed in Chapter IV.

Scheme 1.12 Preparation of phosphonate diesters



Tanaka reported a catalytic hydrophosphonylation of alkenes, alkynes, and allenes with *H*-phosphonates, using palladium- and rhodium-based catalysts (Scheme 1.13).[88] The mechanism of the reaction is based on the insertion of Pd and Rh into the P-H bond of *H*-phosphonates. Tanaka's reaction uses relatively elaborate catalysts, and with alkenes the hydrophosphonylation is limited to pinacol *H*-phosphonate. The latter is a significant limitation because the pinacol phosphonate esters require harsh conditions for cleavage.[89] Therefore the overall approach may not provide significant advantages over the classical Arbuzov or Michaelis-Becker phosphonate syntheses.

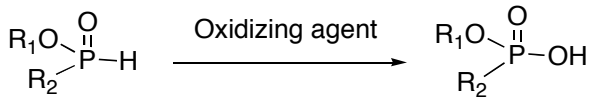
Scheme 1.13 Hydrophosphonylation of alkenes, alkynes and allenes



1.2.2.2 *H*-phosphinic acids as phosphonic acid precursors

Oxidation of *H*-phosphinic acids represent another viable alternative to access phosphonic acids. The preparation of phosphonic acids through oxidation of *H*-phosphinic acids is a well known methodology (Eq. 1.30), which generally requires harsh conditions and strong oxidative agents, such as H_2O_2 (30%, 80 - 90 °C);[90] Br_2, I_2 or Cl_2 in H_2O/DMSO or in conc.

HI/HCl (20 - 75 °C);[26b,91] $HgCl_2$ or HgO in H_2O (90 - 95 °C);[26b,92] $KMnO_4$/KOH in H_2O (50 - 250 °C);[93] H_2SO_4/HNO_3 (100 - 110 °C);[93] $CCl_4/Et_3N/H_2O$ (35°C);[90c,94] pyridinium chlorochromate/TsOH in DMSO;[95] or $NaIO_4$ (50°C),[67e,96] are major disadvantages.



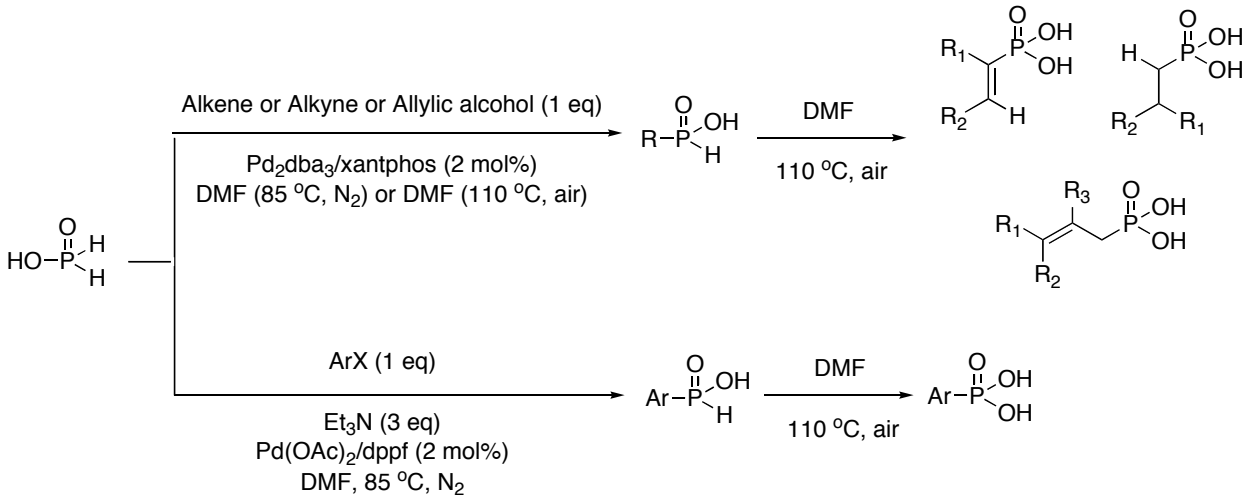
R_1 = H, Alk
R_2 = Ar, Alk

(Eq. 1.30)

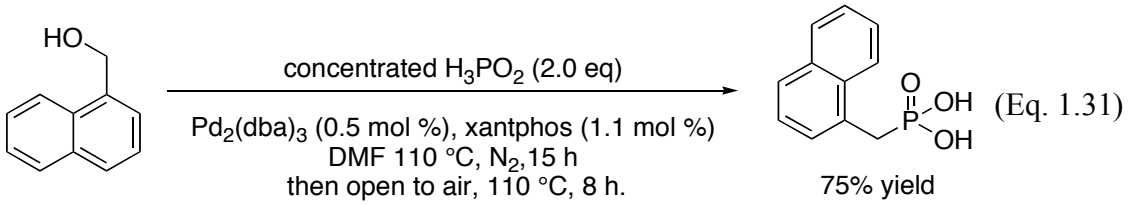
Oxidizing agents: H_2O_2; Br_2; I_2; Cl_2; $NaIO_4$; $KMnO_4$/KOH; $HgCl_2$; H_2SO_4/HNO_3; $CCl_4/Et_3N/H_2O$.

More recently, the Montchamp group discovered a novel access to phosphonic acids via a Pd-catalyzed tandem carbon-phosphorus bond formation/oxidation processes (Scheme 1.14).[28,97] This method provided a variety of phosphonic acids from hypophosphorus acid in very good to quantitative yield.

Scheme 1.14 Montchamp's tandem reactions for the preparation of phosphonic acids



The group also reported the only example of phosphonic acid obtained in a catalytic and environmentally-friendly manner through a one-pot benzylation-oxidation process (Eq 1.31).[59]

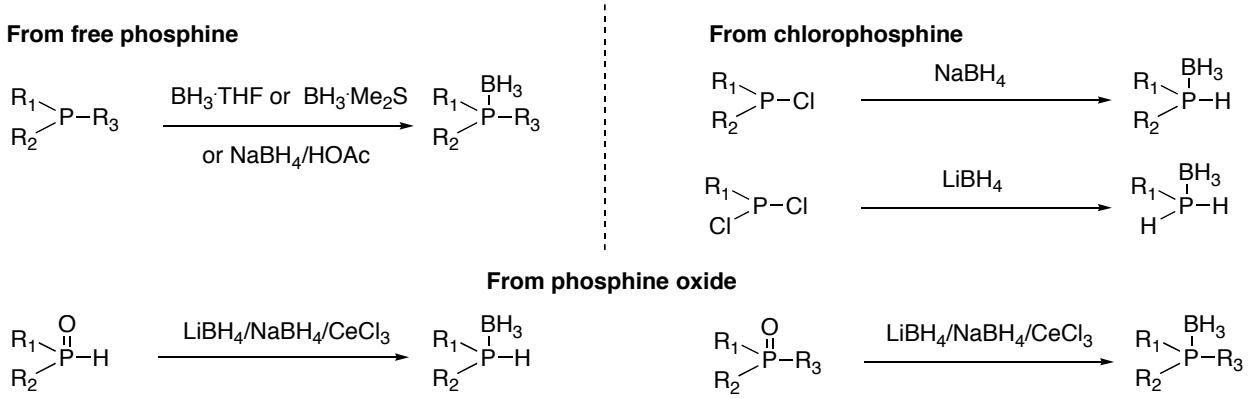


(Eq. 1.31)

1.3 Phosphine-borane complexes, useful organophosphorus synthons

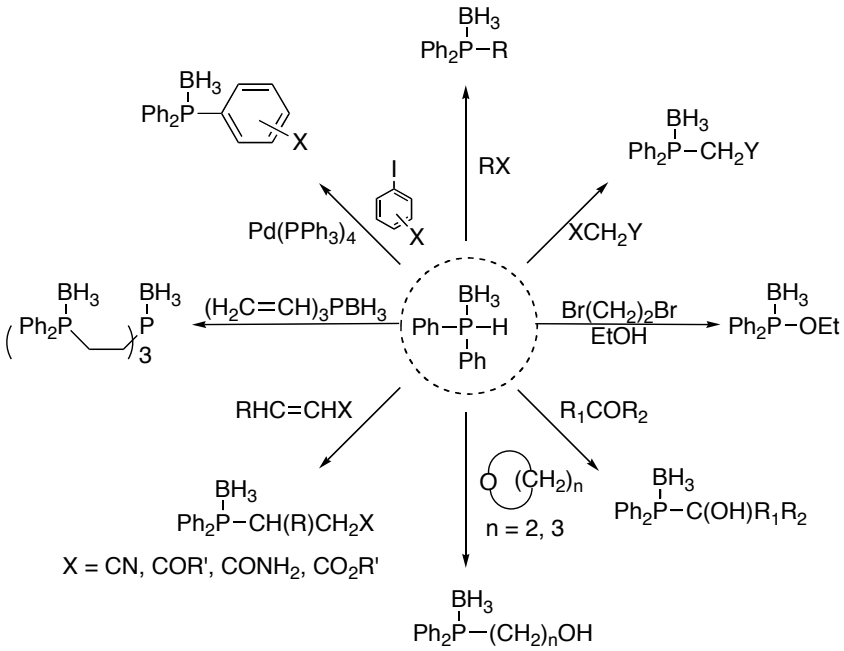
Over the past few years, many articles have been published on the synthetic utility of phosphine-borane complexes as important precursors of phosphine ligands for the preparation of transition metal complex catalysts.[98] Since the first reported synthesis of a phosphine-borane complex over fifty years ago,[99] there has been considerable interest in the preparation and in the controlled reactivity of these phosphine-borane complexes. Applications have been pioneered by Imamoto[100] over the last twenty years or so and now include their use in carbonyl addition,[100] alkene and alkyne additions,[101] alkylation,[100,102] and metal-mediated coupling,[103] as well as conjugate addition processes.[100] The most common synthetic preparations of the phosphine-borane adducts are briefly summarized in Scheme 1.15. Examples include the direct complexation of the free phosphine R_3P with boron adducts,[98c,105] reduction of chlorophosphines with sodium or lithium borohydride,[106] or reduction of secondary and tertiary phosphine oxides[98c] followed by complexation, all affording the corresponding borane complex.

Scheme 1.15 Common synthetic preparations of phosphine-borane complexes



Not only does the BH_3 protect the phosphorus center, but it activates the phosphine toward deprotonation, making the phosphine-borane complexes excellent nucleophiles. These important adducts are valuable substrates in a wide range of organic reactions (Scheme 1.16).[98c] Decomplexation of the borane moiety is typically accomplished with a secondary amine (e.g. diethylamine, morpholine), or with strong acid. The Montchamp group has developed new synthetic methodologies for the preparation of phosphonite-borane complexes.[107,108]

Scheme 1.16 Diphenylphosphine-borane as a nucleophile[98c]



Chapter Two: Organophosphorus functional groups: Synthesis and comparative structural studies of trityl-phosphorus derivatives

2.1 Introduction

Many important and fundamental discoveries about structure, properties, and synthesis, have been made in the modern era of phosphorus chemistry. Organophosphorus compounds are critically important, for example, in the synthesis of pharmaceuticals, herbicides, pesticides, and phosphine ligands. Therefore, methods for the formation of phosphorus-carbon (P-C) bonds continue to receive a significant amount of attention (Chapter I). Chemical and physical properties of these numerous functional groups are well documented.[1] However, no direct comparisons of their structural features has been done. Having such information could be useful in structure-based drug design or in catalysis.[1] This structural information can be obtained with either X-ray crystallography or nuclear magnetic resonance spectroscopy (NMR), or both. Ideally, these two techniques complement one another, and phosphorus chemistry has shared in the immense benefits that spectroscopic techniques offer in the determination of structure and the characterization of compounds. Structural influences have been considered to be important in ^{31}P shielding (Chart 2.1), but other factors (e.g., electron-withdrawing or donating substituents at the phosphorus center, resonance interactions at phosphorus with unsaturated groups that change the electron density on phosphorus, chain lengthening and branching effects, steric interactions) have impacted the chemical shifts in ^{1}H and ^{13}C NMR spectra, bond lengths, strengths, angles, and chemical conformations to name a few (Chart 2.2).

Chart 2.1 Some representative ^{31}P NMR shifts and pertinent bonding values.

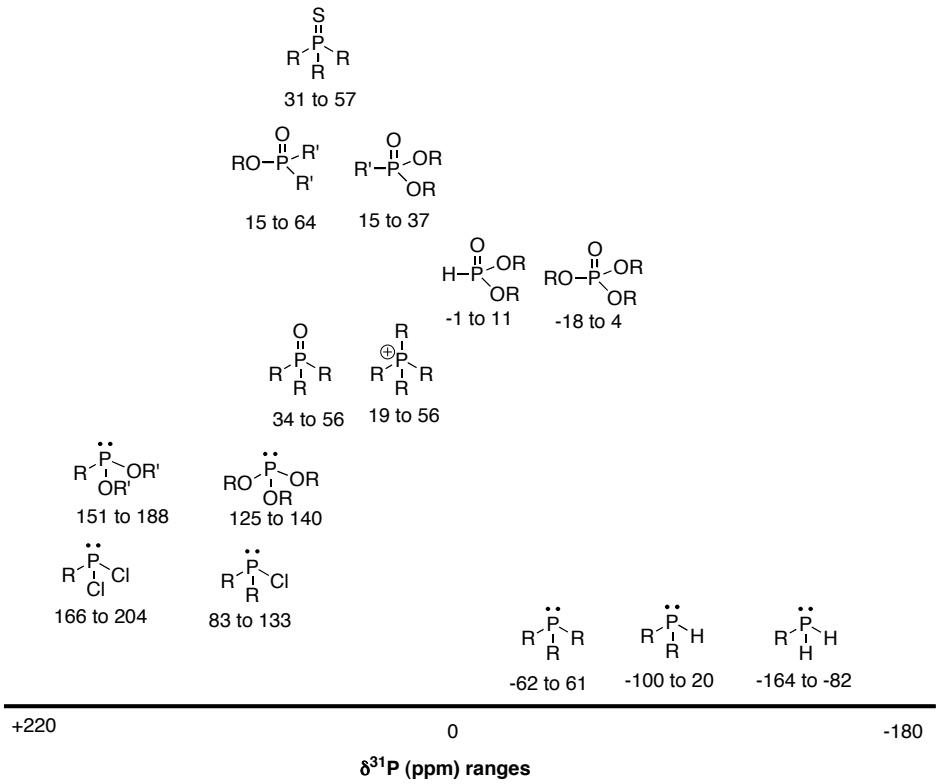
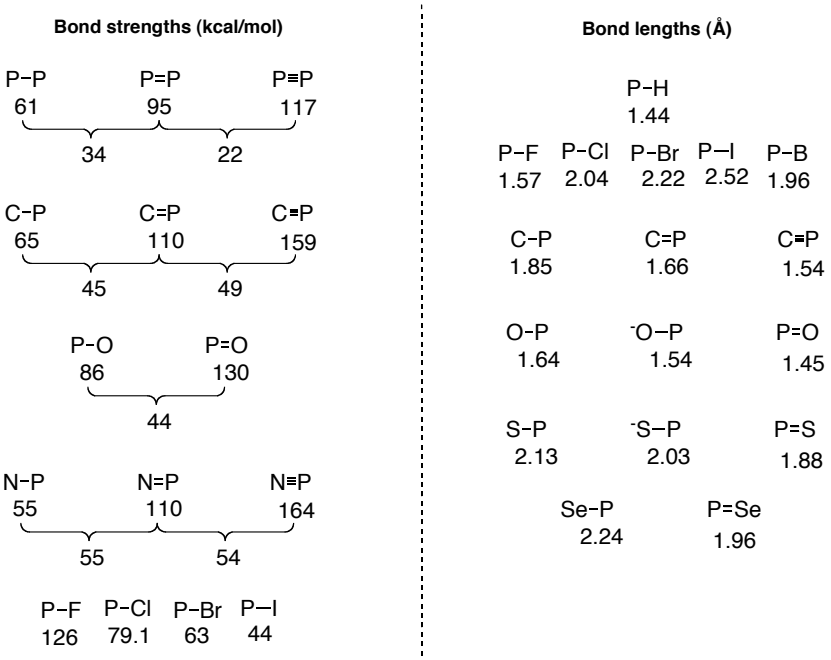
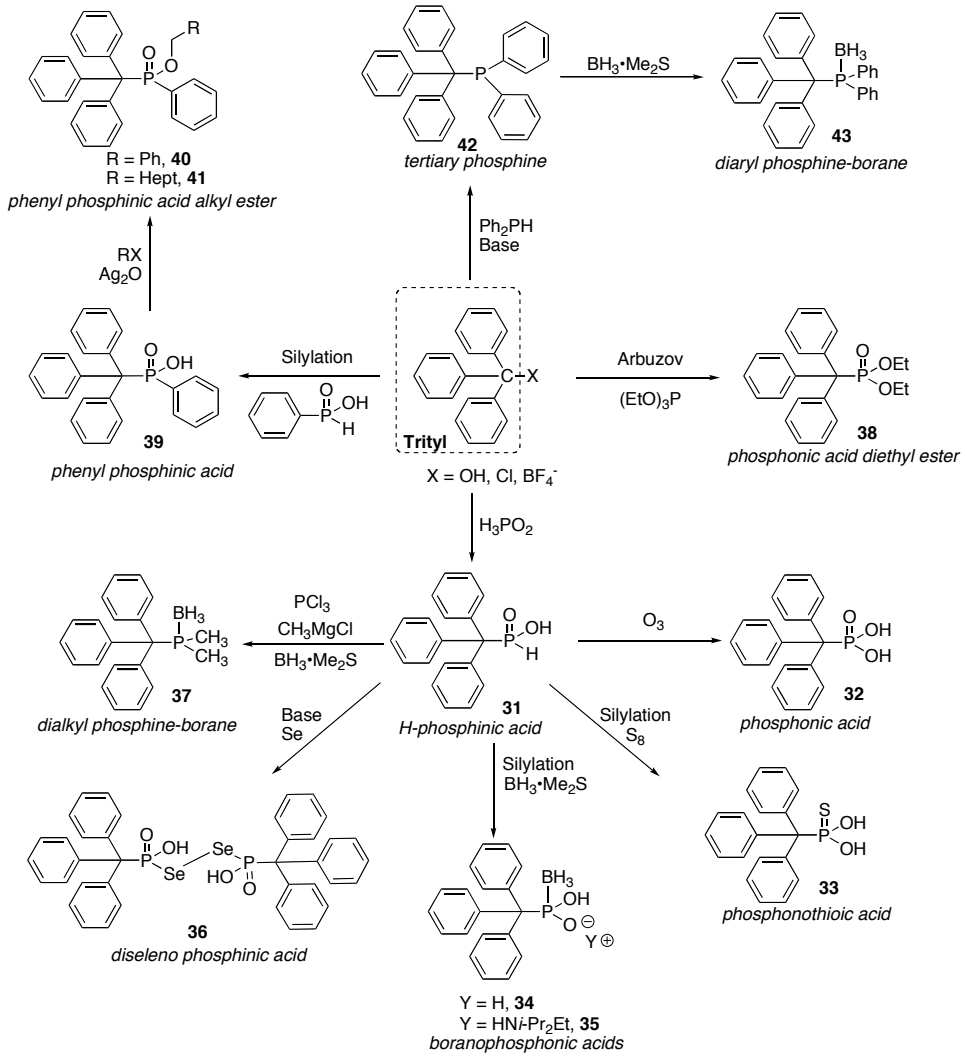


Chart 2.2 Some representative bonding values.



Obviously, some functionalities have useful properties, but there have been no direct comparisons of how these structural features affect the properties within the same series of organophosphorus compounds. We address this issue in the present study. To enable structural comparisons throughout the various classes of organophosphorus compounds, a series of triphenylmethyl-substituted phosphorus containing compounds were synthesized and analyzed (Scheme 2.1).[109] The advantage of using the triphenylmethyl (trityl, Tr) motif is the expected crystallinity of the derived compounds which provides the unique opportunity to compare structural features directly in the same series.

Scheme 2.1 Triphenylmethyl-organophosphorus compounds prepared and characterized



Not only has the trityl motif found some uses in hydride abstraction,[110-112] oxidative cleavage,[110-112] and more recently in stabilization of transition metal clusters,[113] but it also possesses anticancer properties.[114] Syntheses of some trityl-containing phosphorus species are described in the literature, but with limited structural data reported.[115-118] In collaboration with TCU Professor Anne Richards, various trityl-containing phosphorus compounds (Scheme 2.1) were prepared and structurally characterized by single X-ray crystallography.[109] We were able to synthesize two pharmacophores, boranophosphonates (compounds **34** and **35**) and phosphonothioic acid (compound **33**), both structurally characterized for the first time by X-ray diffractometry.

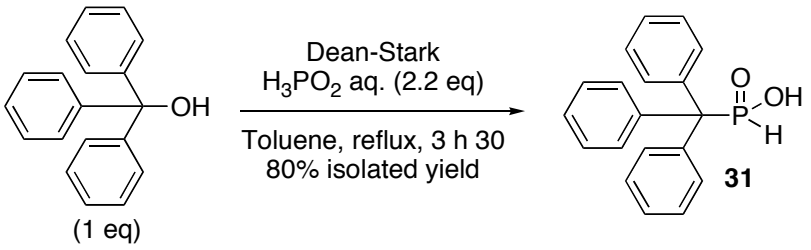
2.2 Preparation and crystal structures of triphenylmethyl-containing phosphorus compounds

2.2.1 *H*-phosphinic acids conversion en route to functionalized triphenylmethyl-containing phosphorus compounds.

2.2.1.1 Preparation of triphenylmethyl-*H*-phosphinic acid

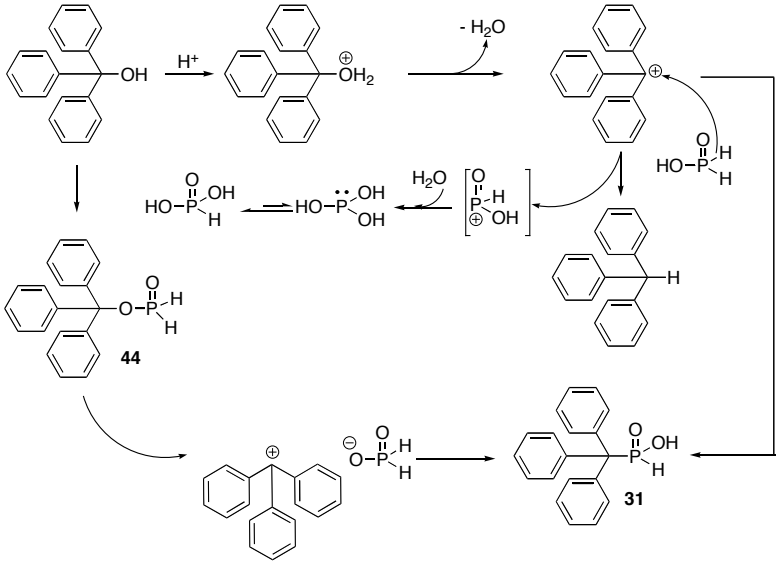
The *H*-phosphinic acid functionality is a valuable synthetic intermediate, nearly ideal for the preparation of many phosphorus functionalities (Chapter I, section 1.1). For our investigation, most of the triphenylmethyl-containing compounds were easily prepared from the known triphenylmethyl-*H*-phosphinic acid (**31**).[115,119] Fosse initially reported the synthesis of **31** via condensation between triphenylmethanol (Ph_3COH) and H_3PO_2,[119] but no yield was reported. In 1933, Hatt developed a method in which the sodium hypophosphite salt of H_3PO_2 reacts with Ph_3COH in presence of acetic acid and sulfuric acid.[115] However, the desired product was reported as impure and no yield was provided.[115] To achieve the synthesis of triphenylmethyl-*H*-

phosphinic acid **31**, the direct nucleophilic substitution of H_3PO_2 with Ph_3COH under azeotropic water removal was employed. This approach led to the formation of the desired product in good yield (Eq. 2.1). However, when performed on multi-gram scale (about 20 g) at reflux for 12 hours, **31** was only obtained in 37% yield, along with the formation of the triphenylmethane reduction by-product (52% isolated yield). This is explained by the facile reduction of Ph_3COH into the corresponding Ph_3CH upon prolonged heating and in the presence of a strong reducing agent, which consequently lowered the yield of **31**. This occurrence was previously observed by Shevchenko and coworkers who postulated the reduction of the triphenylmethyl carbocation by H_3PO_2.[120] If water is removed, esterification of hypophosphorous acid will occur and form the alkyl phosphinate **44**, which then isomerizes to the desired product **31** (Scheme 2.2).



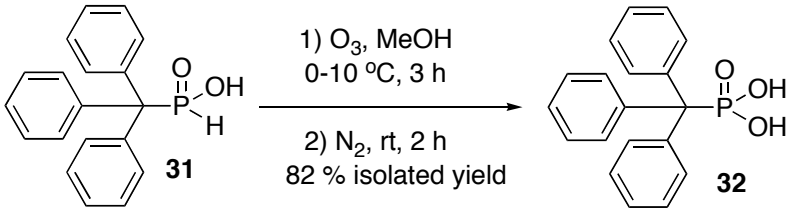
(Eq. 2.1)

Scheme 2.2 Postulated mechanism in the reaction of triphenylmethanol



2.2.1.2 Oxidative conversion of *H*-phosphinic acid into phosphonic acid via ozonolysis

Trityl phosphonic acid (**32**) is typically prepared by reacting triphenylmethanol with PCl_3, followed by hydrolysis with an alcoholic solution of potassium hydroxide and water, yielding **32** in 50% isolated yield.[113,121,122] However, this procedure presents some drawbacks, such as a tedious multistep hydrolysis/purification process involving the use of strong acid-base reagents and several filtration processes. In the first chapter of this dissertation, it was mentioned that, in the past, various strong oxidative agents have been employed for the conversion of *H*-phosphinic acids into the corresponding phosphonic acids, but the harshness of the conditions often make this approach undesirable (Section 1.2.2.2).[26,67,91-94,96] The Montchamp group developed a convenient and practical method of oxidation of *H*-phosphinates using ozone (Chapter V).[12] The methodology was applied for the oxidation of trityl-*H*-phosphinic acid (**31**) via ozonolysis, in a methanolic solution and at low temperature, delivering pure trityl phosphonic acid (**32**) in good yield (82% isolated) (Eq. 2.2). Significant advantages of this oxidation approach are defined by the straightforward process and chromatography-free separations.



(Eq. 2.2)

Although trityl phosphonic acid (**32**) is a well-known and widely used compound,[113,121a] its crystal structure has not been reported. Other phosphonic acids have been structurally characterized, but data are limited. Here, crystal structures are provided to allow structural comparisons to be drawn (Figure 2.1).

Trityl phosphonic acid (**32**) crystallized in the triclinic space group $P\bar{1}$. It has a P=O bond length of 1.5070(10) Å and P-OH bond lengths of 1.5386(10) Å and 1.5518(11) Å. These values compare well with those observed in *t*-butyl phosphonic acid that has a P=O bond length of 1.5083(16) and P-OH bond lengths of 1.5544(17) Å and 1.5448(16) Å.[150]

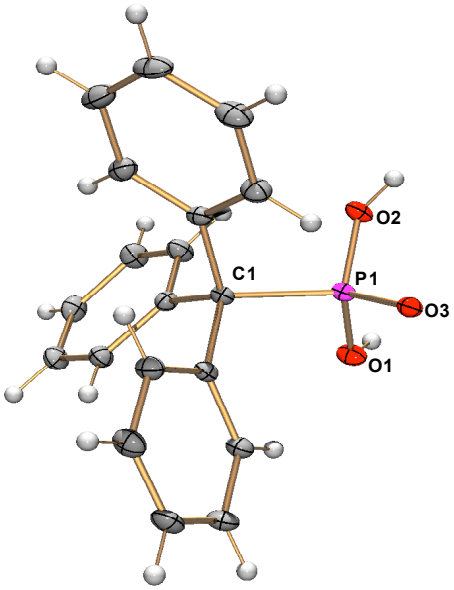


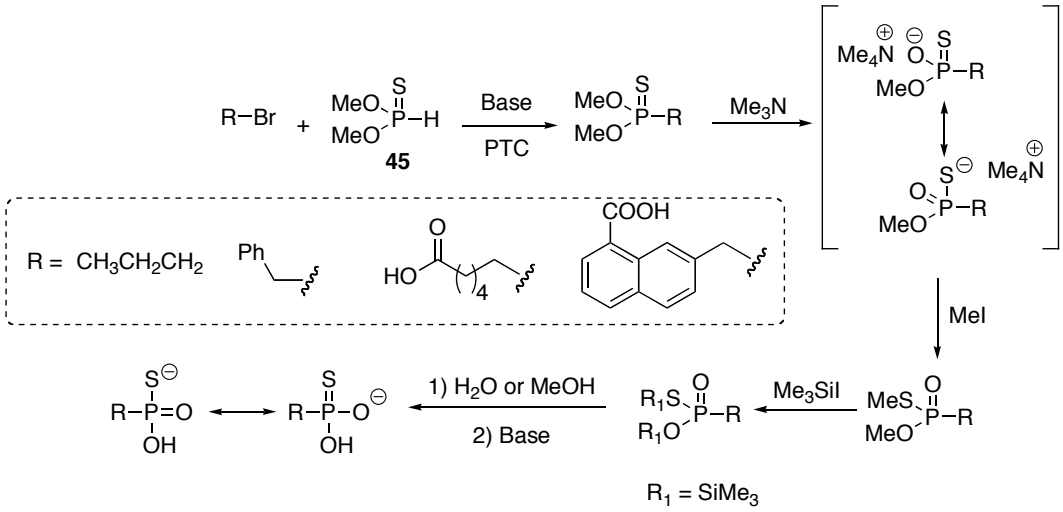
Figure 2.1 X-ray structure of $Ph_3CP(O)(OH)_2$ (**32**). Thermal ellipsoids shown at 50% probability. Selected bond distances (Å) and angles (°): P(1)-O(3), 1.5070(10); P(1)-O(1), 1.5386(10); P(1)-O(2), 1.5518(11); P(1)-C(1), 1.8588(14); O(3)-P(1)-O(1), 111.36(6); O(3)-P(1)-O(2), 112.41(6); O(1)-P(1)-O(2), 108.29(6); O(3)-P(1)-C(1), 110.73(6); O(1)-P(1)-C(1), 105.90(6).

2.2.1.3 Direct conversion of *H*-phosphinic acid into phosphonothioic acid

Thiophosphonates, or phosphonothioate acids have been the subject of a number of patents and publications. Various applications included antiviral compounds,[123] plant growth regulators,[124] inhibitors of a number of different enzymes (e.g., phosphatase),[125] as well as lubricants.[126] Considering their importance it is surprising that, to the best of our knowledge, no

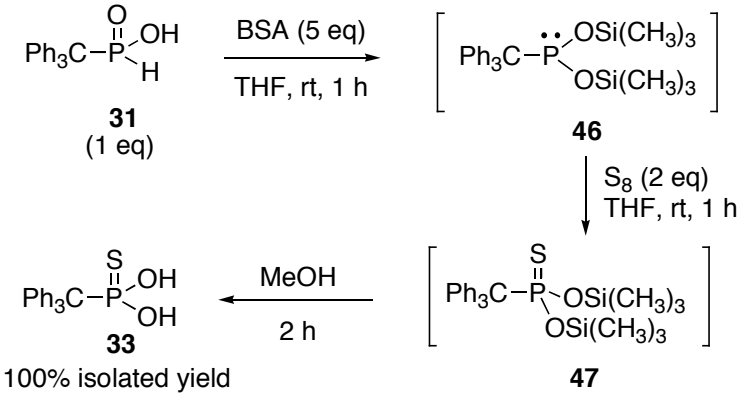
X-ray crystal structures have ever been reported for compounds containing such functional group.[127] The reported methods of preparation vary considerably.[123-127] While these methods are suitable for specific compounds, they often use conditions that would preclude application to the synthesis of derivatives bearing different or more labile functional groups. During syntheses of phosphates and phosphonates, methyl and, to a lesser extent, ethyl esters have often been used as protecting groups. However, while typically dimethyl or diethyl phosphonate esters can be cleaved by treatment with trimethylsilyl iodide or trimethylsilyl bromide, this method fails or gives low yields with sulfur derivatives.[128] Swierczek and coworkers attempted to overcome this issue by developing a multi-step synthesis of phosphonothoic acid derivatives.[129] This method involves a Michaelis–Becker alkylation by an alkyl halide of the anion of dimethyl phosphonothioate (**45**),[130] which can be easily made by treating dimethyl phosphite with Lawesson's reagent (Scheme 2.3).[129] A significant advantage of this approach is the alleviation of the purification of intermediates, and the absence of chromatographic separations. However, the long reaction time, the alkylation-deprotection-dealkylation-hydrolysis processes, and low yields (25 to 41% isolated yield from **45**) make this approach impractical.

Scheme 2.3 Preparation of phosphonothioic acids from the dimethyl phosphonothioate



On the other hand, Gautier,[55a] and later the Archer group,[131] reported a practical method to synthesize phosphonothioic acids from the corresponding *H*-phosphinic acid. Their approach was based on the use of a silylating reagent such as *N,O*-bis(trimethylsilyl)acetamide (BSA) or TMSCl, followed by the trapping of the P(III) form with elemental sulfur.[131] This approach was used for the preparation of the triphenylmethylphosphonothioic acid (**33**) (Scheme 2.4). Trityl-*H*-phosphinic acid (**31**) was silylated with BSA (1 hour) to form the corresponding air-sensitive disilyl phosphonite (**46**) intermediate. The formation of **46** was monitored by ^{31}P-NMR, with a peak at around 130 ppm. Intermediate **46** was easily oxidized with elemental sulfur, resulting in the formation of bis(trimethylsilyl)-phosphonothioate (**47**). Without isolation, intermediate **47** was directly treated with methanol to remove the trimethylsilyl groups, affording pure trityl phosphonothioic acid (**33**) (peak at 92.5 ppm in ^{31}P-NMR) in quantitative yield.

Scheme 2.4 Preparation of the trityl phosphonothioic acid



The triphenylmethyl-phosphonothioic acid (**33**) crystallized in the monoclinic space group $P2_1/c$ (Figure 2.2). Not surprisingly, the P=S bond in **33** is much longer (1.9513(9) Å) than the P=O in **32** (1.5070(10) Å). Interestingly, trityl phosphonothoic acid (**33**) exists only as the thiono P(=S)OH tautomer in both solution and crystalline states.[125c]

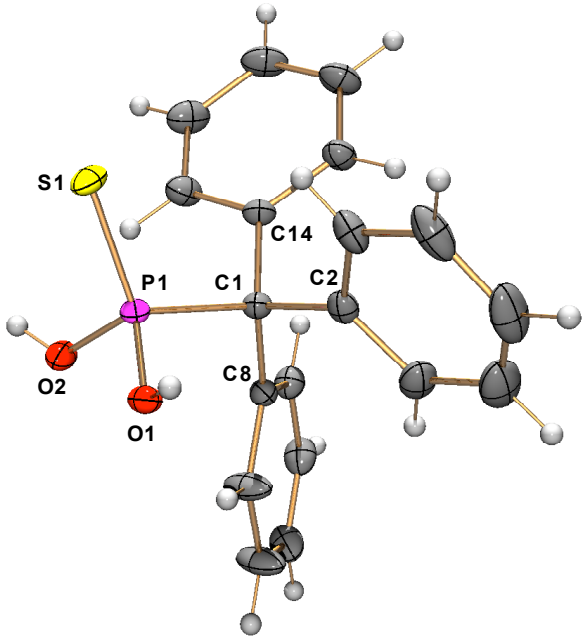


Figure 2.2 Crystal structure of $Ph_3CP(S)(OH)_2$ (**33**), the first structurally characterized example of a thiophosphonic acid. Thermal ellipsoids shown at 50% probability. Selected bond distances (Å) and angles (°): P(1)-S(1), 1.9513(9); P(1)-O(1), 1.560(2); P(1)-O(2), 1.565(2); P(1)-C(1), 1.884(3); O(1)-P(1)-O(2), 101.88(11); O(1)-P(1)-C(1), 105.76(11); O(2)-P(1)-S(1), 113.44(8); C(1)-P(1)-S(1), 114.30(8)

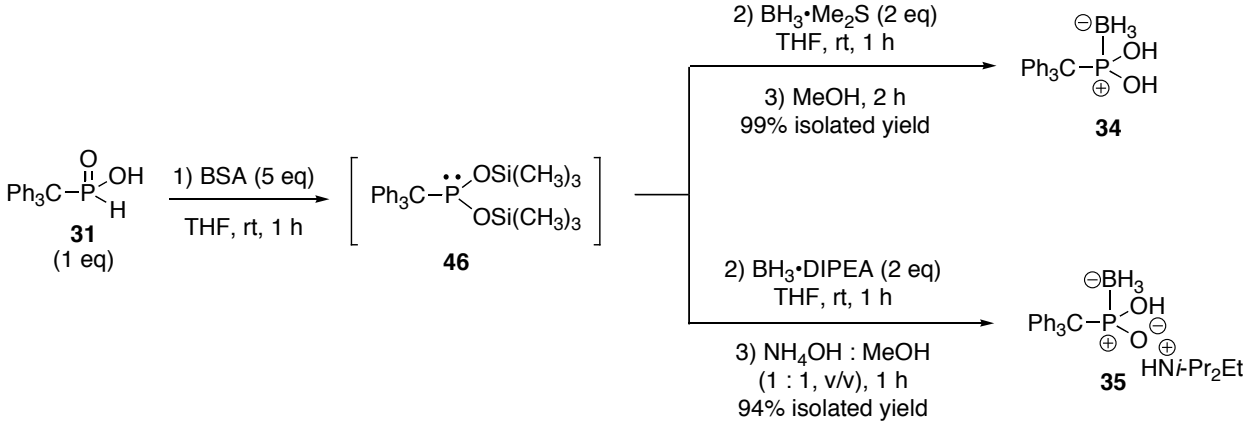
2.2.1.4 *H*-phosphinic acids, precursors of boranophosphonic acids

In recent years, there has been increasing interest in boron-containing compounds due to their potential medicinal and biochemical applications.[132] Boron compounds have been used for several decades as pharmacological agents in boron neutron capture therapy (BNCT) to treat cancers.[133]

Recent developments in boron chemistry and pharmacology have provided significant progress in designing new organoboron compounds. Organoboron exhibits hypolipidemic,[134] anti-neoplastic,[135] anti-inflammatory,[136-138] anti-osteoporotic,[138,139] and analgesic[134a] properties.

Surprisingly, no X-ray crystal structures were reported for boranophosphonates. Herein, we describe the syntheses of compounds **34** and **35** (Scheme 2.5) and their crystal structures with full characterization.

Scheme 2.5 Preparation of the trityl boranophosphonic acids **34** and **35**



Silylation of trityl-*H*-phosphinic acid (**31**) with BSA, and trapping of the resulting intermediate **46** with borane-dimethylsulfide complex followed by methanolysis, afforded **34** in excellent yield. The boranophosphonic acid salt **35** was obtained analogously to **34**, but using BH_3•DIPEA followed by treatment with methanolic ammonium hydroxide.[132f]

Figures 2.3 and 2.4 represent the crystal structures of boranophosponic acids **34** and **35** respectively. Compound **34** crystallized in the monoclinic space group $P2_1/n$, and **35** in the triclinic space group $P\bar{1}$. As it is observed in Figure 2.3, the P-B bond in $[Ph_3CP(BH_3)(OH)_2]$ (**34**) at 1.89(5) Å is slightly longer than in a $PhP(BH_3)(OR)_2$ (1.851(6) Å),[151] and is essentially the same as in the boranophosphates $(MeO)_2P(O)BH_3^-/i\text{-}Pr_2NH_2^+$ (1.887(3) Å),[152] and $(MeO)_2P(BH_3)OK$ (1.895(6) Å).[153]

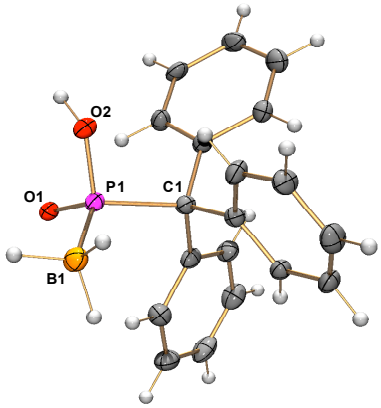


Figure 2.3 Crystal structure of $[Ph_3CP(BH_3)(OH)_2]$ (**34**), the first structurally characterized example of a boranophosphonic acid. Thermal ellipsoids shown at 50% probability. Selected bond distances (Å) and angles (°): P(1)-O(1), 1.53(3); P(1)-O(2) 1.60(3); P(1)-B(1) 1.89(5); P(1)-C(1), 1.91(4); B(1)-H(1), 1.2(6); O(1)-P(1)-O(2), 108.9(16); O(1)-P(1)-B(1), 115(2); O(2)-P(1)-B(1), 106(2); O(1)-P(1)-C(1), 107.9(17); O(2)-P(1)-C(1), 104.4(16); B(1)-P(1)-C(1), 114(2)

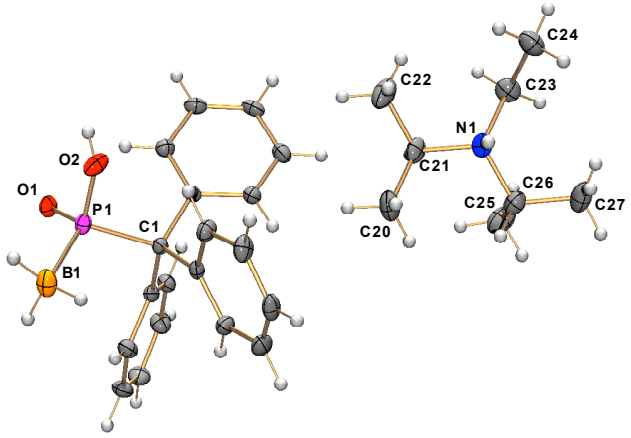
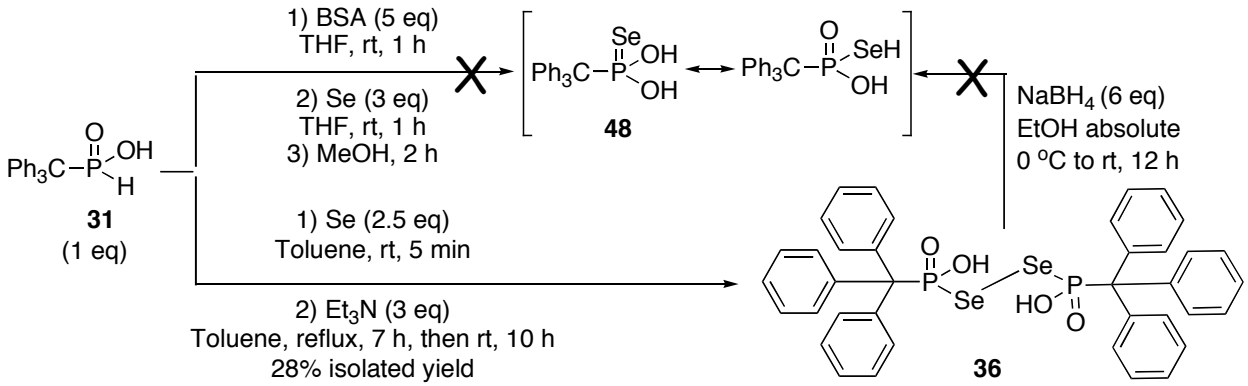


Figure 2.4 Crystal structure of $[Ph_3CP(OH)BH_3^-/i\text{-}Pr_2NEtH^+]$ (**35**). Thermal ellipsoids shown at 50% probability. Selected bond distances (Å) and angles (°): P(1)-O(1), 1.5218(12); P(1)-O(2), 1.5953(15); P(1)-B(1), 1.920(3); P(1)-C(1), 1.9212(17); B(1)-H(4); 1.07(3); O(1)-P(1)-O(2), 108.55(8); O(1)-P(1)-B(1), 116.91(10); O(2)-P(1)-B(1), 106.13(11); O(1)-P(1)-C(1), 108.45(7); O(2)-P(1)-C(1), 102.17(8); B(1)-P(1)-C(1), 113.47(10); P(1)-B(1)-H(2), 108.8(17)

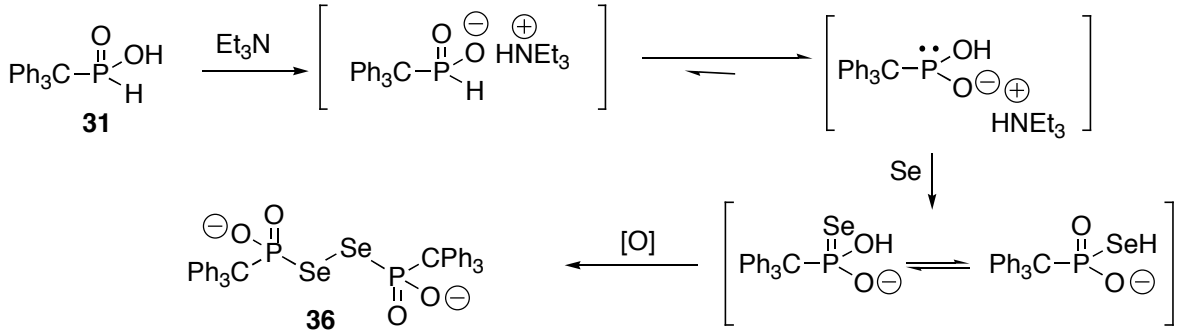
2.2.1.5 Base-promoted conversion of *H*-phosphinic acid into the corresponding diseleno phosphinic acid

Derivatives of monoselenophosphoric acid $P(Se)(OH)_3$ are of special interest, as monoselenophosphate has been described as key intermediate in selenoprotein synthesis.[140] Monoselenophosphate has been chemically synthesized and shown to be identical with the biological selenium donor.[141] We were first interested in the preparation of **48** (Scheme 2.6). Our initial approach was to use the silylation/trapping method but, unfortunately, no reaction occurred. On the other hand, treatment of **31** with selenium powder, under basic conditions, and at reflux in toluene led to the formation of **36** by simple air oxidation (Scheme 2.7). An attempt at recovering **48** by reducing the Se-Se bond of **36** using an excess of sodium borohydride failed.

Scheme 2.6 Preparation of the diseleno tritylphosphinic acid



Scheme 2.7 Proposed mechanism for the diseleno tritylphosphinic acid formation



The selenophosphinic acid $[Ph_3CP(O)(OH)Se]_2$ (**36**) crystallized in the monoclinic space group, $P2_1/c$ (Figure 2.5). The X-ray crystal structure of **36** revealed a Se-Se single bond with a bond length of 2.3326(6) Å. This value can be compared with that of 2.34 Å which is the sum of the covalent radii,[168] and is comparable with the structurally similar bis(diisopropoxy-seleno phosphinoyl) diselenide, that has a Se-Se bond length of 2.351(6) Å.[169,170] The diselenium oragnophosphorus compound **36** has a *anti* PSe-SeP conformation. Additionally, the two phosphorus atoms of **36** are not equivalent and this was confirmed by ^{31}P-NMR, in which two peaks appeared at 39 and 38 ppm. The packing diagram of **36** showed that the molecules arrange themselves so that the protonated oxygen atom aligns with a P=O group from an adjacent molecule. However, the distance is too long for any hydrogen-bonding interaction.

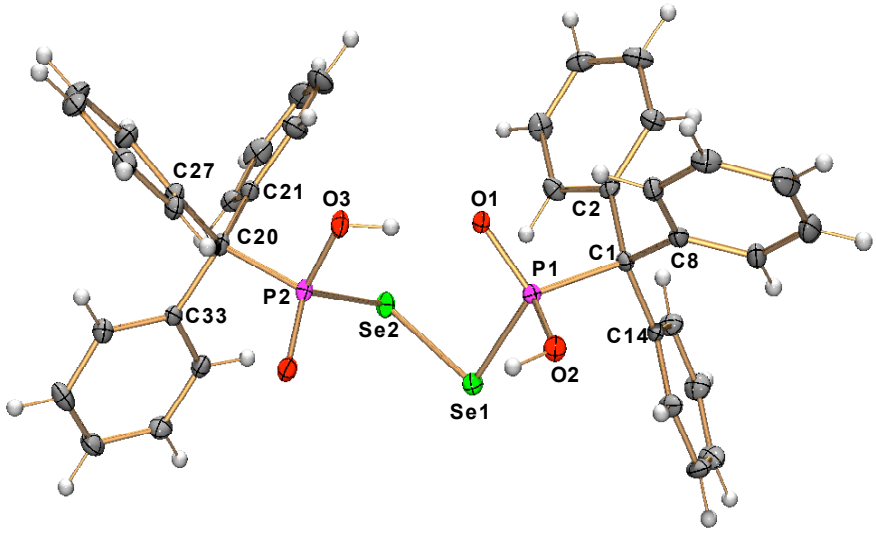


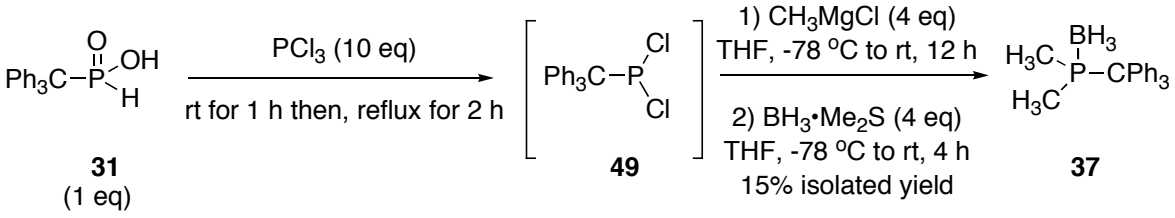
Figure 2.5 Crystal structure of $[Ph_3CP(O)(OH)Se]_2$ (**36**). Thermal ellipsoids at 30% probability. Selected bond lengths (Å) and angles (°): Se(1)-P(1), 2.2686(11); Se(1)-Se(2), 2.3326(6); Se(2)-P(2), 2.2717(11); P(1)-O(1), 1.495(3); P(1)-O(2), 1.559(3); P(1)-O(3), 1.547(3); P(2)-Se(2)-Se(1), 1.9746(3); P(1)-Se(1)-Se(2), 101.65(3).

2.2.1.6 Preparation of dimethyl tritylphosphine-borane ligand from *H*-phosphinic acid

Since the first reported synthesis of a phosphine–borane complex over 50 years ago,[99] there has been considerable interest in the preparation these air-stable complexes. Applications have been pioneered by Imamoto[100] over the last 20 years and now include their use in carbonyl addition,[100] alkylation,[100,102] and conjugate addition[104] processes, as well as metal-mediated couplings.[103] Two reviews[98c,142] highlight the scope of these processes and clearly demonstrate the importance of protecting trivalent phosphorus in the synthesis of chiral phosphine ligands.

We turned our attention to the synthesis of dimethyl tritylphosphine-borane (**37**), which was prepared from the corresponding *H*-phosphinic acid (**31**) via P-C bond formation on the known Ph_3CPCl_2 (**49**),[113,122] using methylmagnesium chloride as Grignard reagent (Scheme 2.8). The protection of the trityl dimethylphosphine with borane-methylsulfide complex produced the corresponding diphenyl tritylphosphine-borane (**37**). Although a complete conversion of **49** into **37** was achieved (reaction monitored by ^{31}P-NMR), only 15% of the desired compound was obtained after purification by chromatography over silica gel. The conditions for the synthesis and purification of this particular compound were not optimized.

Scheme 2.8 Preparation of dimethyl tritylphosphine-borane



Cabrera and coworkers initially reported the structural data of $[Ph_3CPMe_3]^+$ with counter anions of $[B(C_6F_5)_4]^-$ and $[BF_4]^-$.[153a] However, the neutral molecule Ph_3CPMe_2 has not been reported. Crystals of Ph_3CPMe_2 could not be isolated, but the borane adduct $Ph_3CPMe_2(BH_3)$ (**37**) was obtained from a toluene/dichloromethane solution (5:1) and characterized (Figure 2.6).

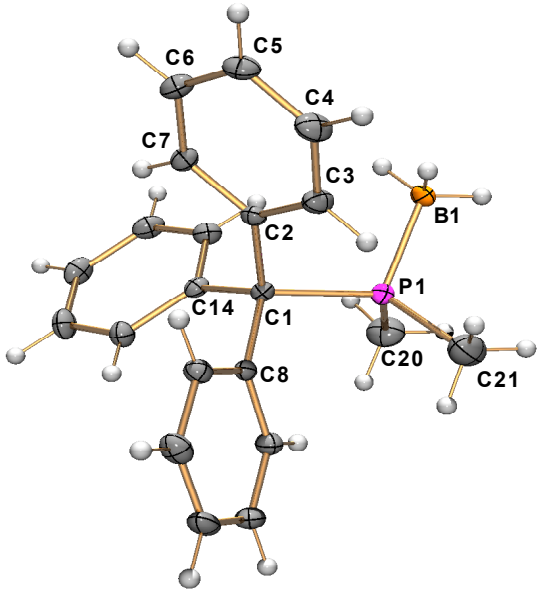
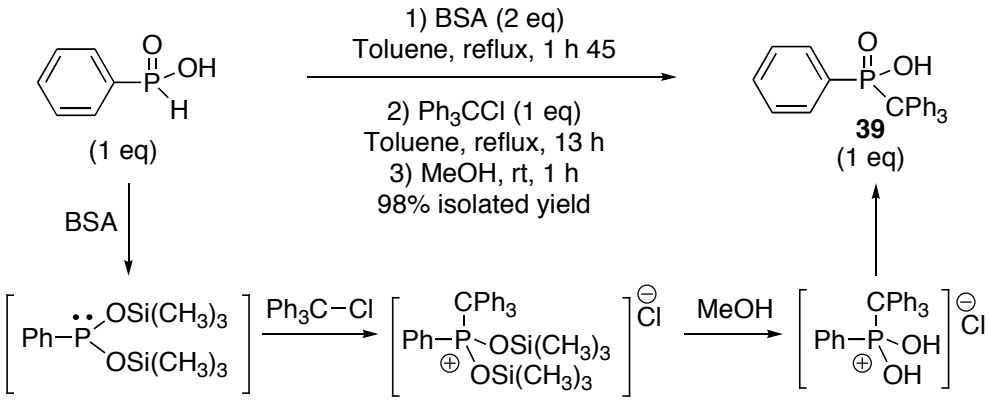


Figure 2.6 Crystal structure of $Ph_3CPMe_2(BH_3)$ (**37**). Thermal ellipsoids drawn at 30% probability. Selected bond lengths (Å) and angles (°): P1-C21 1.854(3), P1-C20 1.858(3), P1-B1 1.803(3), C1-P1-B1 108.14(11)

2.2.1.7 Preparation of trityl phenylphosphinic acid and ester derivatives

The synthetic routes to trityl phenylphosphinic acid (**39**) are shown in scheme 2.9. Silylation with BSA of the commercially available phenyl phosphinic acid PhP(O)(OH)H, followed by the addition of triphenylchloromethane Ph_3CCl and methanol, afforded pure phosphinic acid (**39**) in excellent isolated yield (98%). Gallagher and coworkers reported the formation of compound **39** (only 5% isolated yield) when $Ph_3CP(O)(Cl)(Ph)$ was subjected to a prolonged alkaline hydrolysis.[143]

Scheme 2.9 Preparation of trityl phenylphosphinic acid



Phenyl tritylphosphinic acid (**39**), which crystallized as colorless crystals in the triclinic space group $P\bar{1}$ (Figure 2.7), exhibits common tetrahedral geometry at the P atom.

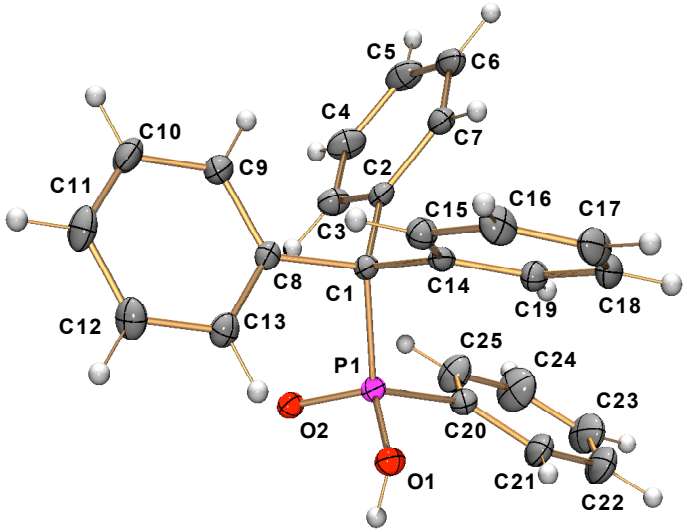
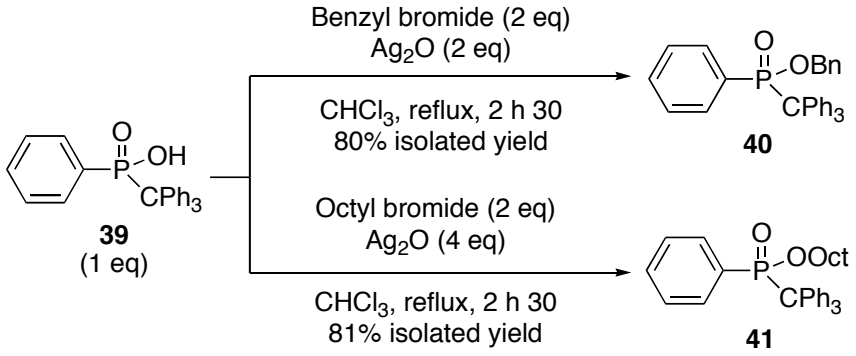


Figure 2.7 Solid-state analysis of phenyl tritylphosphinic acid (**39**). Thermal ellipsoids drawn at 30% probability.

A mild and practical method for the esterification of **39** with various halides, promoted by silver(I) oxide, was employed (Scheme 2.10). Iwamura and coworkers used these esterification conditions on phosphonates while looking to develop photolabile and highly

fluorescent protecting groups for biologically important molecules.[144] Both ester derivatives **40** (benzyl ester) and **41** (octyl ester) were isolated in good yields (80% and 81% respectively).

Scheme 2.10 Preparation of phenyl tritylphosphinic acid alkyl ester derivatives



The conversions of compound **39** into the corresponding secondary phosphine $Ph_3CP(H)(Ph)$ and phosphine-borane $Ph_3CP(BH_3)(H)(Ph)$ were attempted, but the reduction of the P(O)(OH) moiety into P-H by using phenyl silane ($PhSiH_3$),[3f] or $SOCl_2$ with $LiAlH_4$[145] was unsuccessful.

$Ph_3CP(O)(OBn)(Ph)$ (**40**) crystallized in the monoclinic space group $P2_1/c$ and exhibits common tetrahedral geometry at the P atom (Figure 2.8). A survey of the Cambridge Crystallographic Data Centre (CCDC) uncovered **40** as the first structurally characterized example of a benzyl ester of a phosphinic acid.[167]

Interestingly, two crystallographically independent molecules were found within the asymmetric unit. Those two molecules of $Ph_3CP(O)(OBn)(Ph)$ (**40**) carried slightly different bond lenghts (P-C and P=O) and angles: P-C of 1.8753(19) / 1.8769(18)Å, P1-O1 of 1.4752(14) versus P2-O3 of 1.4744(14) Å.

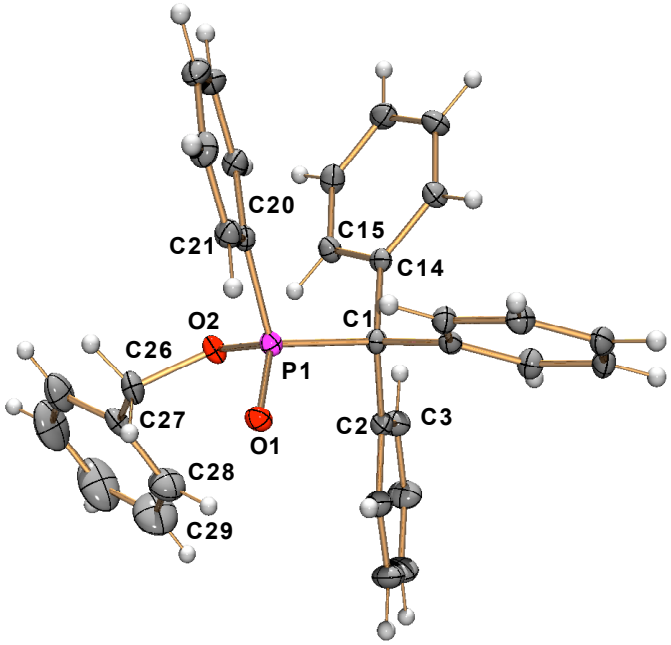
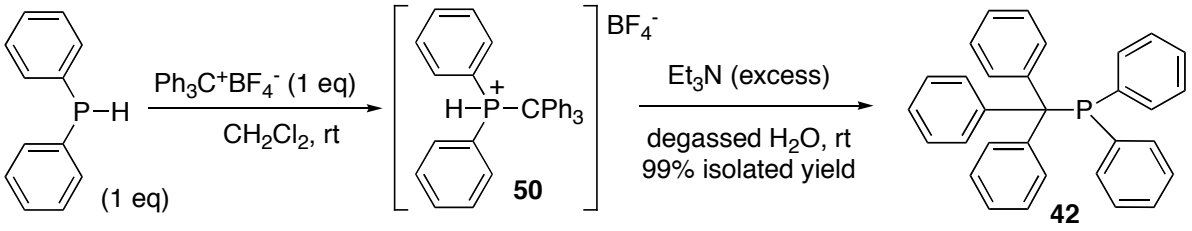


Figure 2.8 X-ray crystal structure of phenyl tritylphosphinic benzyl ester (**40**). Thermal ellipsoids drawn at 30% probability.

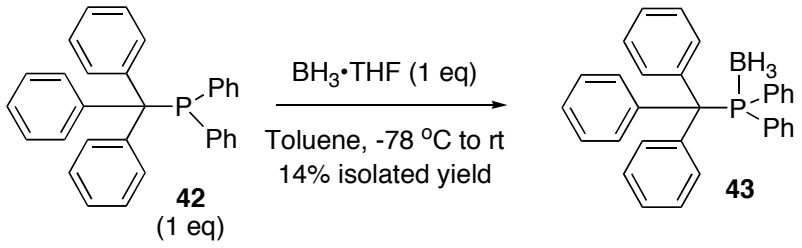
2.2.2 Synthesis of diphenyl tritylphosphine-borane from diphenyl phosphine

The air-sensitive diphenyl tritylphosphine (**42**) was prepared via decomplexation of the quaternized phosphonium ion **50** under basic conditions (Scheme 2.11). Lambert and So initially reported the synthesis of **42** by reacting a stoichiometric amount of diphenylphosphine with trityl tetrafluoroborate,[146] but no X-ray crystal structure was reported.

Scheme 2.11 Preparation of diphenyl tritylphosphine



The conversion of **42** into the corresponding air-stable phosphine-borane **43** was carried out with a stoichiometric amount of borane-tetrahydrofuran complex, affording pure product after crystallization, but in only 14% yield (Eq. 2.3).



(Eq. 2.3)

Diphenyl tritylphosphine $Ph_3CP(Ph)_2$ (**42**) crystallized in the triclinic space group $P\bar{1}$ (Figure 2.9). Diphenyl tritylphosphine-borane (**43**) crystallized as monoclinic colorless crystals, $P2_1/c$ (Figure 2.10). The geometry around the P center of $Ph_3CP(Ph)_2$ (**42**) is trigonal pyramidal and distorted tetrahedral for the borane complex **43**. ^{31}P-NMR chemical shift of **42** is displayed as a singlet at 27.9 ppm, whereas for **43**, it is displayed at 39.6. The P–C(trityl) bond lengths of 1.9433(19) Å in **42** and 1.9265(19) Å in **43** are at the longer end of documented P–C bonds, but reflect of the steric congestion around the P center. For instance, $[P(t\text{-}Bu)_4]BF_4$, sterically congested, has a P–C bond distance of 1.924(4) Å.[163] The related cation, tris(p-methoxyphenyl)(triphenylmethyl)phosphonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, has a P–C bond length of 1.931(1) Å.[164]

A typical tetrahedral geometry is adopted by the central carbon C(1). The three phenyl groups attached to this C(1) displayed a propeller rearrangement. The remaining metric parameters are unexceptional.

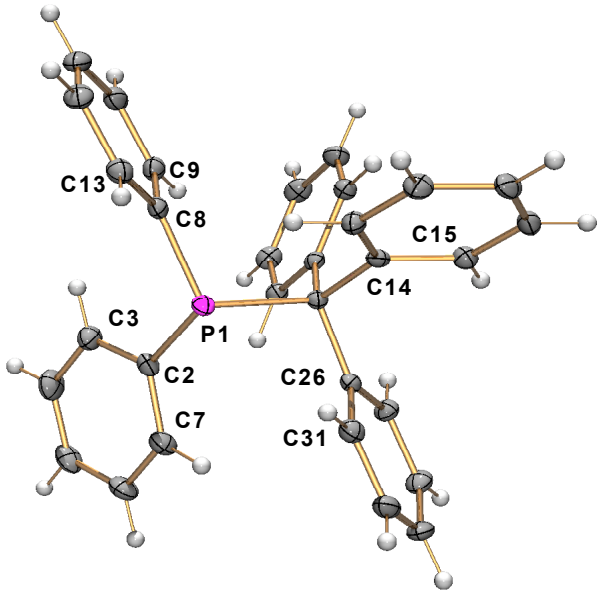


Figure 2.9 X-ray crystal structure of Ph_3CPPh_2 (**42**). Thermal ellipsoids drawn at 30% probability level. Selected bond lengths (Å) and angles (°): P(1)-C(2), 1.8368(19); C(1)-P(1)-C(2), 104.23(8); C(2)-P(1)-C(8), 104.30(9)

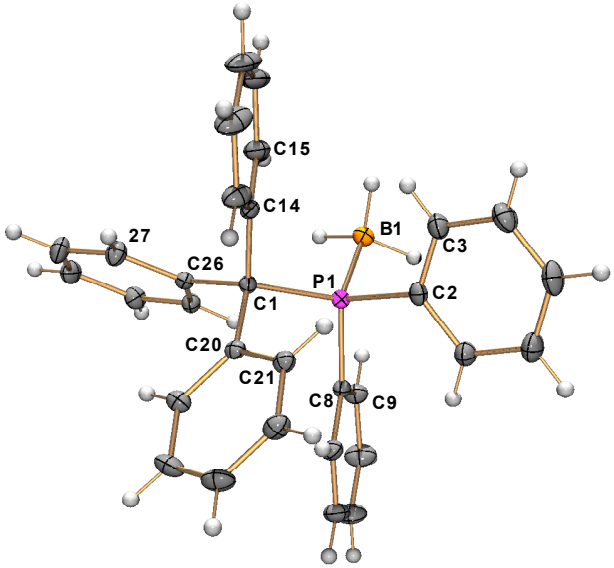
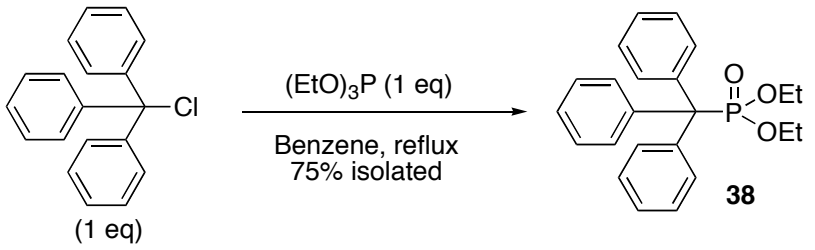


Figure 2.10 X-ray crystal structure of $Ph_3CPPh_2(BH_3)$ (**43**). Thermal ellipsoids drawn at 30% probability level. Selected bond lengths (Å) and angles (°): P(1)-C(2), 1.8302(19); P(1)-B(1), 1.939(2); C(1)-P(1)-B(1), 117.49(10).

2.2.3 Known synthesis of triphenylmethyl phosphonate diester via Arbuzov reaction.

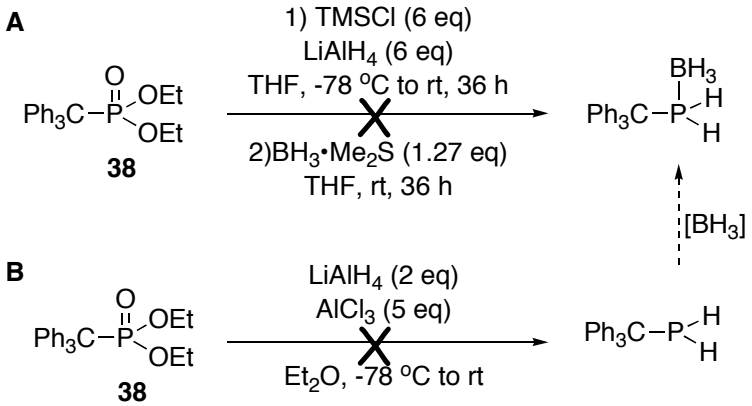
The Arbuzov reaction is one of the most versatile method for the formation of carbon-phosphorus compounds (Chapter I, Section 1.1.2.1). Known trityl phosphonic acid diethyl ester (**38**) was prepared according to the literature procedures by reacting triethylphosphite with triphenylchloromethane in refluxing benzene (Eq. 2.4).[147]



(Eq. 2.4)

Unfortunately, the reduction of phosphonate (**38**) into the corresponding secondary phosphine $Ph_3CP(H)_2(BH_3)$ by using either a mixture of [TMSCl, $LiAlH_4$, $BH_3{\bullet}Me_2S$],[148] or a mixture of $LiAlH_4$ and $AlCl_3$,[149] was not successful (Scheme 2.12).

Scheme 2.12 Reaction conditions for the phosphonate reduction



This diethylphosphonate ester (**38**) crystallized in the triclinic space group $P\bar{1}$ and exhibits common tetrahedral geometry at the P atom (Figure 2.11). Similarities between

complexes **38** and **40** were found: the P1-O1 bond length of 1.4671(14) Å is indicative of a P=O bond, while the phosphonate ester bonds differ slightly, P1-O2 1.5770(14) and P1-O3 1.5813(14) Å.

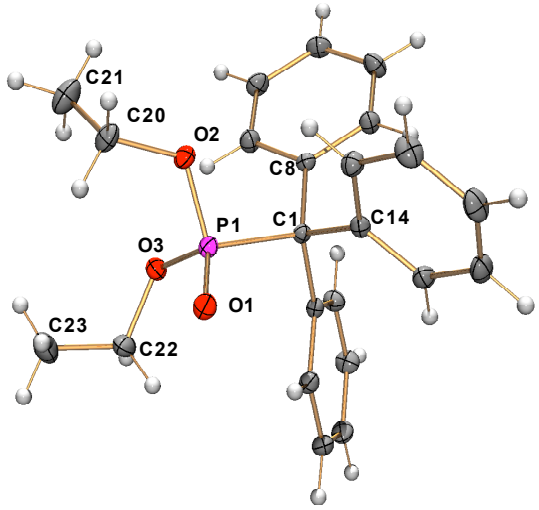


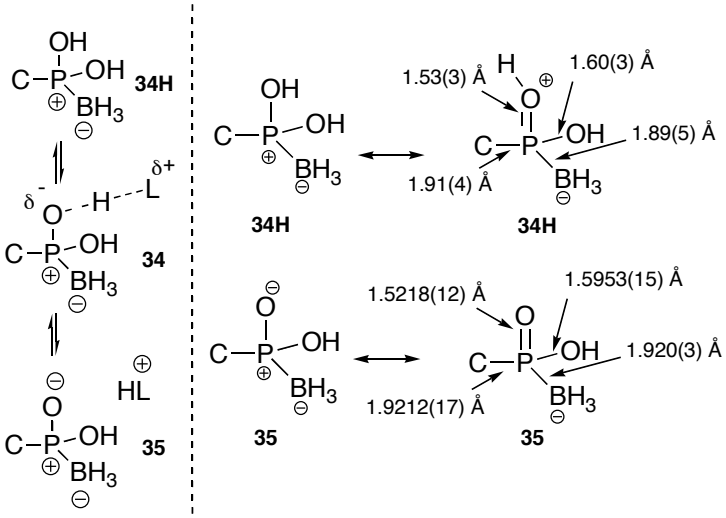
Figure 2.11 X-ray crystal structure of $TrPO(OEt)_2$ (**38**). Thermal ellipsoids drawn at 30% probability.

2.3 Comparative studies of the crystal structures and spectroscopic analyses.

Crystal structures showed that compounds $Ph_3CP(O)(OH)_2$ (**32**), $Ph_3CP(S)(OH)_2$ (**33**), $Ph_3CP(BH_3)(OH)_2$ (**34**), and [$Ph_3CP(OH)BH_3^-$/*i*-Pr_2NEtH^+] (**35**) have similar P-O single bonds, stretching from 1.560(2)-1.60(3) Å. The P-C bond lengths increase slightly from $Ph_3CP(O)(OH)_2$ (**32**) to [$Ph_3CP(OH)BH_3^-$/*i*-Pr_2NEtH^+] (**35**) (from 1.8588(14) to 1.9212(17) Å). Compounds **32-35** were also fully characterized by IR, mass spectrometry, and NMR spectroscopy (See experimental section for details). The ^{31}P-NMR chemical shifts in $CDCl_3$ are: **31**, 40.9 ppm; **32**, 32.7 ppm; **33**, 92.5 ppm; **34**, 108.1 ppm (93.3 ppm in water at pH 11.2, similar to other reported boranophosphonate salts)[132f]; and **35**, 108.0 ppm. The replacement of oxygen with sulfur induced a very large downfield shift (**33** versus **32**), which is a typical occurence.[1]

The signals for boranophosphonates **34** and **35** are consistent with literature values indicating a phosphoryl character (i.e, less as a bonding description as a P(III) borane complex).[151] The solid-state structural analogy between **34** and **35** is supported by the almost identical ^{31}P-NMR chemical shifts observed with these two compounds. Both boranophosphonates have a formally negatively charged boron atom, as would be expected for the representation $RP(^{+})(BH_3^{-})(OH)_2$. Despite careful examination of the residual electron density map, locating the hydrogen for O(1) proved unsuccessful. It is likely that the hydrogen atom is disordered or located between the phosphonate oxygen and lattice ethanol, with significant ionization of one OH bond in **34** (Scheme 2.13).

Scheme 2.13 Bonding representations and structural comparisons for the boranophosphonates[a]



[a] Ph_3 of the trityl group is omitted for clarity

As a matter of fact, one of the P-O bond is shortened significantly, and in the range of a formal phosphoryl P=O group.[154] To have a better understanding, the structural characterizations of **35** were compared to the ones of **34**: the hydrogen atoms on the amine nitrogen N(1), and the phosphorus oxygen O(2), were located from the difference map. Comparison of bond lengths

and angles show excellent structural agreement with **34**. This indicates that $RP(^{+})(BH_3^{-})(OH)_2$ is a much stronger acid than **32**, and therefore **34** is better represented as $RP(O)(BH_3^{-})(OH)H^{+}$, where partial protonation of lattice ethanol is probably occurring, and P=O bond character is very pronounced (Scheme 2.13). The P-B bond in **34** is also intermediate between that of $PhP(BH_3)(OR)_2$ and $(MeO)_2P(O)BH_3^{-}$, but closer to the latter.

The measured pKas for $Ph_3CP(O)(OH)_2$ **32** are 5.6 and 9.8, and for $Ph_3CP(S)(OH)_2$ **33** are 4.4 and 8.9. These results confirm the previously observed lower pKas for phosphonothioic acids versus the corresponding phosphonic acids.[155] The only measurable pKa for compound **34** was 5.9. This was independently verified by titrating **35**, suggesting that the first pKa for boranophosphonates is much lower than in compounds **32** and **33**. These results were found to be also in agreement with the X-ray data. Some decomposition of **34** (~10%) leading to the *H*-phosphinate salt of **31** was observed when the pH of the buffer was higher. Structural studies of boranophosphates[152,156,157] have shown that although the P-B bond is much longer than in the corresponding phosphate, the compounds are good phosphate mimics and capable of entering an enzyme active site, much like phosphonothioates. Similarly, the structural data of boranophosphonate **34** indicate good mimicry for a phosphonate, in spite of the long P-B bond. Therefore, boranophosphonates might be useful pharmacophores, although there are limited studies currently available.[132f]

Phosphinic and phosphonic acids can act simultaneously as proton donor and acceptor by forming strong hydrogen bonds.[1,157-160] Phosphinic acids usually dimerize[157,158] or form one-dimensional polymers,[159] while phosphonic acids typically crystallize as polymeric aggregates.[160]

In the solid state, the trityl phosphonic acid **32** adopts a motif in which the molecules are interlinked by hydrogen bonds to the solvent lattice molecules, such as acetone. For instance, H(8)-O(5) are H-bonded at a distance of 1.567, and H(1)-O(4) at 1.675 (Figure 2.12).

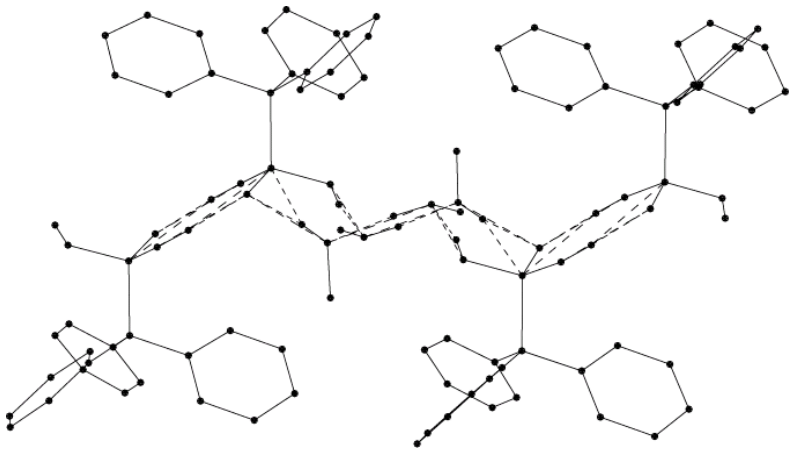


Figure 2.12 Packing Diagram of tritylphosphonic acid, $Ph_3CP(O)(OH)_2$ (**32**)

When compared with **32**, **34** and **35**, we observed that phosphonothioic acid (**33**) has a different packing arrangement. In this case, H-bonding to acetone (solvent) occurs but no intermolecular phosphonic packing is observed (Figure 2.13).

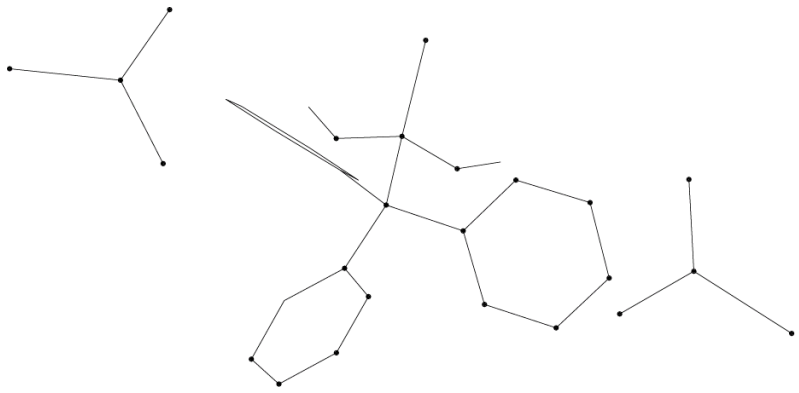


Figure 2.13 Solid-State Arrangement of trityl phosphonothoic acid, $Ph_3CP(S)(OH)_2$ (**33**)

Looking at the packing diagrams of the borano-complexes **34** and **35**, similar structural arrangements are observed (Figures 2.14 - 2.16). Each P=O and P-OH oxygen atoms participate in hydrogen bonding, the P-OH group H bonds to P=O affording dimeric interactions as depicted in figures 2.14-2.16. In molecule **34**, the lattice solvent molecules show little intermolecular interaction with the phosphonic acid. Their presence fills the voids in the crystal lattice. However, in **35**, the protonated amine occupies a position between two phosphonic acid moieties allowing O(1) (P=O) to form a second hydrogen bond with the amine proton (N-H). This double hydrogen accepting of P=O results in weaker hydrogen bonding,[161] which is confirmed through the O••O intermolecular separations of **34** and **35**. The measured intermolecular O••O bond lengths and O-H••O angles that characterize the H-bond strength are found to be 2.573/151.41 for **34** and 2.710 /151.41 for **35**. These values are consistent with literature data.[150,162]

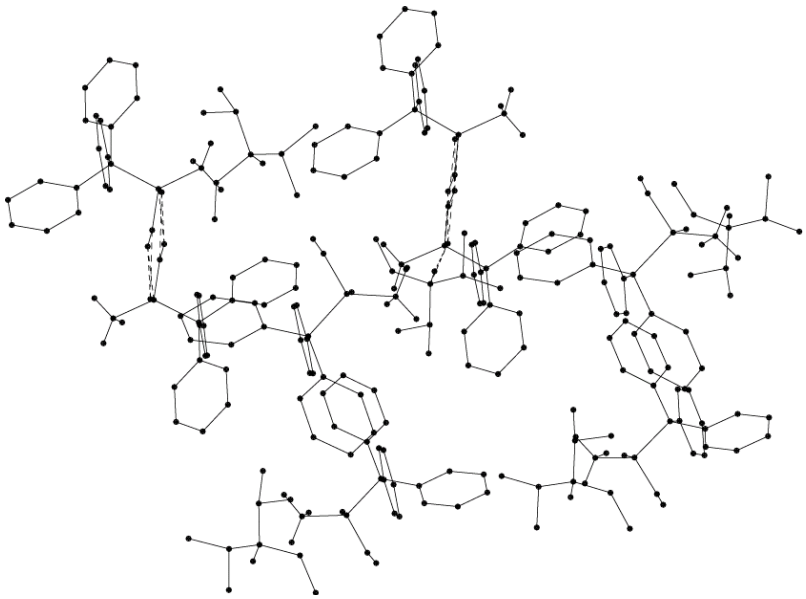


Figure 2.14 Packing Diagram of [$Ph_3CP(OH)BH_3^-$/*i*-Pr_2NEtH^+] (**35**)

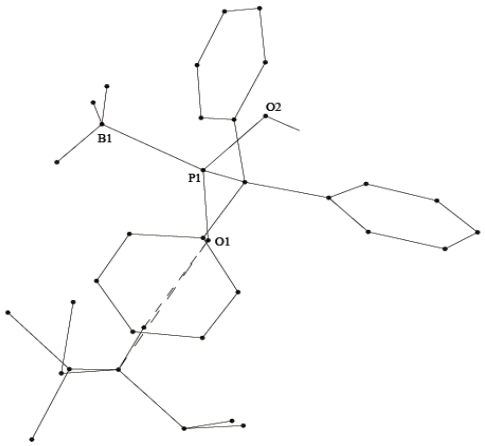


Figure 2.15 Diagram showing H-bonding between the ions in [$Ph_3CP(OH)BH_3^-$/*i*-Pr_2NEtH^+](**35**)

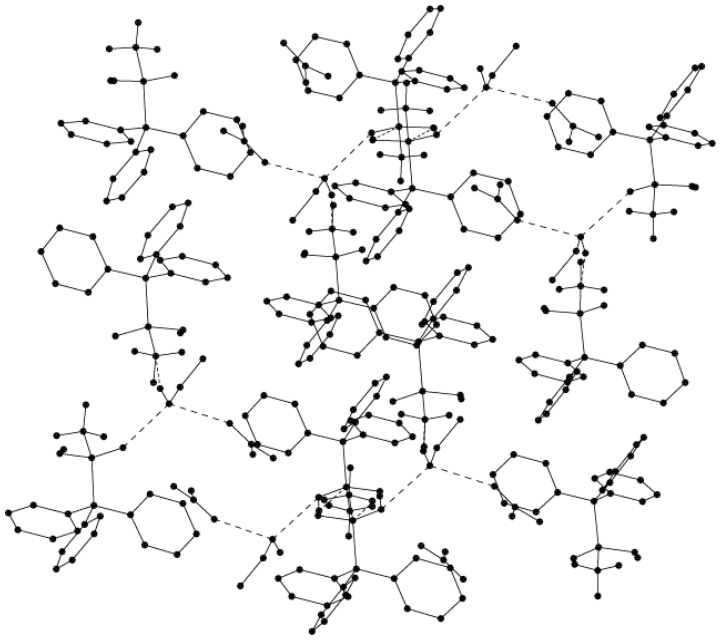
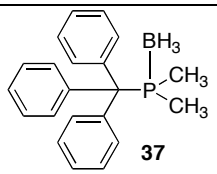
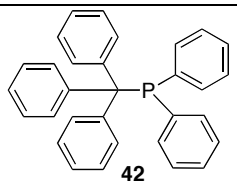
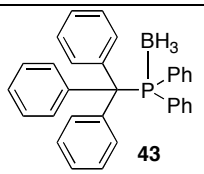


Figure 2.16 Packing diagram of $Ph_3CP(BH_3)(OH)_2$ (**34**)

Pertinent bond lengths and angles of organophosphorus compounds **37**, **42**, and **43** are summarized and compared in Table 2.1.

Table 2.1 A comparison of pertinent bond lengths and angles.[a]

Bond/Angle	 **37**	 **42**	 **43**
P-C (trityl)	1.913(2)	1.9433(19)	1.9265(19)
C1-P1-R1	113.79(12)	105.57(8)	107.91(8)
P1-O1	n/a	n/a	n/a
P1-O2	n/a	n/a	n/a
^{31}P NMR (δ ppm)	27.7 (dm) $J_{P\text{-}B}$= 33 Hz	27.9	39.6

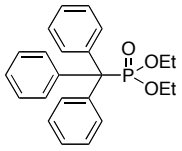
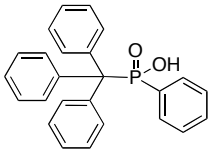
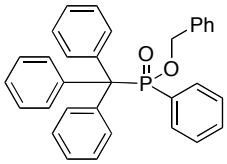
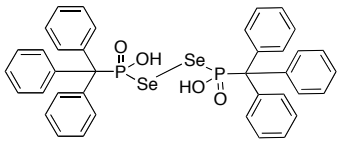
[8] See experimental section for details of the procedures.

To compare the effects of the steric congestion around the phosphorus atom, the phenyl groups were substituted for methyl groups (Figure 2.6). Reducing the steric bulk around the phosphorus atom only leads to a slight shortening of the P–C bond to 1.913(2) Å while the P–B bond of 1.803(3) Å is considerably shorter than that observed in **43** at 1.939(2) Å. The P–C bond length in **37**, is longer than that of 1.887(4) Å observed in $[Ph_3CPMe_3]^+$,[153a] attributed to the removal of electron density from the P-center by the coordinated borane.

Infrared spectroscopy of **43** and **37** exhibit stretches of 2,370 and 2,327 cm^{-1} respectively, corresponding to B–H stretches and absorption at 654 cm^{-1} for **37** associated with the P–B stretch.[165] The ^{31}P chemical shifts of **42** and **37** are similar (at 27.9 for **42** and 27.7 for **37**) while complex **43** has a slightly more downfield shift at 39.6 ppm. The ^{31}P NMR of **42** confirms the solid-state structural assignment of the neutral phosphine as can be compared with the doublet observed at 13.6 ppm for $[Ph_3CP(^+)(H)Ph_2]BF_4^-$.[146,166]

Some pertinent bond lengths and angles of organophosphorus compounds **36**, **38**, **39**, and **40** are summarized and compared in the Table 2.2.

Table 2.2 A comparison of pertinent bond lengths and angles.[a]

Bond/Angle	 **38**	 **39**	 **40**	 **36**
P-C (trityl)	1.8748(19)	1.8753(19)	1.8616(18)	1.876(4)
P1-O1	1.5398(14)	1.4752(14)	1.4671(14)	1.495(3)
P1-O2	1.5106(14)	1.5913(13)	1.5770(14)	1.559(3)
C1-P1-R1	113.93(9)	111.84(8)	113.49(8)	111.89(17)
^{31}P NMR (δ ppm)	45.5	43.9	27.0	39 & 38 (2:8)

[8] See experimental section for details of the procedures.

As expected, the phosphorus species $Ph_3CP(O)(OH)(Ph)$ **39**, $Ph_3CP(O)(OBn)(Ph)$ **40**, $Ph_3CP(O)(OEt)_2$ **38**, and $[Ph_3CP(O)(OH)Se]_2$ **36** exhibit common tetrahedral geometry at the P atom with P–O bonds of 1.5398(14) Å (P1–O1) and (P1–O2) 1.5106(14) Å (Figures 2.5, 2.7, and 2.8).

The change in the oxidation state from P(III) to P(V) causes a shortening of the P-C bond length to 1.8743(19) Å (see lengths of **37**, **42**, **43** versus **36**, **38**-**40**). The hydrogen atom on the protonated oxygen atom was located using the electron density difference map and confirmed by spectroscopic techniques.

When compared with phenyl tritylphosphinic acid (**39**), the diselenophosphinic acid (**36**) contains a slightly shorter P=O bond length (1.495(3) Å), whereas P-OH bond length is slighlty longer (1.559(3) Å for **36** versus 1.5398(14) Å for **39**). Additionally, both carried similar P-C(trityl) bond length (1.8748(19) Å for **39** versus 1.876(18) Å for **36**), which make the bond angle around the P-atom of **36** smaller (111.89(17)° than the one of **39** (113.93(9)°), but equivalent to that of the phosphinic acid benzyl ester **40** (111.84(8)°). It is well known that phosphinic acids dimerize or form species that are hydrogen-bonded.[150,157,158] However, of the

four P(V)-trityl complexes case (**38**, **39**, **40** and **36**), no hydrogen bonding was observed. Comparison of the structural features of **38**, **39**, **40** and **36** with **37**, **42**, and **43** revealed that P-C bond length decreases as the phosphorus oxidation increases from +3 to +5 arising from less repulsion. Consequently, ^{31}P chemical signals shifted downfield.

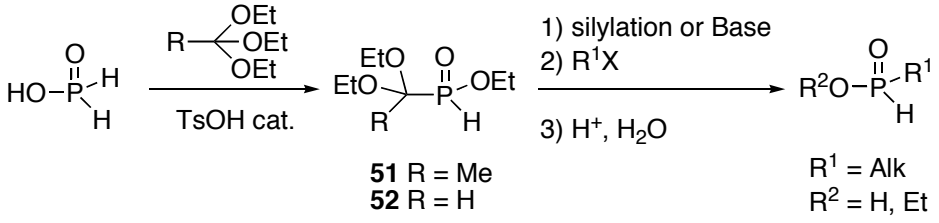
In summary, we have synthesized and fully characterized through single crystal X-ray analysis, and other spectroscopic methods, a series of trityl-containing organophosphorus compounds. As the oxidation state increases from +3 to +5, the length between the phosphorus and the carbon decreases, influencing the ^{31}P chemical shifts. Both phosphonothoic acid $RP(=S)(OH)_2$, and boranophosphonic acids $[RP(O)(BH_3^-)(OH)]LH^+$ (where L is a Lewis base) have been structurally characterized for the first time. The pKa measurements for **34** and **35** indicate that at physiological pH, complete deprotonation would be achieved. Given the importance of the structural parameters for the design of bioactive molecules, and the significant role of the trityl motif along with synthetic and biological value of the organophosphorus compounds, this work provides sets of comparable structural data that can be used as reference for prospective medicinal applications.

<u>Chapter Three:</u> Preparation and reactivity of borane complexes of the hypophosphorous acid P(III) tautomer.

3.1 Introduction

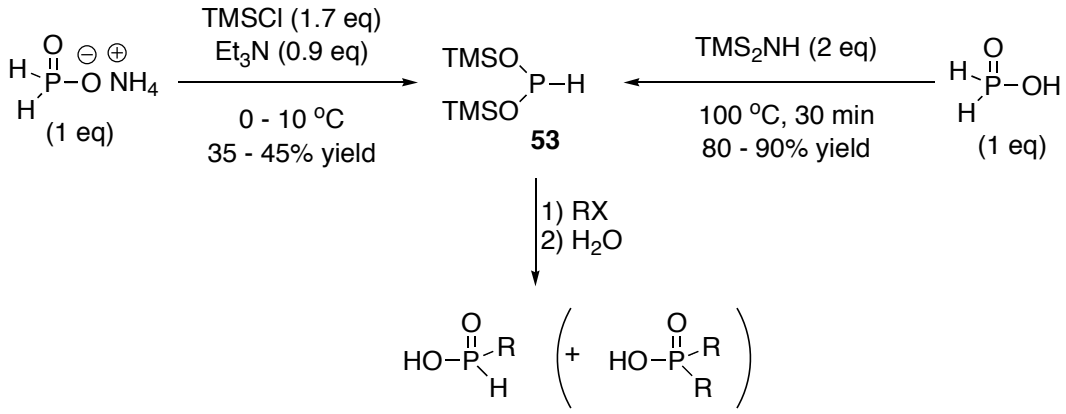
Phosphorus-carbon bond formation remains an active and important research area, as new reactions are continuously being developed for the preparation of organophosphorus compounds. Chapters I and II showed that *H*-phosphinic (phosphonous) acids and derivatives $R_1P(O)(OR)(H)$ are valuable synthetic intermediates for the preparation of other more common phosphorus functionalities. *H*-Phosphinic acids are characterized by the presence of a phosphinylidene [P(O)(H)] moiety that works as a bridge between the P(V) and P(III) forms via a tautomeric equilibrium (Chapter I, Scheme 1.1). The so-called "Ciba-Geigy reagents" $RC(OEt)_2P(O)(OEt)H$ (R = Me, H; **51** and **52**)[4a,4b,38] have been used extensively to prepare *H*-phosphinic acids and esters under a variety of conditions (Chapter I, Section 1.1.1.7), and especially base-promoted alkylation (Scheme 3.1).[68]

Scheme 3.1 "Ciba-Geigy reagents" in the synthesis of phosphinic acid derivatives



Bis(trimethylsiloxy)phosphine **53** ($(TMSO)_2PH$, BTSP)[22a] has also been employed for the synthesis of *H*-phosphinic acids. However, this approach exhibits some problematic issues: the reagent is pyrophoric, and a large excess of BTSP (**53**) is typically required to favor monosubstitution (Scheme 3.2).[22,24,171]

Scheme 3.2 Preparation and reactivity of BTSP

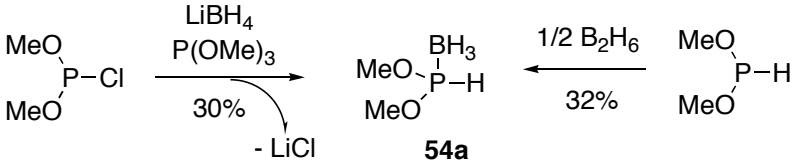


The Montchamp group has been involved in the development of P-C bond forming methodologies based on hypophosphorous acid (H_3PO_2) and its derivatives (alkyl phosphinates $ROP(O)H_2$ and hypophosphite salts) (Chapter I, Section 1.1.1.1)[19,32] for the synthesis of *H*-phosphinates. When successful, the reagents are more suitable than the above alternatives (atom-economy and ready availability). Our group reported recently a butyl lithium-promoted alkylation of alkyl phosphinates $ROP(O)H_2$, but the approach is limited to the more reactive electrophiles (alkyl iodides, and allylic/benzylic bromides) (Chapter I, Eq. 1.12).[37] In 2007, the alkylation of the Ciba-Geigy reagents and other *H*-phosphinate esters using equimolar amounts of reagents was described (Chapter I, Eq. 1.27).[68] The simplicity of the reaction allows the use of various *H*-phosphinate esters and takes place with a wide range of electrophiles. However, the Ciba-Geigy synthons are always deprotected to the desired products (i.e., unmask the P-H bond) under acidic conditions.[4a,4b,38]

In connection with studies aiming at the preparation of bioactive compounds such as GABA analogs, it was desirable to look for a different kind of approach. Therefore, the borane complexes derived from the P(III) form of H_3PO_2 were investigated.[104] Although secondary phosphine-boranes are well known,[98-106] the reactivity of dialkoxyphosphine-boranes

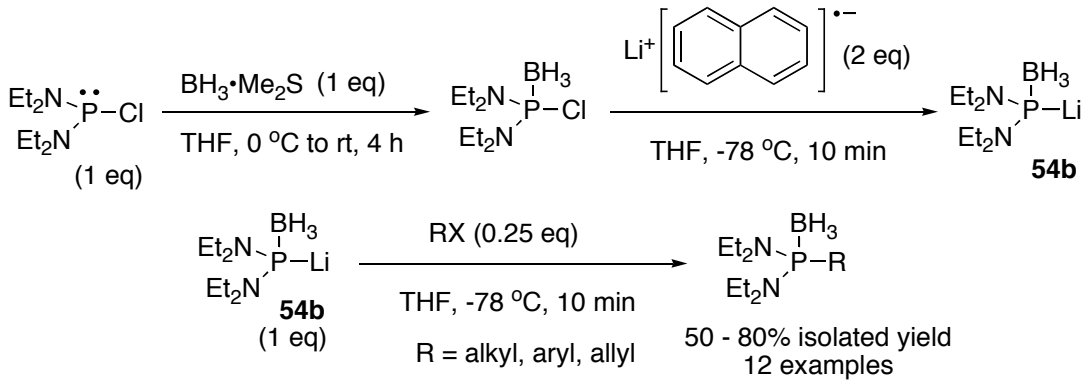
($(RO)_2P(BH_3)H$) towards P-C bond formation has never been reported. In fact, only one previous example of such a dialkoxyphosphine-borane complex was reported in the literature: $(MeO)_2P(BH_3)H$ (Scheme 3.3, compound **54a**).[172] Centofanti described the synthesis of pyrophoric $(MeO)_2P(BH_3)H$, but no further investigation was conducted.[172] We have repeated Centofanti's work and similarly found that the compound is pyrophoric and difficult to purify, resulting, therefore, in a low yield of product. Thus, dimethoxyphosphine-borane (**54a**) is ill-suited for use as a practical reagent.

Scheme 3.3 Centofanti's synthesis of $(MeO)_2P(BH_3)H$

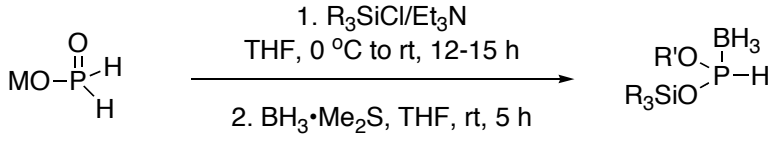


Knochel described a related reagent $(Et_2N)_2P(BH_3)Li$ (Scheme 3.4, compound **54b**) as a phosphorus nucleophile.[173] Reagent **54b** undergoes nucleophilic substitution with primary and secondary alkyl halides, allylic and benzylic bromides, and aryl iodides or bromides, furnishing bis(diethylamino)organophosphine-borane complexes in moderate to good yields.

Scheme 3.4 Preparation and reactivity of the lithiated diaminophosphine-borane complex **54b**



The syntheses and reactivities of novel $(R^1O)(R^2O)P(BH_3)H$ [$R^1 = R^2 = i\text{-}Pr_3Si$ (triisopropylsilyl,[174] TIPS), **55**; R^1 = Et, $R^2 = i\text{-}Pr_3Si$, **56**] reagents as alkyl phosphinate equivalents (Eq. 3.1), along with the diethoxyphosphine-borane[107] $(EtO)_2P(BH_3)H$ (**57**), were investigated. The synthesis of the complexes is straightforward. It was observed that their reactivities are similar to that of the related, but well-known dialkyl-*H*-phosphonates $(RO)_2P(O)H$.



(Eq. 3.1)

M = Et, $PhNH_3$
R_3 = Ph_2Me, Et_3, *t*-$BuMe_2$, *t*-$BuPh_2$, *i*-Pr_3
R' = Et, *i*-Pr_3Si

55 R = *i*-Pr, R' = *i*-Pr_3Si

56 R = *i*-Pr, R' = Et

These reagents (**55-57**) exhibit a significant advantage as they can be employed for the syntheses of *H*-phosphinates, unsymmetrically disubstituted phosphinic derivatives,[108] and boranophosphonates. The latter approach is particularly interesting because, at least conceptually, the initial silylation step constitutes both a protection step, and formation of a latent phosphonite poised for a sila-Arbuzov[23,61,175] reaction upon decomplexation. Notably, the Ciba-Geigy reagents have also been derivatized using sila-Arbuzov reaction. However, this reaction must be performed separately from the initial protection as an acetal.

Also, considering the biochemical potential of boron-containing compounds (Chapter II),[69a,132-139] the synthesis of boranophosphonates, which are phosphonic acid analogs, was investigated and achieved (results discussed in Section 3.2.4.2).

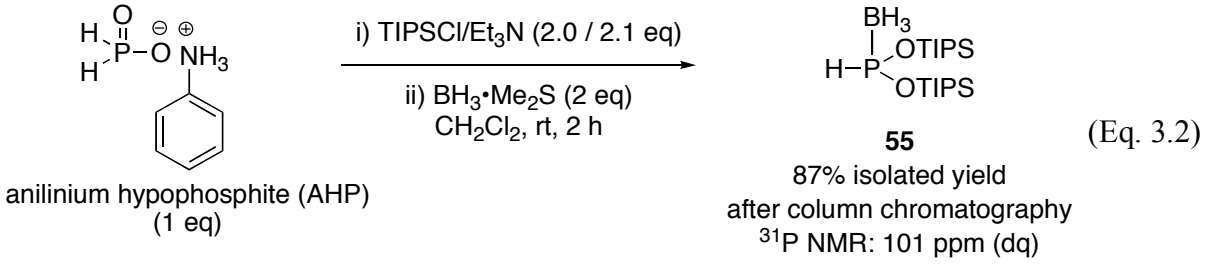
After functionalization through alkylation and related methods, the phosphonite-borane complexes can be directly converted into unsymmetrical disubstituted phosphinic acid

derivatives via a one-pot decomplexation/Arbuzov reaction.[108] Related to this chemistry, Montchamp previously reported that the decomplexation can be conducted under either basic (amine) or acidic (HBF_4) conditions,[108] consequently expanding in a significant way the range of applications. Furthermore, the *H*-phosphinate ester was obtained without hydrolysis of the P-O bond.[108]

3.2 Results and discussion

3.2.1 Synthesis

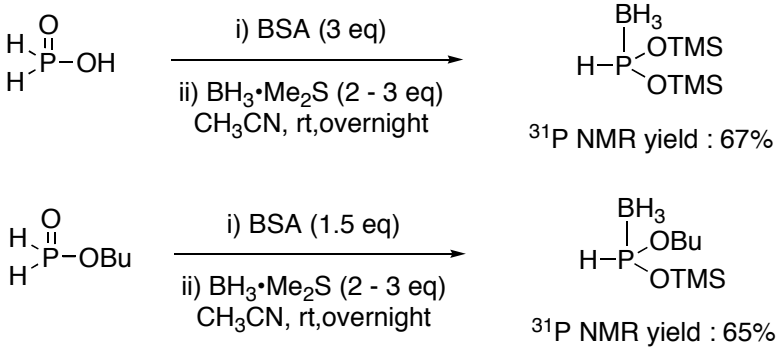
We first examined the formation of borane complexes of BTSP (**53**) and related species. Since the borane complex of BTSP is too easily hydrolyzed to be useful, a study of more robust silicon groups was undertaken. It was found that the triisopropylsilyl group (TIPS)[174] provided excellent stability of the complex, so much so, in fact, that the complex $(TIPSO)_2P(BH_3)H$ (**55**) can be isolated uneventfully by chromatography over silica gel. Complex **55** was found to be completely stable to air and moisture (Eq. 3.2).



(Eq. 3.2)

Jennifer Tellez, a co-worker in the Montchamp group, has observed that, reacting either H_3PO_2 or butyl phosphinate $BuOP(O)H_2$ with an excess of BSA afforded the expected phosphine-borane complexes in moderate crude ^{31}P-NMR yields (Scheme 3.5), along with the formation of various by-products. Using TIPS furnished better results in terms of yield and stability of the product (Eq. 3.2).

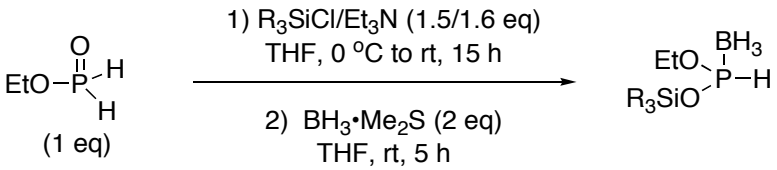
Scheme 3.5 Silylation-complexation of hypophosphorous derivatives

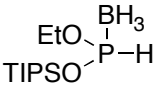
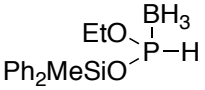
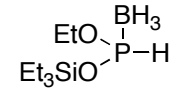
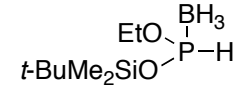
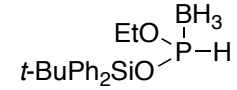


Gratified by the results obtained with TIPS, the silylation/borane complex-formation with various chlorosilanes was also investigated on ethyl phosphinate $EtOP(O)H_2$ and the results are summarized in Table 3.1. Ethyl phosphinate was prepared and used in situ by following the previously reported procedure (Chapter I, Section 1.1.1.1).[14,20]

Although some silicon protecting groups provided reasonably stable products **58** and **59** (Table 3.1, entries 4 and 5), once again the best result was obtained with TIPS[174] both in terms of stability and yield (entry 1, compound **56**). Consequently, the resulting $(EtO)(TIPSO)P(BH_3)H$ (**56**) was selected for subsequent reactivity studies, and the results will be discussed in section 3.2.2.

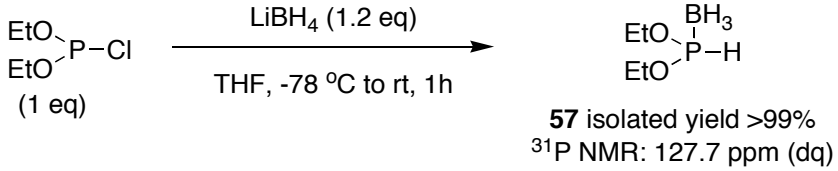
Table 3.1 Preparation of (ethoxy)(trialkylsiloxy)phosphine-borane complexes[a]



Entry	R_3SiCl	Product[b]		^{31}P NMR chemical shift (δ ppm)	Isolated yield %[c] (NMR yield %)[d]
1	TIPSCl		**56**	116.8	100 (100)
2	$Ph_2MeSiCl$			117.7	(62)
3	Et_3SiCl			114.2	(69)
4	*t*-$BuMe_2SiCl$		**58**	114.7	79 (81)
5	*t*-$BuPh_2SiCl$		**59**	114.5	91 (94)

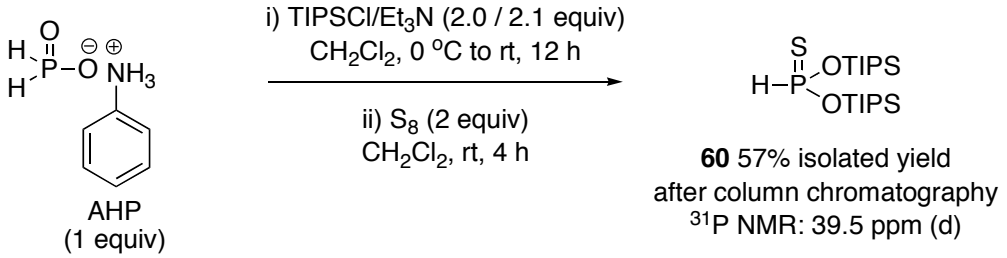
[a] See Experimental Section for details of the procedures; [b] (a) 1 equiv $EtOP(O)H_2$, 1.5 equiv R_3SiCl, 1.6 equiv Et_3N, THF, 0 °C to rt, 15 h, (b) 2 equiv BH_3•Me_2S, THF, rt, 5 h; [c] Isolated yield of pure compounds after chromatography on silica gel; [d] NMR yields are determined by integrating all the resonances in the ^{31}P NMR spectra of the reaction mixtures.

Next, diethoxyphosphine-borane complex $(EtO)_2P(BH_3)H$ (**57**) was prepared from the commercially available chlorodiethoxyphosphine (Eq. 3.3). Reduction with lithium borohydride provided **57** directly, and in excellent isolated yield after chromatographic purification. The yield and stability of **57** are quite remarkable considering the reported and verified low yield and pyrophoric nature of the methyl analog **54** (Scheme 3.3).[172] Replacing lithium borohydride by the inexpensive sodium borohydride would be much more practical and cost-effective. However, sodium borohydride did not give satisfactory results under a variety of conditions for the preparation of complex **57**.



(Eq. 3.3)

Based on the unique stabilities observed with the TIPS-borane complexes, we decided to turn our attention to the preparation of the sulfur equivalent to complex **55** (Eq. 3.4). As expected, compound **60** was stable even to chromatography on silica gel. Although Voronkov described the spectral properties of $(TMSO)_2P(S)H$, no synthesis, yield, nor discussion of its chemical properties were included.[23a] It is however likely that the TMS esters are too labile. Complex **60** could be a useful synthon for the preparation of compounds with biological interests such as phosphonothioic acids (Chapter II), but this was not investigated.



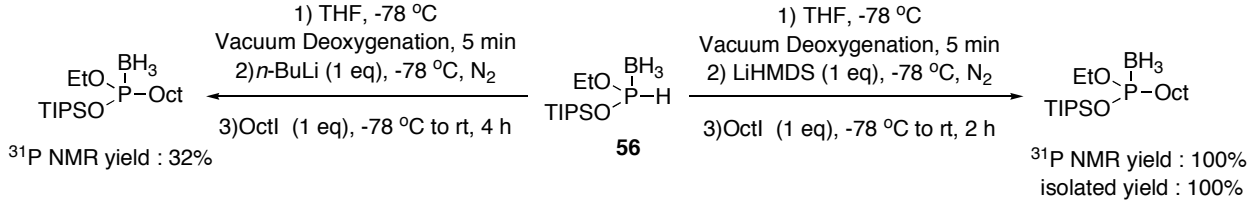
(Eq. 3.4)

3.2.2 Reactivity of borane complexes: alkylation

The Montchamp group recently reported a general alkylation protocol for *H*-phosphinate esters using LiHMDS as a base (Chapter I, Section 1.1.2.2, Eq. 1.27).[68] The main features are the equimolar ratios of the base, phosphorus nucleophile, and carbon electrophile, and the broad scope of these conditions. A moderate, deoxygenation protocol was found to be necessary with less reactive electrophiles. The reaction provided a viable alternative to the Arbuzov-like

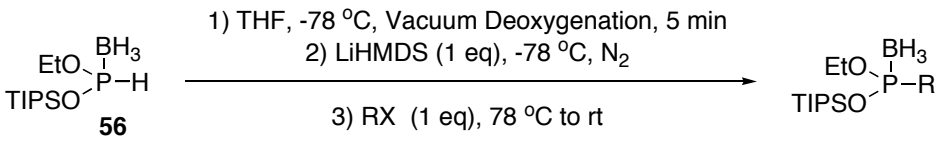
silylation methodology. Considering the efficiency of the reported alkylation protocol,[68] we envisioned the possibility to conduct the base-mediated alkylation of complexes **56** and **57**. Reagent **56** was selected as a test substrate to determine the choice of base (*n*-BuLi or LiHMDS), with octyl iodide as the electrophile (Scheme 3.6). The phosphorus nucleophile, octyl iodide and base were used in equimolar quantities, and the results were studied by ^{31}P-NMR of the crude mixture. Although alkylation takes place in both cases, significant differences are observed. The nucleophilic base *n*-BuLi gives lower yield, whereas the strong non-nucleophilic base LiHMDS gives better results (compound isolated in quantitative yield).

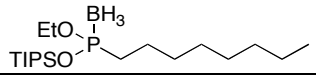
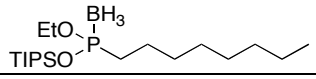
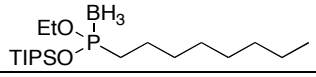
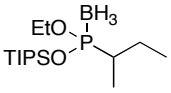
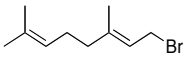
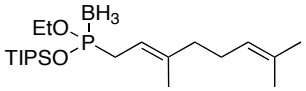
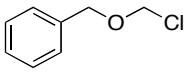
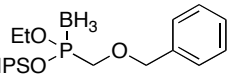
Scheme 3.6 Base-mediated alkylation of (TIPSO)(EtO)P(BH$_3$)H (**56**) with octyl iodide



Therefore, LiHMDS was selected as the base of choice in the alkylation studies with borane complexes. As described for the alkylation of *H*-phosphinates,[68] moderate deoxygenation affords better yields. Alkylation generally took place smoothly under these conditions. The results obtained with complex (EtO)(TIPSO)P(BH$_3$)H (**56**) are summarized in Table 3.2. In general, the alkylation products were isolated in excellent yields. Various alkyl halides, and a tosylate reacted uneventfully. Entry 4 shows that even a secondary iodide could be employed, leading to the desired product in 85% isolated yield.

Table 3.2 Scope of the base-promoted alkylation of (TIPSO)(EtO)P(BH_3)H (**56**)



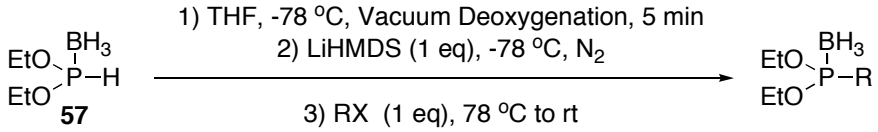
Entry	Electrophile	T °C	Reaction Time	Product	Isolated yield, %[b] (NMR yield, %)[c]
1	CH_3I	-78 °C to rt	4 h		100 (100)
2	OctBr	-78 °C to rt	5 h		100 (100)
3	OctOTs	-78 °C to reflux	12 h		90 (94)
4		-78 °C to rt	4 h		85 (100)
5		-78 °C to rt	5 h		80 (94)
6		-78 °C to rt	12 h		100 (92)

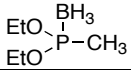
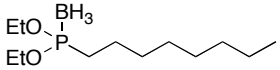
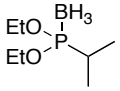
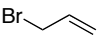
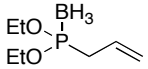
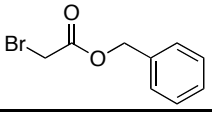
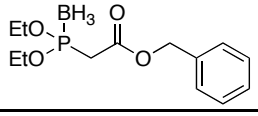
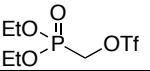
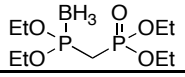
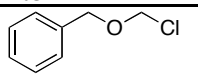
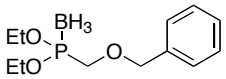
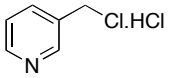
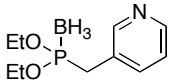
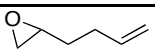
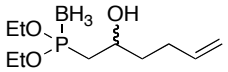
[a] Deoxygenation was conducted by placing a THF solution of the (EtO)(TIPSO)P(BH_3)H under vacuum at -78 °C for 5 min, then adding N_2. [b] Isolated yield of pure compounds after chromatography on silica gel. [c] NMR yields are determined by integrating all the resonances in the ^{31}P NMR spectra of the reaction mixtures.

These results are at least comparable to those reported with the Ciba-Geigy reagents.[1,68] Unfortunately, 2-chlorooctane did not react satisfactorily, even with higher temperature and longer reaction time.

Diethoxyphosphine-borane complex $(EtO)_2P(BH_3)H$ (**57**), was similarly alkylated in moderate to good isolated yields (Table 3.3). The reaction performed on a secondary iodide gave a moderate yield of alkylated product (entry 3). Unfortunately, the reaction with a bromoacetate (entry 5) did not give a good yield of product, even when excess base (> 2 equiv) was employed.

Table 3.3 Scope of the Base-Promoted Alkylation of $(EtO)_2P(BH_3)H$ (**57**)

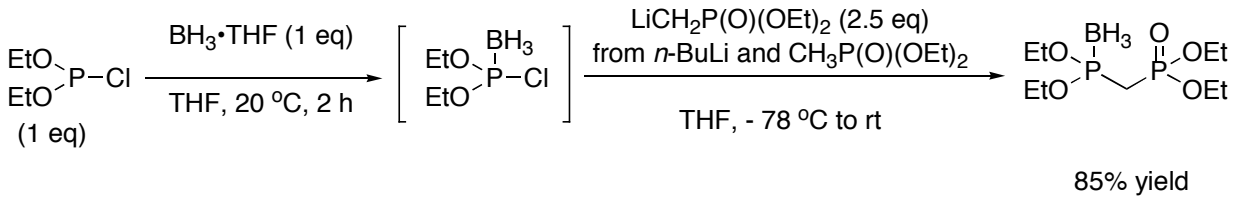


Entry	Electrophile	Reaction Time	Product[a]	^{31}P NMR chemical shift (ppm)	^{11}B NMR chemical shift (ppm)	Isolated yield, %[b]
1	CH_3I	2 h		149.7	-41.8	80
2a	OctI	4 h		148.9	-42.2	74
2b	OctBr	4 h				77
3		4 h		154.8	-45.0	49
4		12h		144.0	-42.9	69
5		12 h		139.1	-42.2	25
6		12 h		138.8 & 19.9	-41.4	52
7		20 min		138.0	-43.0	89
8[c]		12 h		143.0	-43.0	69
9a		12 h		146.8	-42.2	36
9b	$+BF_3{\bullet}Et_2O$	12 h				50

[a] See Experimental Section for details of the procedures; [b] Isolated yield of pure compounds after chromatography on silica gel; [c] 2 eq of LiHMDS were used.

Entry 6 shows that a phosphonate-phosphonite borane complex can be also prepared and obtained in moderate yield. Bisseret prepared the same phosphonate-phosphonite borane by a different (and admittedly simpler) route, and he demonstrated its use for the preparation of various pyrophosphate analogs (Scheme 3.7).[176] The methodology revealed that phosphine-borane complex **57** reacted satisfactorily with an epoxide, and in this case, the use of a Lewis acid improved the yield significantly (entry 9a versus entry 9b).

Scheme 3.7 Preparation of phosphonate-phosphonite borane complex via Bisseret method[176]

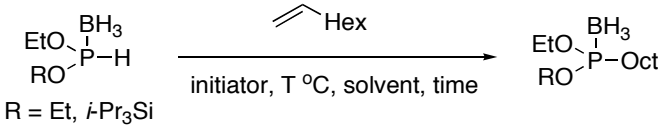


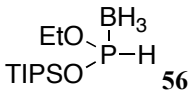
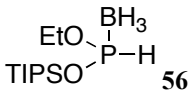
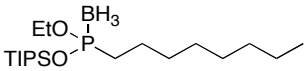
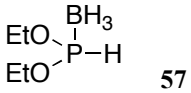
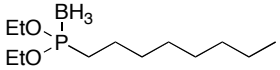
3.2.3 Other reactions

3.2.3.1 Radical Reactions

The radical-based methodology for carbon-phosphorus bond formation has found significant development in various research groups (Chapter I, section 1.1.1.9). Montchamp has recently reported an efficient approach for the free-radical addition of hypophosphorous compounds to unsaturated substrates (Chapter I, Scheme 1.7).[52] Using Et_3B/O_2 as initiator, addition of H_3PO_2 (its salts AHP and $NaOP(O)H_2$, or its esters) to alkenes occurs at room temperature, in an open flask.[52] AIBN-initiated radical hydrophosphinylation of alkenes and alkynes with alkyl phosphinates proceeds effectively at 80°C.[53] In addition, room temperature radical addition of $NaOP(O)H_2$ to terminal alkynes produces the previously unknown 1-alkyl-1,1-bis-*H*-phosphinates,[12,54] which are novel precursors of the biologically important 1,1-bisphosphonates (Chapter V).[13] Considering the significant impact of this methodology, the reactivity of borane complexes **56** and **57** in free radical reactions was also briefly investigated. The results are shown in Table 3.4. Interestingly, the thermal AIBN-initiated reaction was completely unsuccessful, whereas our Et_3B/air protocol for generating P-centered radicals[52] gave good yields of isolated products. Note that the reaction conducted with AIBN afforded the desired product in 31% crude yield only, and complete decomplexation and hydrolysis was observed after long periods of heating (18 hours).

Table 3.4 P-C bond formation via radical-mediated addition of 1-octene[a]



Entry	Substrate	Reaction conditions	Product	Isolated yield,[b] %
1	 **56**	AIBN (3 x 0.2 equiv), CH_3CN, under N_2, reflux, 12 h	-	-
2	 **56**	Et_3B (1 equiv), MeOH/dioxane (5:1), air, rt, 5 h		67
3	 **57**	Et_3B (1 equiv), MeOH/dioxane (5:1), air, rt, 4 h		66

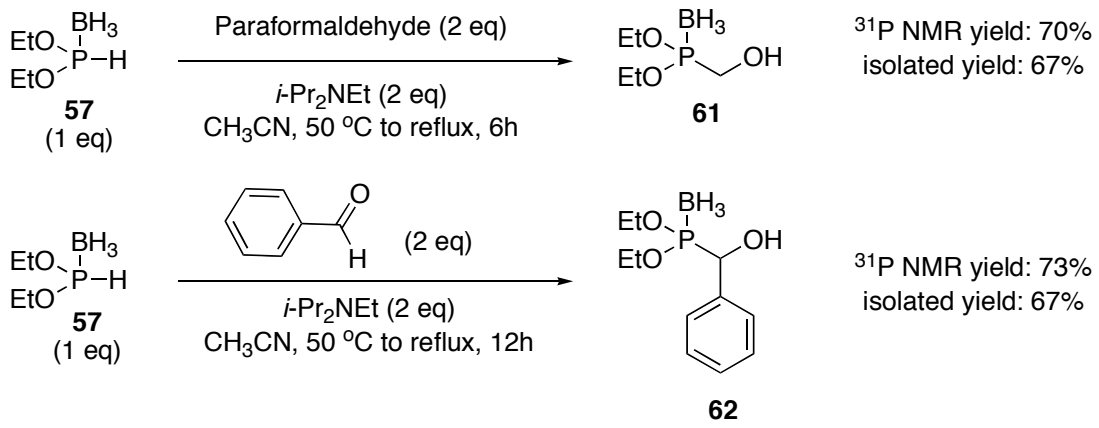
[a] See Experimental Section for details of the procedures; [b] Isolated yield of pure compounds after chromatography on silica gel.

Once again, the direct radical reaction of $ROP(O)H_2$ reported previously by our group is superior to the present reaction (Chapter I, Section 1.1.1.9).[14,20,52] However, the possibility to extend this chemistry to chiral borane complexes could provide an approach to asymmetric P-C bond-forming reactions. It is also important to note that the radical reactions of the Ciba-Geigy reagents **51** and **52**, are either inefficient, or require specialized initiators.[4g] Thus, the new synthons described herein provide added flexibility in terms of the range of available reactions.

3.2.3.2 Addition to carbonyl compounds

Borane complex **57** could also be added to carbonyl compounds using *i*-Pr_2NEt as the base (Scheme 3.8). Phosphine-borane complexes **61** and **62** were obtained in good yield. While the direct addition of $ROP(O)H_2$ to carbonyl compounds is superior,[14,20] the possibility to examine chiral dialkoxyphosphine-borane complexes is intriguing in this context. On the other hand, complex **56** did not add to carbonyl compounds under identical conditions.

Scheme 3.8 Reaction of Complex **57** with carbonyl Compounds

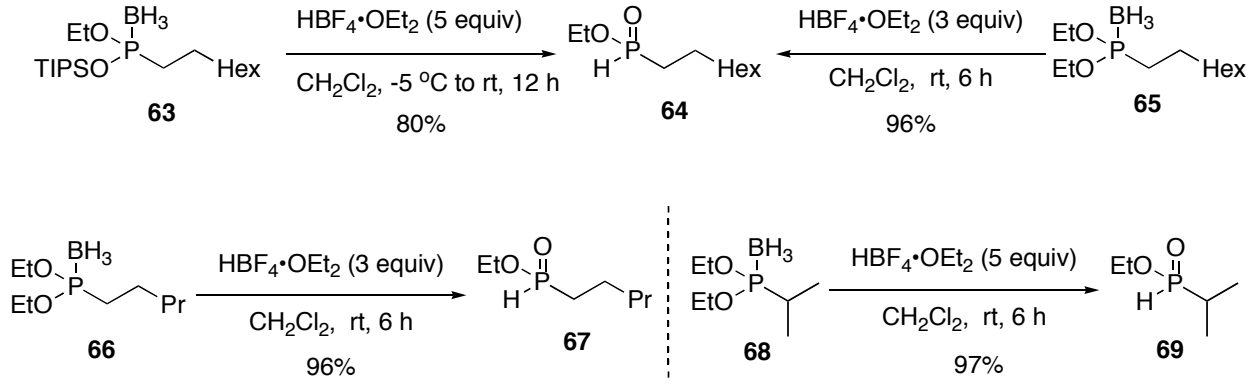


3.2.4 Deprotection of phosphonite-boranes complexes

3.2.4.1 Decomplexation: conversion into *H*-phosphinates and disubstituted phosphinates

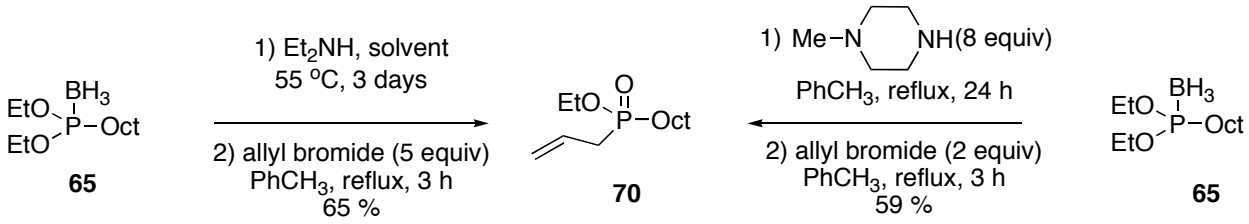
For the strategy to be useful, the ability to deprotect the borane complexes must be available. Thus, we investigated the conversion of the phosphonite complexes (**63**, **65**, **66**, and **68**) to the corresponding *H*-phosphinates. As with the related phosphine-borane complexes,[177] treatment with tetrafluoroboric acid (HBF_4•Et_2O) leads readily to the *H*-phosphinate esters **64**, **67** and **69** in excellent yields (Scheme 3.9). The P-O ester bond is not cleaved in this process. It should be noted that with the Ciba-Geigy reagents, only **51** can be deprotected ($TMSCl/CHCl_3$) without cleavage of the phosphorus ester functionality.[1]

Scheme 3.9 Decomplexation of phosphonite-borane complexes into *H*-phosphinate esters



Interestingly, decomplexation of compounds derived from **57** can also be conducted through treatment with an amine base. In addition, the Montchamp group previously reported a tandem decomplexation/Arbuzov reaction leading to a disubstituted phosphinate ester in "one-pot" (Scheme 3.10).[107,108] 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.

Scheme 3.10 Conversion of phosphonite-borane complexes into phosphinate esters



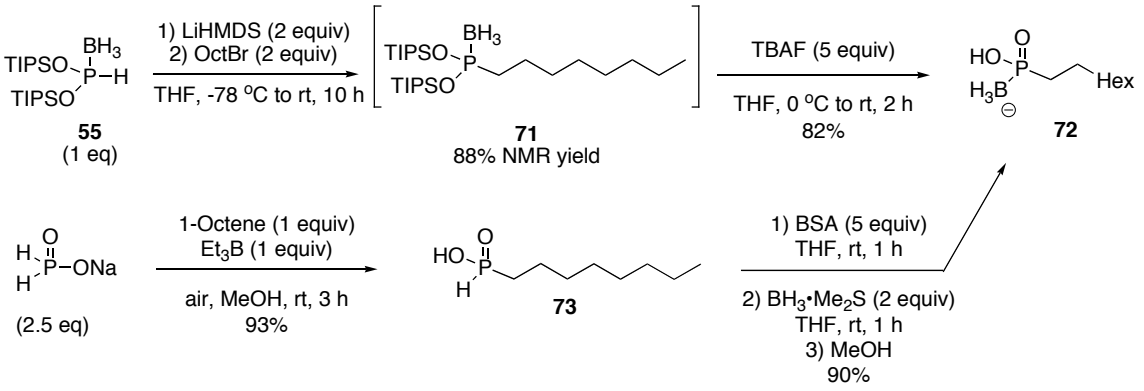
3.2.4.2 Boranophosphonate synthesis

While the chemistry of boranophosphonates is still limited, this class of compounds could constitute biologically active analogs of phosphonates, or prodrugs of *H*-phosphinates (Chapter II).[109,132,151] Scheme 3.11 shows an application of our reagent $(TIPSO)_2P(BH_3)H$ (**55**) in the preparation of a boranophosphonate. LiHMDS-mediated alkylation of **55** with octyl bromide afforded complex **71** in good yield. Without purification, complex **71** was directly converted into the corresponding boranophosphonate **72** by using a large excess of tetrabutylammonium fluoride (TBAF). The final product was isolated in good yield (82%) after simple extractive work-up.

Alternatively, boranophosphonates can be easily prepared from the corresponding *H*-phosphinic acid **73**, via silylation/borane complex formation/hydrolysis (Scheme 3.11). Although this approach is more straightforward than the one which uses **55**, it obviously implies the availability of the *H*-phosphinic acid precursor. Furthermore, the use of **55** provides added

flexibility in terms of the variety of compounds which could be synthesized from the same intermediate (i.e. more divergent). However, Wada and coworkers recently claimed that the methodology using silyl *H*-boranophosphonate derivatives as precursors of alkylboranophosphonates is difficult to apply to the synthesis of more functionalized molecules, such as nucleotide analogues.[132g]

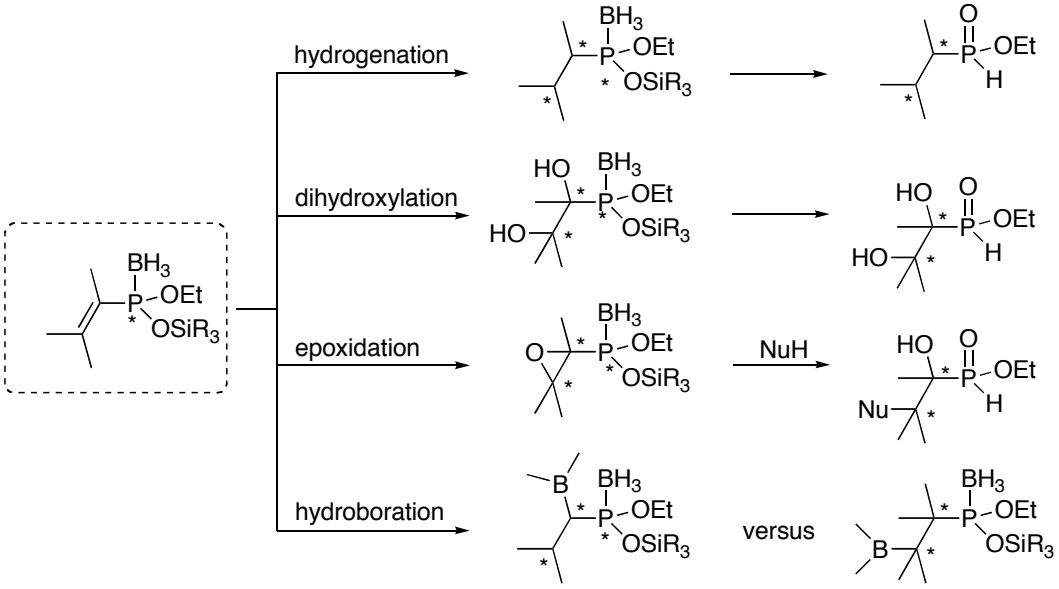
Scheme 3.11 Boranophosphonate synthesis.



3.2.5 Temporary protection of *H*-phosphinates with TIPSCl and BH_3

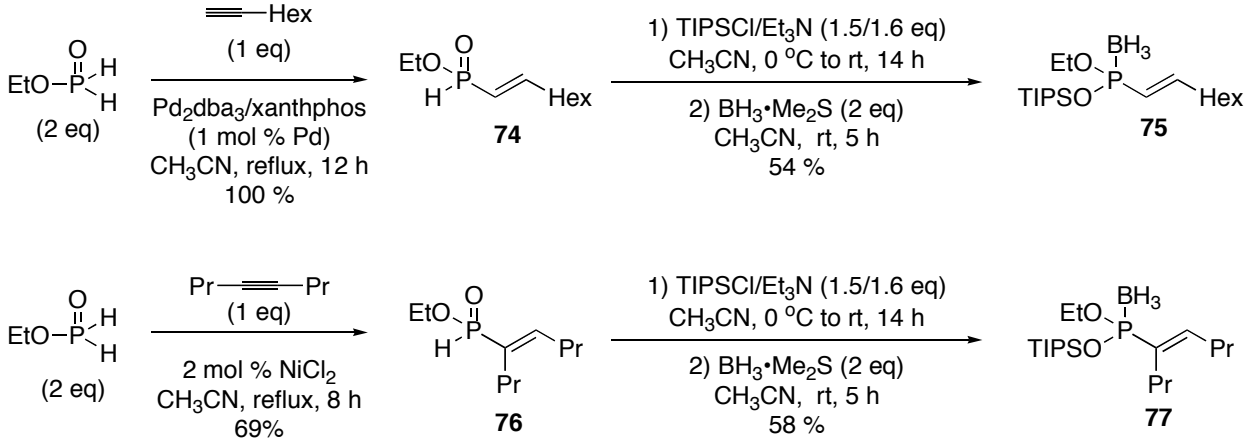
Many reactions are not compatible with the presence of the phosphinylidene group P(O)H (Chapter I, Scheme 1.1). The Montchamp group has developed new synthetic methodologies for the synthesis of *H*-phosphinates RPO_2H_2 and RP(O)(OR')H (Chapter I), but obstacles still exist. The easily oxidized P-H bond prevents the synthesis of highly functionalized *H*-phosphinates. A similar silylation strategy with TIPSCl can be employed for the temporary protection of *H*-phosphinate esters. Thus, using a temporary protection as the TIPS/borane-phosphonite complex could not only allow the elaboration of the carbon chain, but also potentially lead to asymmetric reactions (Scheme 3.12). In the instances shown in the following scheme, various reactions, such as asymmetric dihydroxylation, epoxidation, hydroboration, or hydrogenation, could be conceived after protection.

Scheme 3.12 Proposed asymmetric reactions of protected H-phosphinates

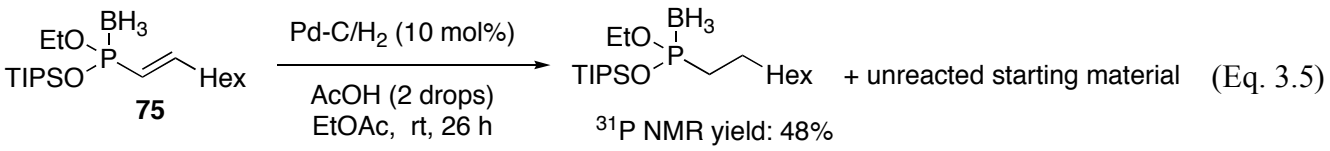


The Pd- or Ni-catalyzed hydrophosphinylation of $(EtO)P(O)H_2$ with terminal[56,57] or internal[58] alkyne respectively afforded unsaturated *H*-phosphinate esters **74** and **76** (Scheme 3.13). Both were converted into their corresponding phosphonite-borane complexes **75** and **77** in moderate yields.

Scheme 3.13 Protection of *H*-Phosphinates as Phosphonite-Borane Complexes



Reduction of the unsaturated carbon-carbon bond of complex **75** via hydrogenation was investigated. Preliminary results showed that complex **75** reacted sluggishly in the presence of acetic acid. Even after 26 hours, the reaction did not reach completion (Eq. 3.5).



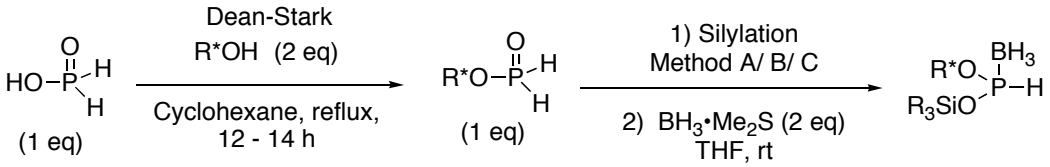
(Eq. 3.5)

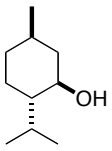
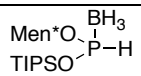
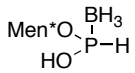
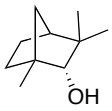
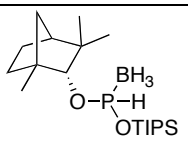
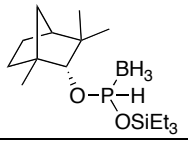
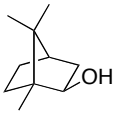
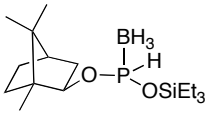
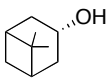
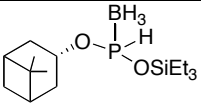
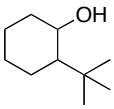
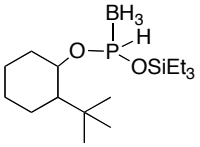
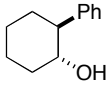
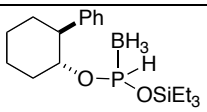
3.2.6 Chiral phosphorus equivalent: expanding the methodology

Guided by the prospect of developing an asymmetric approach to *P*-chiral phosphine-borane complexes, various hindered chiral auxiliaries have been employed for the preparation of new chiral phosphonite-borane synthons. Preliminary results are summarized in Table 3.5. A series of chiral phosphinate esters was easily prepared via esterification using a Dean-Stark trap. Phosphinate esters were directly used for the formation of the corresponding phosphonite-boranes. Due to the steric hindrance of the chiral auxiliaries, silylation with TIPS appeared to be problematic in general. However, when a smaller silicon group, such as Et_3Si (entries 2-6, Method C), was used, the formation of the phosphine-borane complexes occured.

In principle, isolation of the diastereoisomers would provide a useful synthesis of *P*-chiral synthons. However, due to the fact that the diastereoisomeric phosphine-boranes are extremely non-polar, their separation by simple column chromatography was impossible (entry 1, Method B and entries 3-5) .

Table 3.5 Preparation of chiral dialkoxyphosphine-borane complexes[a]

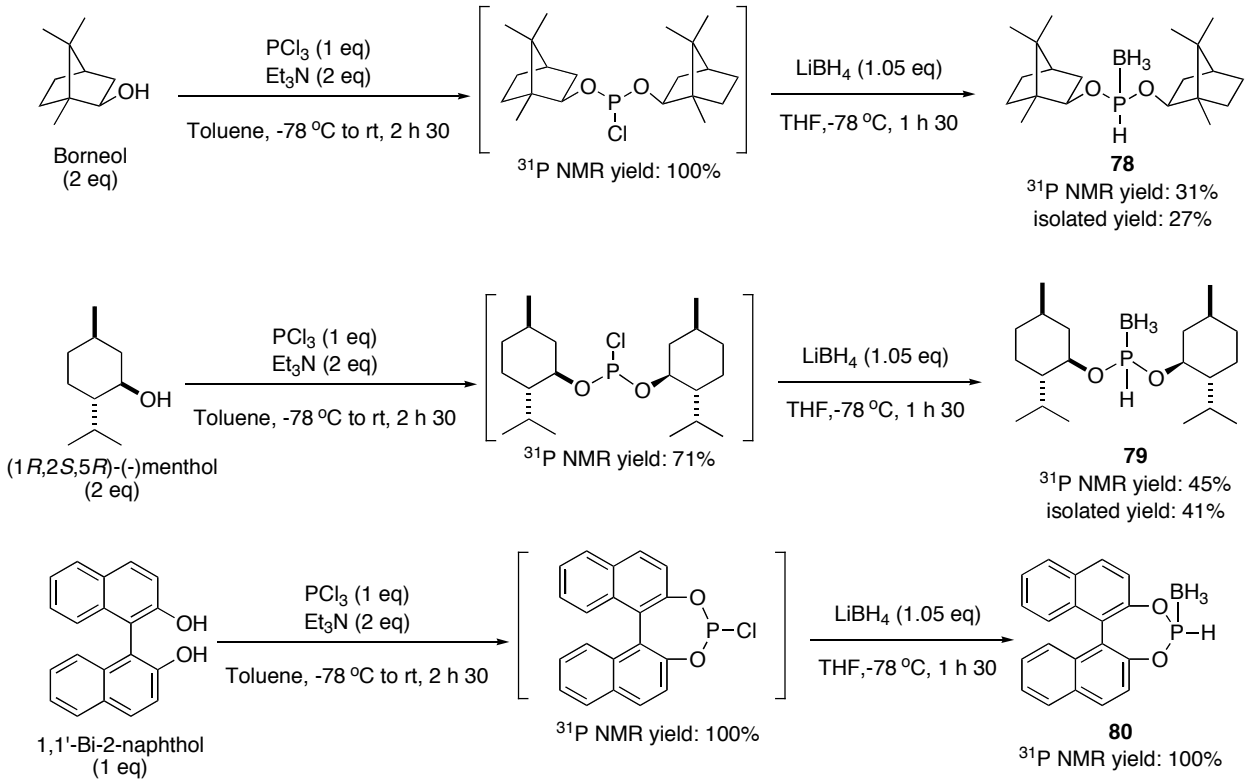


Entry	R*OH	R*O–P(O)H–H Yield, %	Reaction conditions Silylation/borane protection[b]	Product	Isolated Yield,[c] % (NMR Yield, %)
1		84	A		65 (90)
			B		51[e] (100)
2		100	A[d]		89 (93)
			C		70 (74)
3		100	C		67[e] (74)
4		100	C		51[e] (60)
5		100	C		39[e] (43)
6		82	C		(22)

[a] See Experimental Section for details of the procedures. [b] Method A: (a) 1 equiv R*OP(O)H_2, 1.5 equiv TIPSCl, 1.6 equiv Et_3N, 0 °C to rt, 12 h (b) 2 equiv BH_3•Me_2S, rt, 3 h. Method B: (a) 1 equiv R*OP(O)H_2, 1 equiv BSA, 0 °C to rt, 2 min (b) 2 equiv BH_3•Me_2S, rt, 1 h. Method C: (a) 1 equiv R*OP(O)H_2, 1.5 equiv Et_3SiCl, 1.6 equiv Et_3N, 0 °C to rt, 12 h, (b) 2 equiv BH_3•Me_2S, rt, 2 h. [c] Isolation after extractive workup followed by chromatography on silica gel. Mixture of isomers. [d] After addition of TIPSCl and stirred for 10 h, no silylated product was formed, therefore 1.5 equiv BSA was added. Within a minute, silylation occurred and reaction mixture quenched with 2 equiv BH_3•Me_2S at rt. [e] Mixture of isomers.

Another approach for the preparation of chiral synthons relies on the methodology used for the formation of **57**, which consists of the preparation of $(R^*O)_2PCl$ (with R* = chiral auxiliary) and subsequent conversion into the corresponding $(R^*O)_2P(BH_3)H$ (Scheme 3.14, compounds **78**, **79**, and **80**). The yields were moderate to low. Note that the biaryl derivative **80** was not isolated due to the fact that this phosphine-borane is extremely sensitive to air and moisture (compound readily oxidized). Once again, these results are just preliminary.

Scheme 3.14 Preparation of chiral phosphonite-borane synthons



In summary, the straightforward preparation of three novel phosphorus synthons displaying remarkable stabilities was described. When available, the direct reaction of alkyl phosphinates $(RO)P(O)H_2$ is always superior to this protecting group strategy, as it was demonstrated in the past. However, limitations still exist for the direct synthesis of *H*-phosphinate esters, especially through alkylation with alkyl halides. While the "Ciba-Geigy"

reagents have solved a number of problems, these always require acidic conditions to unmask a P-H bond, and the preparation of the reagents is not shorter or more convenient.

The advantages of the borane complexes described herein are: 1) possible unmasking under either basic or acidic conditions, 2) the possibility for tandem decomplexation-Arbuzov functionalization to disubstituted phosphinates, and 3) the preparation of boranophosphonates. Therefore, the novel borane complexes which are derived from the $HP(OH)_2$ tautomer, provide added flexibility for the preparation of organophosphorus compounds. The present strategy should be useful for the preparation of functionalized phosphinates, and the extension to a chiral version of **56** and **57** is under investigation. Preliminary reactivity studies indicate a broad range of applications. The trapping of *H*-phosphinates as P(III) borane complexes is also potentially useful to modify the carbon chain under conditions which might otherwise not be compatible with the P(O)-H functionality, and this strategy will be explored further.

In addition, the protection of *H*-phosphinates as stable TIPS/borane phosphonite complexes opens up the possibility for functionalizing the carbon chain of *H*-phosphinate precursors.

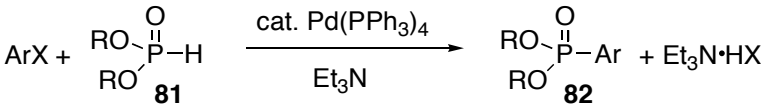
While much work remains to be explored, the chemistry described herein provides a platform for numerous extensions and applications. For example, the direct conversion of the phosphonite-borane complexes into phosphonothioates (useful as antiviral agents, antibacterial agents, and pesticides)[1] is also a possibility that needs to be considered.

<u>Chapter Four:</u> Palladium-catalyzed cross-coupling reaction of aryl and heteroaryl halides: Hirao's cross-coupling revisited

4.1 Introduction

Advances in organometallic catalysis, especially transition-metal-catalyzed bond forming reactions, have revolutionized organic synthesis. During the past few years, intensive investigations have been conducted for the formation of carbon-carbon[178] and carbon-heteroatom[179] bonds by transition-metal-catalyzed cross-coupling methodology. Most notably, palladium, and to a lesser extent, other transition metals such as copper and nickel, have shown their utility and have become exceedingly important for the formation of carbon bonds to nitrogen,[180] oxygen,[181] and sulfur.[182] Bonds to phosphorus are no exception.

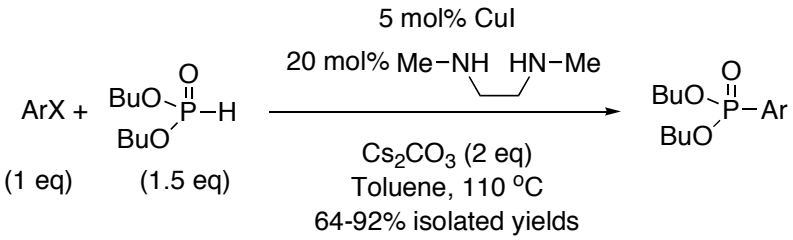
In pioneering studies, Hirao reported in the early 1980s, the palladium-catalyzed cross-coupling of dialkylphosphites $(RO)_2P(O)H$ (**81**) with aromatic halides (Eq. 4.1).[87] Even if some transition-metal (e.g. copper and nickel) were previously used for the preparation of phosphonates,[183] the Hirao reaction has since become the standard method for the synthesis of functionalized aromatic phosphonate alkyl esters **82** using *H*-phosphonate.[184]



(Eq. 4.1)

H-Phosphonates are important synthetic precursors in the preparation of a diverse array of biologically important phosphonates and their analogs.[1] However, the preparation of the latter via palladium-mediated cross-coupling is not economically attractive, especially since the reported conditions require a high catalyst loading (not lower than 3 mol% and usually 5 mol% in the case of Hirao's conditions),[87,183] and a multi-gram scale syntheses are still lacking.

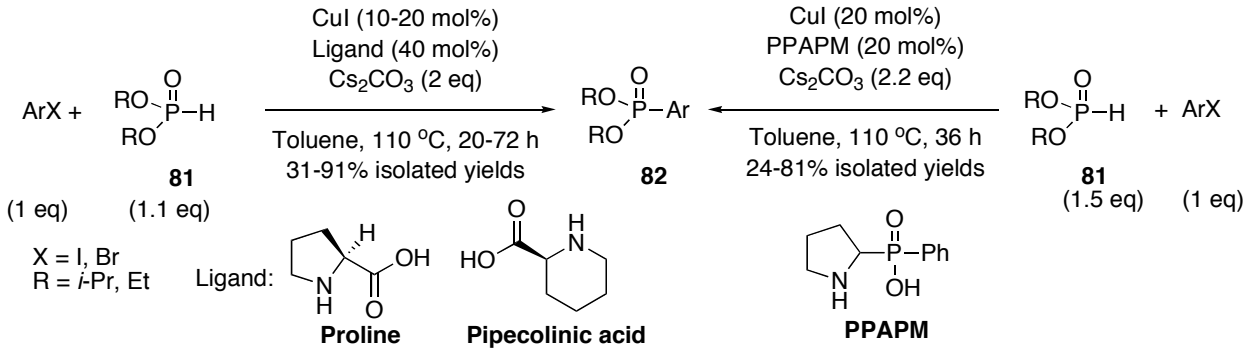
To overcome this drawback, recent efforts have been directed towards replacing palladium with copper.[185,186] Buchwald and coworkers used a copper-catalyzed cross-coupling protocol to prepare the aryl phosphonates in good to excellent yields (Eq. 4.2),[185] but the scope was demonstrated with aryl iodides (only a few examples of aryl bromides were reported). Additionally, this method required a high catalyst loading.



(Eq. 4.2)

Recently, the H. Fu group developed a base promoted copper-catalyzed *P*-arylation of organophosphorus compounds containing P-H, by using either a CuI/proline or CuI/pipecolinic acid catalyst system,[186a] or CuI/pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM) catalyst system (Scheme 4.1).[186b] However, the success of the reactions required the use of a large quantity of ligand-catalyst (10 to 40 mol%) and were limited to aryl iodides, with a few aryl bromides.

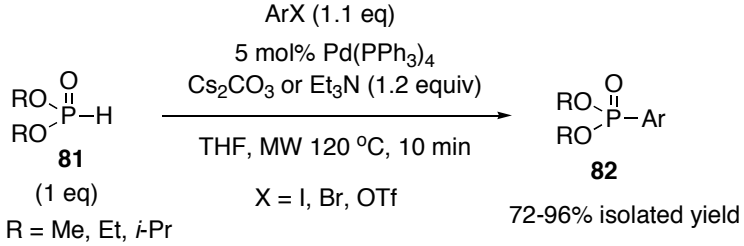
Scheme 4.1 Copper-catalyzed cross-coupling of aryl halides and dialkyl phosphites[186]



In comparison, Hirao prepared aryl phosphonates from aryl bromides or iodides using $Pd(PPh_3)_4$ as the catalyst and triethylamine as the base (Eq. 4.1).[87] However, when we tried applying these conditions with a reduced amount of palladium, yields were significantly lower. In an extensive survey of the reaction, we could not find any example in which the catalyst loading was lower than 3 mol%, and using Pd is a major drawback especially on large, multi-gram scales. Additionally, some substrates gave low yields or did not react at all in the P-C bond-forming reaction. This prompted the present study.

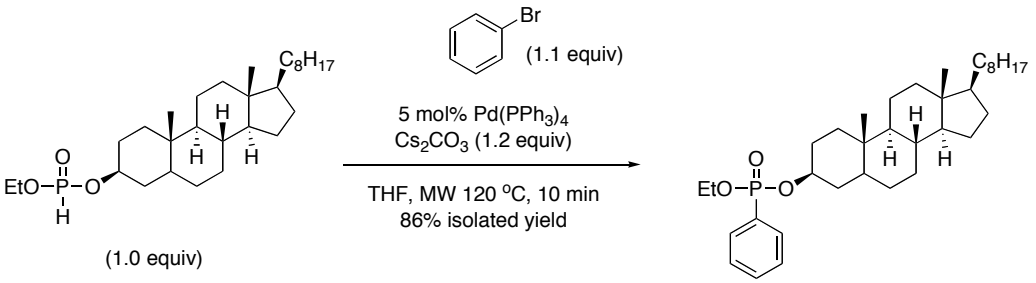
Our own cross-coupling investigations with hypophosphorous derivatives[41,44] had indicated that the ligand plays a crucial role, and 1,3-bis(diphenylphosphino)propane (dppp) or 1,1'-bis(diphenylphosphino)ferrocene (dppf)[42] were found to be best suited. Of course, hypophosphorous compounds also feature the added complication of the potential transfer hydrogenation pathways (Chapter I, Section 1.1.1.8).[32,19] While Hirao reported marginal problems with this side-reaction,[87] dialkylphosphites are much less prone to transfer hydrogenation since they are weaker reducing agents than hypophosphorous compounds.

Not long ago, Stawinski and coworkers reported an efficient microwave-assisted palladium-catalyzed cross-coupling reaction of aryl halides (X = I, Br, OTf), successfully leading to aromatic phosphonates (Eq. 4.3).[187] The reactions were conducted at 120 °C, using 5 mol% of $Pd(PPh_3)_4$. However, only one example of nitrogen-containing heteroaromatic phosphonate was described and more importantly, the reactions were performed on small scales, i.e, 0.5 to 1.25 mmoles.



(Eq. 4.3)

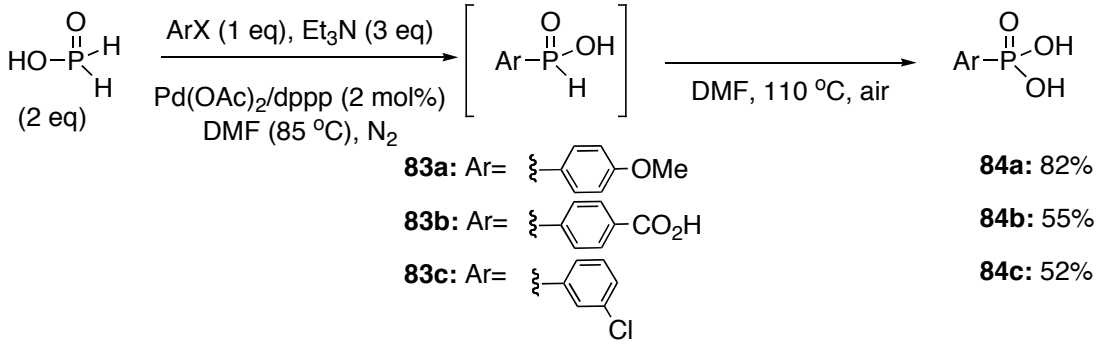
The above conditions were also applied to more complex (functionalized) systems such as steroids (Eq. 4.4)[187] or dinucleoside *H*-phosphonates. One of the main advantages of this method is the dramatic reduction of the reaction time (3 to 10 min), but the reaction-scale is limited (0.50 mmol of cholesteryl ethyl *H*-phosphonate; no scale up was reported), which does not make this route very attractive from an industrial point of view.



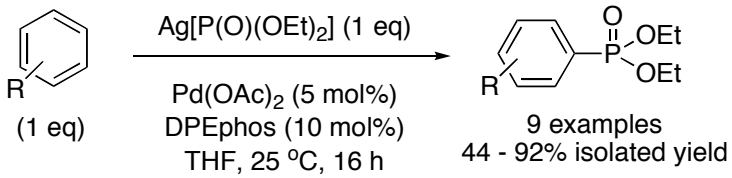
(Eq. 4.4)

On the other hand, a different approach to access phosphonic acids was developed in the Montchamp group[97] via the Pd-catalyzed tandem carbon-phosphorus bond formation-oxidation of *H*-phosphinic acids [RP(O)(OH)H] (Scheme 4.2). The corresponding phosphonic acids were isolated by an aqueous extractive work-up, followed by a recrystallization, in moderate to good yields (52-82%).[97]

Scheme 4.2 Synthesis of phosphonic acids via tandem C-P bond formation-oxidation reactions

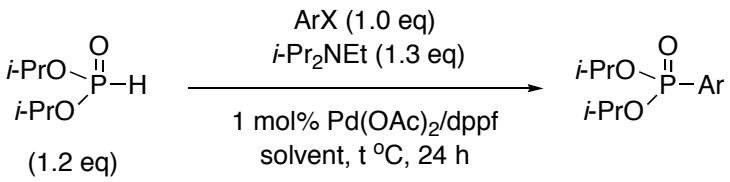


In some cases, this method would be competitive with the Hirao cross-coupling. However, heterocyclic compounds, especially the nitrogen-containing ones, would require an additional esterification step, or ion exchange chromatography in order to be purified, since competitive protonation of the heterocycles occurs and the acidification/extraction is consequently problematic.[44] In 2009, Stockland and coworkers described a room temperature synthesis of aryl phosphonates through Pd-catalyzed coupling of aryl iodide with stoichiometric silver phosphonate $Ag[P(O)(OEt)_2]$ (Eq. 4.5).[188] The reaction were performed on small scale (less than 0.41 mmol) with 5 mol% of $Pd(OAc)_2$ complexed to the supporting ligand bis(2-diphenylphosphinophenyl)ether (DPEphos). The process requires prior preparation of $Ag[P(O)(OEt)_2]$. The products were obtained in moderate to good yields using aryl iodides, known to be already very reactive.



(Eq. 4.5)

As part of our ongoing efforts aiming at the development of new phosphorus-carbon bond-forming reactions,[19,28,32,41,44,45,52,56-58] and particularly at the preparation of heterocyclic phosphinic acids for the construction of MOFs,[189] we re-investigated the Hirao cross-coupling reaction[83] through the adaptation of our hypophosphite coupling methodology.[19,28,32,41,44,45,52,56-58] The critical need for improving the reported cross-coupling conditions led us to look for the best conditions that could provide a general method to prepare an extended range of functionalized organophosphorus compounds, while using a low amount of palladium catalyst (Eq. 4.6).[83] Several novel heterocyclic phosphonates, as well as the first successful transition-metal catalyzed cross-couplings with aryl and heteroaryl chlorides, will be discussed in the following section.

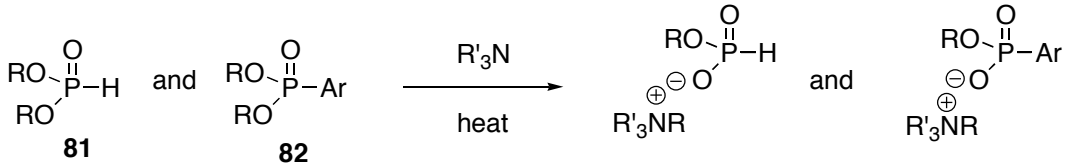


(Eq. 4.6)

4.2 Results and discussion

4.2.1 Reaction conditions

Our initial approach to this project consisted of the selection of ligands and reaction conditions. Based on the hypophosphite coupling, $Pd(OAc)_2$ complexed to either dppp or dppf was tried. In comparison to hypophosphorous acid derivatives known to be strong reducing agents,[19,28,32,41,44,45,52,56-58] dialkylphosphites are much less prone to transfer hydrogenation (Chapter I, Section 1.1.1.8). However, Hirao reported in his seminal work that an undesirable partial triethylamine-promoted dealkylation of the diethylphosphonate product **82** and diethylphosphite reagent **81** occurred.[87] This dealkylation proceeds when the diethylphosphite $(EtO)_2P(O)H$ reacts with aryl halides in the presence of triethylamine, thus affording the desired products in lower yields (Eq. 4.7).[87b] Since the dealkylation takes place via S_N2, we decided to address this problem by using a more hindered base and replacing the primary ester with a secondary ester (Eq. 4.6).[83] Hence, both *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) and diisopropylphosphite $(i\text{-PrO})_2P(O)H$[190] were used for the cross-coupling reaction with aryl and heteroaryl halides.



(Eq. 4.7)

The work on palladium-catalyzed cross-coupling reaction with hypophosphorous acid derivatives demonstrated that the choice of the ligand has a dramatic effect on the yield of the desired products.[28,41] Inspired by the results obtained with the hypophosphite cross-coupling,[19,28,32,41,44,45,52,56-58] we decided to adapt these optimized conditions to our reaction by using $Pd(OAc)_2$ with dppp or dppf as ligand.

The reaction conditions were tested on the initial target molecule, dialkyl-2-pyrazine phosphonate, for the preparation of MOFs.[189] Under Hirao's conditions, the cross-coupling reaction of the commercially available 2-chloropyrazine, and even 2-iodopyrazine, failed. Fortunately, the reaction took place in good yield (67% yield) when 1 mol% of $Pd(OAc)_2$ complexed to dppf reacted with 2-chloropyrazine and diethylphosphite $[(EtO)_2P(O)H]$ in the presence of triethylamine. Nonetheless, some unwanted dealkylation (ca. 20%) was observed, confirming the need for the more hindered *i*-Pr_2NEt.

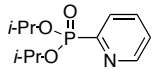
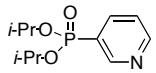
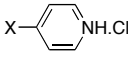
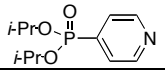
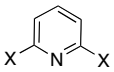
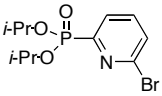
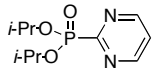
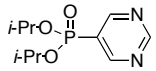
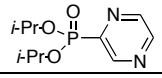
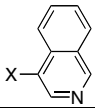
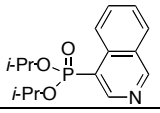
Among all the reaction parameters studied, the choice of solvent was found to have a strong influence on the reaction outcome. In most cases, acetonitrile (CH_3CN) provided excellent results. However, the use of *N,N*-dimethylformamide (DMF) was required for some specific substrates. After the identification of convenient and reliable reaction conditions for the Hirao coupling, we investigated the scope of the new reaction protocol using a variety of aryl and heteroaryl halides (iodides, bromides and even chlorides) (Eq. 4.6).

The reactions were carried out by adding successively diisopropylphosphite, aryl halide, *N*,*N*-diisopropylethylamine, $Pd(OAc)_2$ and dppf at room temperature. The reaction mixture was then heated at reflux in CH_3CN, or at 110 °C in DMF, for 24 h (reaction time not optimized), under nitrogen.

4.2.2 Scope of the reaction

Nitrogen-containing heteroaromatic halides were initially studied as cross-coupling partners (Table 4.1).[83] A variety of commercially available heteroaryl bromides and chlorides participated in the reaction, providing the corresponding phosphonates in moderate to excellent isolated yields.

Table 4.1 Scope of the cross-coupling with N-containing heterocyclic halides

Entry	Substrate	X	Solvent	T (^{o}C)	Product	^{31}P NMR (ppm)	Isolated yield[a] (%)	Literature Yields (%) R= *i*-Pr	Literature Yields (%) R= Et
1		Br	CH_3CN	Reflux		9.9	85	12[c,194a]	67[c,195]
2		Br	CH_3CN DMF	Reflux 110 ^{o}C		14.6	61 48	-	0- 79[196]
3[b]		Br	DMF	110 ^{o}C		13.6	63	30	71
4		Br	DMF	110 ^{o}C		7.6	30	-	51[196]
5		Br Cl	CH_3CN DMF	Reflux 110 ^{o}C		4.7	67 62	72 [c,195]	-
6		Br	CH_3CN	Reflux		10.9	83	-	70[196]
7		Cl	CH_3CN	Reflux		7.7	97	-	-
8		Br	DMF	110 ^{o}C		19.3	46	-	84[196]

[a] Isolated yield of pure compound after chromatography on silica gel. [b]3 equiv of Et_3N used instead of 1.3 equiv of *i*-Pr_2NEt. [c]compounds obtained following the non-catalytic method.[194a,195]

For instance, 2-bromopyridine reacted smoothly to provide the desired product in 85% isolated yield (entry 1).

In comparison, the non-catalytic synthesis of this product was previously reported in the literature, by reacting diisopropylphosphite with pyridine-*N*-oxide in presence of dimethylsulfate and sodium hydride, but only 12% was isolated (entry 1).[194a] Redmore synthesized the ethyl analog in 67% isolated yield using *n*-butyllithium instead of sodium hydride.[195]

Diisopropyl-3-pyridylphosphonate (entry 2) was obtained in both CH_3CN and DMF in 61% and 48% isolated yields, respectively. Hirao initially reported the isolation of the diethylphosphonate analog in 77% yield starting from 3-bromopyridine and using 5 mol% $Pd(PPh_3)_4$,[87b] but no significant improvement was observed when the Pd catalyst was replaced by Pd_2dba_3/PPh_3 (5 mol%).[196]

Gooßen and Dezfuli recently attempted to improve the Pd-catalyzed cross-coupling reaction of diethyl phosphite by lowering the amount of Pd catalyst (2 mol% of $Pd(OAc)_2$ and 6 mol% PPh_3) and diluting the reaction mixture in a protic solvent (ethanol).[197] However, only specific substrates (aryl bromides) were suitable to form their corresponding phosphonates and particularly, the preparation of the diethyl-3-pyridylphosphonate failed completely under their optimized conditions (entry 2).

4-Bromopyridine hydrochloride gave the corresponding phosphonate (entry 3) in good isolated yield (63%). The literature preparation of this compound was initially attempted using 3 mol% Pd,[184d] but we only obtained 30% instead of the reported 71% yield.

Entry 4 shows that only 30% of monobromopyridine phosphonate was obtained from the 2,6-dibromopyridine. This can be explained by the expected competing disubstitution due to the presence of two reactive carbon-bromine bonds.

As shown in entry 5, either 2-chloropyrimidine or 2-bromopyrimidine provided the corresponding phosphonate in good yield (62% and 67%, respectively). The thermal Arbuzov reaction of 2-halopyrimidine was previously described by Gennady and Roy,[198] yet a violent decomposition took place when this reaction was repeated.

As discussed in Section 4.1, our initial interest was to prepare pyrazine phosphonic acid. Following our optimized conditions, 2-chloropyrazine provided the corresponding diisopropyl phosphonate (entry 7) in 97% isolated yield on a multi-gram scale.

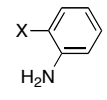
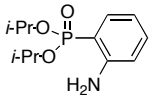
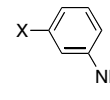
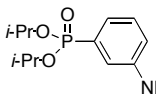
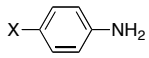
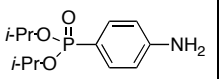
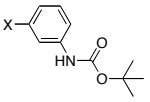
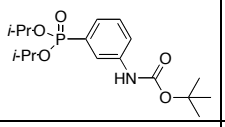
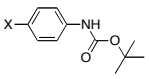
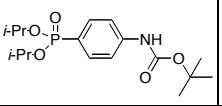
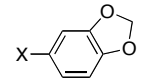
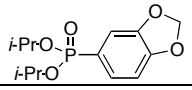
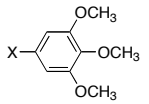
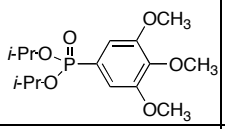
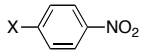
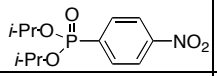
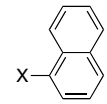
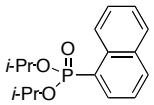
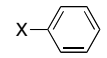
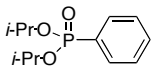
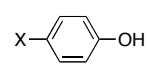
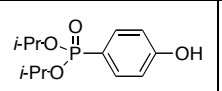
Subsequently, the cross-coupling reaction of diisopropyl phosphite with other aromatic derivatives was investigated (Table 4.2). With anilines (entries 1-5), satisfactory results were obtained even when unprotected iodoaniline isomers were used (entries 1-3).

Following Hirao's method, Savignac and co-workers did not obtain the corresponding phosphonates from these unprotected anilines.[199] However, a photostimulated nucleophilic substitution of the anilines allowed the preparation of those products in excellent yield (entries 1-3).[199]

The reaction of unprotected 2-iodoaniline (entry 1) did not give satisfactory results in CH_3CN (19%), but when the reaction was performed at higher temperatures and in DMF, the more efficient coupling took place (70% isolated yield).

In contrast, under Buchwald's conditions, which uses a larger amount of catalyst (5 mol% CuI and 20 mol% *N,N'*-dimethylethylenediamine),[185] the reported dibutylphosphonate analog was isolated in 86% yield. This result proves that our reaction is quite competitive with the Cu-catalyzed coupling reaction.

Table 4.2. Scope of the reaction with anilines, activated and deactivated aryl halides

Entry	Substrate	X	Solvent	T (^{o}C)	Product	^{31}P NMR (ppm)	Isolated yield[a] (%)	Literature Yields (%) RO, RO, O, P–Ar	
								R= *i*-Pr	R= Et
1[b]		I	CH_3CN	Reflux		20.2	19	-	87[e]
			DMF	110 ^{o}C			70		
2		I	CH_3CN	Reflux		18.5	72	-	0[f] 90[e]
3		I	CH_3CN	Reflux		19.2	70	-	90[e]
		I	DMF	110 ^{o}C			92		
4		Br	CH_3CN	Reflux		17.4	81	-	-
5		Br	CH_3CN	Reflux		18.1	82	-	-
6		Br	CH_3CN	Reflux		17.8	99	-	-
7		Br	CH_3CN	Reflux		18.3	61	-	-
8		Br	DMF	110 ^{o}C		13.9	60	47	73
9[c]		TfO	DMF	110 ^{o}C		17.8	86	-	73[g]
10		I	CH_3CN	Reflux		17.6	93	73	traces - 96
		I	CH_3CN	Reflux			82[d]		
		TfO	DMF	110 ^{o}C			47		
11		I	CH_3CN	Reflux		19.9	27	-	3
		I	DMF	110 ^{o}C			51		
		Br	CH_3CN	Reflux			27		
		Br	DMF	110 ^{o}C			76		

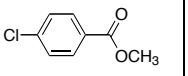
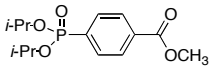
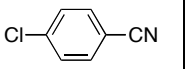
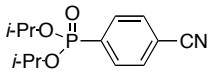
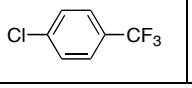
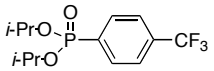
[a] Isolated yield of pure compound after chromatography on silica gel. [b] Reaction conducted in a sealed tube. [c]reaction performed in a sealed tube. [d]reaction performed with 0.1 mol% $Pd(OAc)_2$ for 48 h. [e]compounds obtained via a photostimulation method.[199] [f]Under Hirao's conditions.[87] [g]compound prepared by microwave-assisted Pd-catalyzed cross-coupling.[187]

Of greater interest, a structural analog of gabaculline, a dihydro-*m*-aminobenzoic acid which is a potent inhibitor of γ-aminobutyric acid ketoglutarate transaminase ($GABA_T$) and an anticonvulsant,[200] was also synthesized in excellent yield (entry 2, Table 4.2). Our conditions for the reaction of Boc-protected anilines (entries 4 and 5) proceeds uneventfully in good yields on multi-gram scales. Furthermore, 3-Boc-protected aniline phosphonate (entry 4) was easily isolated as a crystalline solid.

The palladium-catalyzed cross-coupling reaction with various electron-poor and electron-rich substrates was also investigated (entries 6-11, Table 4.2). It was found that such substrates were also suitable candidates for the revised Hirao cross-coupling and, in general, the aryl phosphonate products were isolated in good to excellent yields. Via the Cu-catalyzed cross-coupling reaction,[186a] 4-nitrophenyl phosphonate was synthesized in 47% yield whereas, under our conditions, it was isolated in 60% yield (entry 8). Predictably, iodobenzene gave the corresponding phosphonate in excellent yield (entry 10). Even with 0.1 mol% of palladium, the product was obtained in good yield (82% yield) after 48 h. Entry 11 shows that 4-hydroxyphenylphosphonate can be obtained in good yield when unprotected *p*-bromophenol reacted in DMF at 110 °C.

To date, no one has ever reported a successful P-C bond coupling formation of phosphite with any chloride electrophiles (including the activated ones) under catalytic conditions. Hence, we investigated our method on some activated (electron-poor) aryl chlorides (Table 4.3). The best conditions were obtained when diisopropyl phosphite reacted in DMF at 110 ^oC with an electron-deficient aryl chloride and with 1 mol% of $Pd(OAc)_2$. The desired products were obtained in low to moderate yields. The results presented here are only preliminary. Although additional investigations on the optimum conditions of this particular cross-coupling of aryl-chlorides is required, the results are promising.

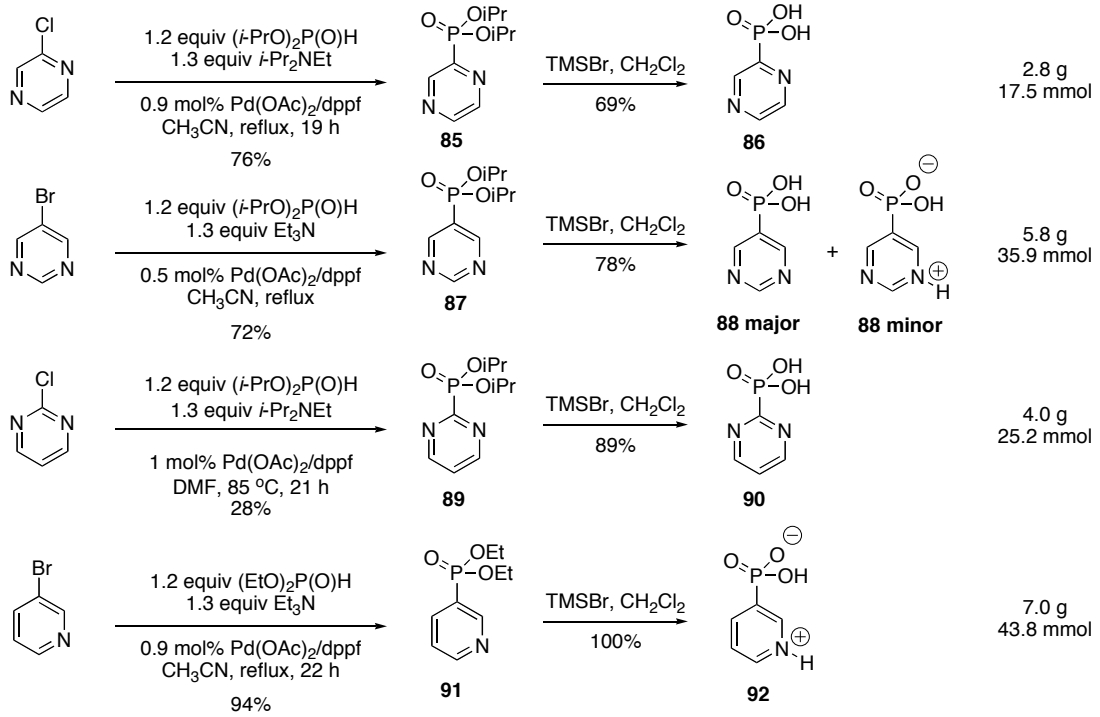
Table 4.3 Scope of the reaction with activated aryl chlorides

Entry	Substrate	Solvent	T (°C)	Product	^{31}P NMR (ppm)	Yield (%)
1		DMF	110 °C		14.7	44[a]
2		DMF	110 °C		14.2	57[a]
3		DMF	110 °C		16.5	22[b]

[a] Isolated yield of pure compounds after chromatography on silica gel. [b] Conversion according to the ^{31}P-NMR spectra.

Finally, we applied our modified conditions for the multi-gram scale preparation of some heterocyclic phosphonic acids as potential metal organic framework (MOF) precursors.[189] Following McKenna's deprotection protocol of the phosphonate diesters,[84] the corresponding phosphonic acids were obtained in good to excellent yields (Scheme 4.5).

Scheme 4.5 Preparation of some phosphonic acids



The phosphonate diester precursors were prepared either using $(i\text{-PrO})_2P(O)H/i\text{-Pr}_2NEt$ or $(EtO)_2P(O)H/Et_3N$ with 0.5-1.0 mol% $Pd(OAc)_2$/dppf. The 2-pyrimidyl ester intermediate **89** was obtained in only 28% isolated yield (compare with Table 4.1, entry 5). The conceivable explanations of this result are the incomplete protonation of the pyrimidine phosphonate during work-up and the fact that the reaction was not performed using optimum conditions. Interestingly, while the deprotected pyridine compounds such as **92** generally exist as the zwitterion, the 5-pyrimidine-derived phosphonic acid **88** exists as a mixture of the neutral compound and the zwitterion, and the pyrazine- or 2-pyrimidine phosphonic acids (**86** and **90**) exist as the neutral compounds since the nitrogen atoms are very weak bases.[201]

In summary, we have demonstrated a facile, economically attractive multi-gram scale synthesis of aromatic and heteroaromatic phosphonates via palladium catalyzed conversion of aryl halides. The process was found to be general and even competitive to the Cu-catalyzed cross-coupling reaction.

Chapter Five: Radical Reaction of Sodium Hypophosphite with Terminal Alkynes

5.1 Introduction

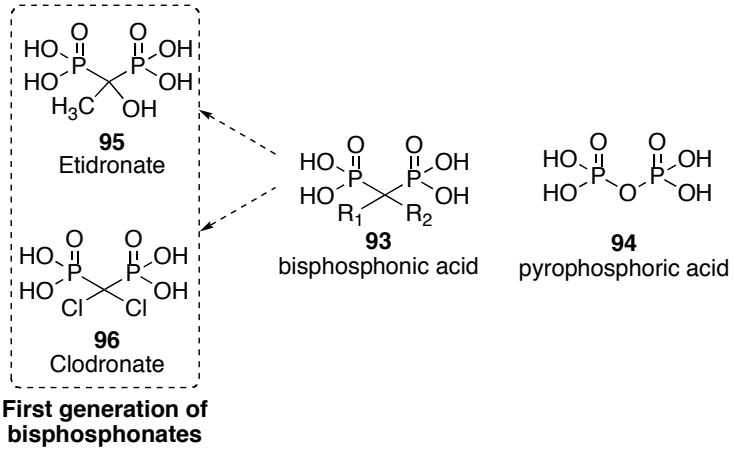
In 2001, the Montchamp group reported a novel and general approach toward *H*-phosphinate derivatives based on the room-temperature triethylborane-initiated radical addition of hypophosphorous compounds to alkenes (Chapter I, Section 1.1.1.9, Scheme 1.7).[52] Since then, an extensive study on the reactivity of various alkynes with sodium hypophosphite under similar conditions was performed and the formation of a new class of compounds was discovered in our group: 1-alkyl-1,1-bis-*H*-phosphinates,[8,54] novel precursors of the biologically important 1,1-bisphosphonates (see section 1.2.1).

5.1.1 The major role of bisphosphonates

Bisphosphonates (BPs) represent a multi-billion dollar global pharmaceutical market and are of great interest in medicinal chemistry.[1,202-236] The BPs (originally called diphosphonates) have been known by chemists since the middle of the nineteenth century,[202,203] and the first clinical uses of BPs appeared in the late 1960s. BPs were initially used as antiscaling and anticorrosive agents, and as complexing agents in the textile, fertilizer, and oil industries.[204] They also have activity as herbicides,[205,206] anticancer agents,[207,208] and antiparasitics.[209-211] Their potential for the treatment of various diseases of bone mineral metabolism became evident beginning in the mid-1960s because of their avidity for bone and their ability to inhibit bone resoprtion. It included their use as agents for bone scan (a nuclear scanning test that identifies new areas of bone growth or breakdown) based on their ability to adsorb to bone mineral, for which they remain outstandingly useful.[205] Fleish pioneered the studies of the physiological properties of the geminal bisphosphonates.[212,213] The BPs (Chart 5.1, compound **93**) are metabolically stable analogues of the naturally occuring inorganic pyrophosphate (Chart 5.1, compound **94**), impairing the formation and the dissolution of calcium phosphate crystals *in*

vitro.[212,213] More recent studies have shown that the mode of action of bisphosphonates is more complex and that they can modulate various biological pathways and receptors[214] (e.g., inhibition of isoprenoid biosynthesis), although their impact on calcium metabolism remains a major component of their medicinal use.[1,202-236]

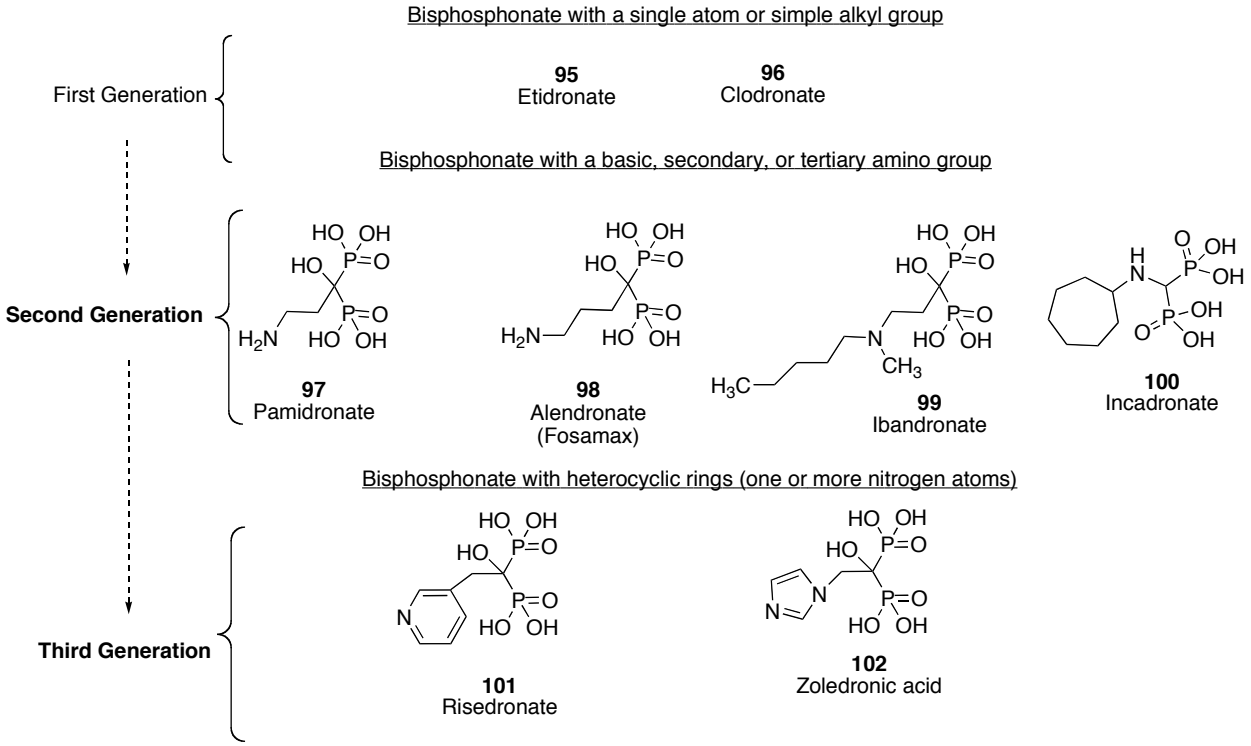
Chart 5.1 First functionalized bisphosphonates



Like inorganic pyrophosphate, BPs have a high affinity for divalent metals, such as Ca^{2+} and Mg^{2+}.[215] In contrast to pyrophosphate, BPs are orally active. However, their low bioavailability often limits the usefulness of oral administration and high dosage is associated with side effects.[216] More importantly, the replacement of the oxygen atom between the two phosphonic acid moieties opened up the possibility of attaching side chains (Charts 1.5 and 5.1). The affinity for hydroxyapatite is a property of the P-C-P motif because BPs (like pyrophosphate) can chelate calcium ions by bidentate coordination through the oxygen atoms of the phosphonate groups. Ideally, R_1 should be an OH or NH_2 group, which increases the calcium affinity through a tridentate mode (i.e., act as tridentate ligands). The nature of the R_2 side chain is the critical determinant of antiresorptive potency and it influences the ability of the drug to interact with specific molecular targets.

Over the past thirty years, several generations of bisphosphonates with increasing potency have been developed.[217] In the 1970s and 1980s, the first-generation of BPs, such as etidronate (**95**) and clodronate (**96**), was successfully used in clinical trials (Chart 5.2).[218] These generation compounds were relatively weak inhibitors of bone resorption, but, in recent years, attention has shifted to derivatives with aminoalkyl side chains (second-generation compounds). The search for more potent BPs by many pharmaceutical companies has resulted in a number of novel, highly potent derivatives with improved clinical efficacy and tolerability.[219]

Chart 5.2 Selected medicinally important nitrogen-containing bisphosphonates



Pamidronate (Chart 5.2, compound **97**) was the first member of the second-generation BPs and was originally synthesized by Henkel as an additive for detergents. Subsequently, pamidronate was licensed to Ciba-Geigy for development as a pharmaceutical agent (pamidronate disodium, marketed by Novartis under the brand name Aredia). Pamidronate was

the first BP to contain a basic nitrogen atom in its alkyl side chain.[220] It exhibits increased potency as an inhibitor of bone resorption and has been extensively used clinically in patients with osteolytic bone metastases, tumor-induced hypercalcaemia arising from breast cancer, and Paget's disease.[220] Consequently, numerous nitrogen-containing bisphosphonates (N-BPs) for increasing potency have been developed for the treatment of both benign and malignant bone diseases (Chart 5.2).[221-224] Second-generation compounds, such as alendronate **98**,[221] ibandronate **99**,[222] or incadronate **100**,[223] are 10- to 100-fold more potent than the first-generation compounds.[224] Further enhancement of potency was achieved by incorporation of nitrogen-containing heterocycles (third-generation compounds, Chart 5.2),[225,226] in which zoledronic acid **102** has shown the highest potency in preclinical assays.[226]

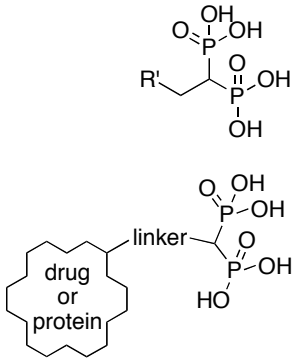
In 2008, a new dinuclear platinum complex with a nitrogen-containing geminal bisphosphonate was described as a potential anticancer compound specifically targeting bone tissues.[227] Notably, activity against bone disease is not the only useful medicinal property of bisphosphonates. Current research has improved the development of bisphosphonates as bioavailable prodrugs. In 2004, Burgada and coworkers were looking for non-toxic ligands that could form stable complexes in vivo with radioactive heavy metals, in case of nuclear accident or war, with the expectation of being eliminated by the renal or gastrointestinal barrier.[228] The authors found out that bisphosphonic acids efficiently complexed to uranyl, cobalt, and iron ions.

A successful commercial introduction of fuel cells as environmentally benign power sources will depend on the development of several new multifunctional materials to reduce costs, improve performance, and extend the life-time of fuel cell systems. In 2008, the first report on the fuel cell related properties of polymer membranes functionalized with bis-phosphonic acid was disclosed.[229] These properties are not only important for fuel cell applications, but are also relevant for other membrane applications, including reverse-osmosis and heavy metal ion

separation. Primarily, the interest in these materials originates from their potential to efficiently transport protons at high temperatures and low humidity through intrinsic conduction mechanisms.[229]

Furthermore, BPs are of interest in the context of the future development of novel anti-infectives for HIV-1. It was recently reported that they may have utility as inhibitors of AZT-excision catalyzed by HIV-1 RT (reverse transcriptase).[230] Suitable formulations or delivery vehicles are available to facilitate uptake of the charged bisphosphonates into HIV-infectable target cells (e.g., T-lymphocytes). The preparation of bisphosphonate conjugates is becoming a popular approach to achieve targeted biological activity. Figure 5.1 summarizes the structures of some biologically important BPs, and examples from recent literature include conjugates of steroids (estrogenic bone remodeling), prostaglandin (bone-growth stimulant), methotrexate (anticancer), carboranes (targeted radiotherapy), and albumin (model protein for growth factor delivery).[13a,13b,67c,203,204,210b,231-236]

Figure 5.1 Some known biologically important bisphosphonates

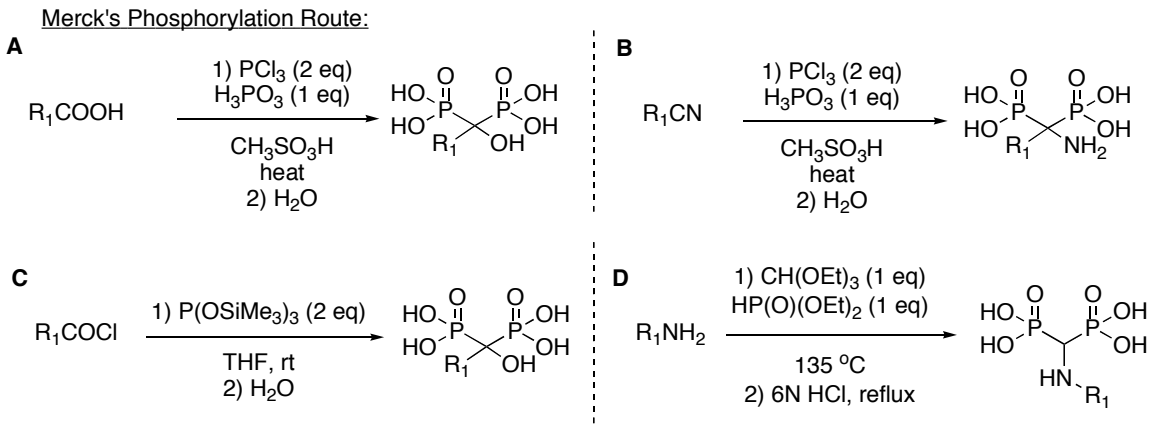


R' = CH_2NH_2 (active against bone resoprtion)
R' = CH_2COO-steroid (active against osteoporosis)
R' = CH_2-farnesyl (cholesterol lowering drug)
R' = CH_2-geranyl (cholesterol lowering)
R' = N-fluoroquinolones (active against bone infections)
R' = CH_2S-albumin (model for growth factor delivery)
R' = any substituants with radioisotope (^{99m}Tc, $^{184 \text{ or } 186}$Re, ^{125}I, ^{117m}Sn) or fluorescent label (radiolabelling, imaging dyes, radiotherapy)

5.1.2 Synthetic methodologies of bisphosphonates in the literature

An examination of Chart 5.2 reveals the structural simplicity of the BPs, however their synthesis is not always trivial and only few methodologies have been widely employed for their preparation (Scheme 5.1).[237,238] None of the syntheses proceed through mild conditions, thus limiting functional group tolerance.

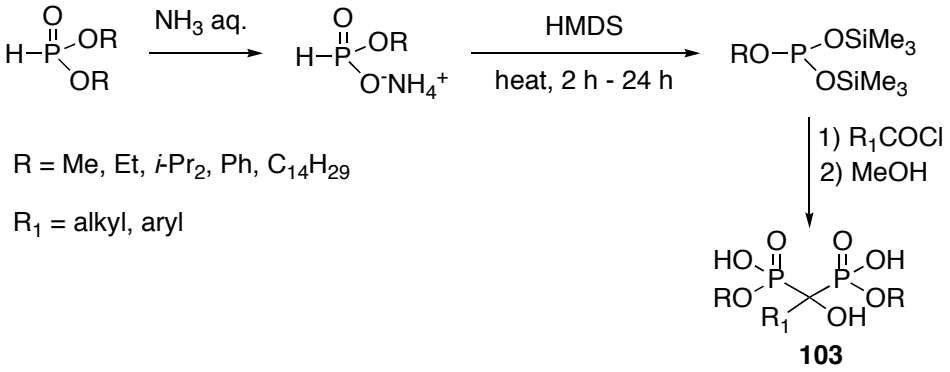
Scheme 5.1 Synthetic approaches for the preparation of bisphosphonates



Nonetheless, for the compounds shown in Schemes 5.1 and 5.2, the Merck-type approach (Scheme 5.1, **A** and **B**) is satisfactory and widely employed because the BPs targets are structurally simple.[237a,237b] It involves the reaction of a carboxylic acid or a nitrile as starting material with phosphorus trichloride (PCl_3) and phosphorous acid (H_3PO_3). Yields may vary from good (pamidronate, 57%) to excellent (alendronate, 89%). Major drawbacks include: heat, long reaction time, the extreme acidity of the reaction medium, which precludes the application of acid-sensitive functional groups, and the use of excess hazardous chemicals. The reaction of acid chlorides with tris(trimethylsilyl)phosphite $P(OSiMe_3)_3$ (Scheme 5.1, **C**) is chemically related to the Merck-type reaction and was described a few years ago by Lecouvey et al. (product usually isolated in 90% yield).[237c,237d] However, aside from the fact that the reaction is strongly

exothermic, the unpractical handling of acid chlorides and the occurrence of important side reactions make this method potentially problematic, which explains why it has not been commonly employed. Satisfactory results for the preparation of BPs were obtained when amines were used as starting material (Scheme 5.1, **D**).[237j,237k] The reaction requires relatively harsh conditions to reach completion, thus limiting the usage of temperature sensitive products. Lecouvey's team attempted to improve their previous methodology by developing the synthesis of 1-hydroxymethylene-1,1-bisphosphonate partial ester (HMBP) by using several alkyl or aryl substituents of acid chlorides,[237d] followed by methanolysis (Scheme 5.2, compound **103**).

Scheme 5.2 Preparation of HMBPs by Lecouvey[237d]

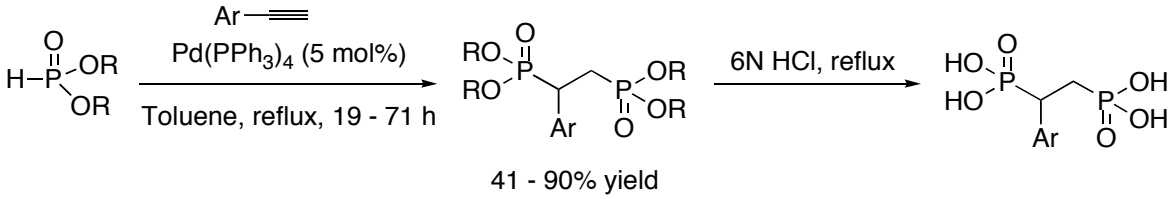


Even though good to excellent yields were obtained (50 – 95% yield), this multi-step approach required anhydrous conditions (reaction performed under nitrogen and with freshly distilled HMDS), careful handling (exothermic reaction after addition of 30% ammonia solution at 0 ºC and use of acid chlorides), and a long period of heating/reaction time (90 ºC for 2 h to reflux for 24 h).[239] When ester derivatives of the BPs are first synthesized (as in procedures **C**, **D**, of Scheme 5.1 and as Scheme 5.3), an additional deprotection step is required to obtain the desired products.[233a]

In 2000, Lin and coworkers reported a novel palladium catalyzed bis-hydrophosphonylation of terminal alkynes and dialkyl phosphites (Scheme 5.3),[237f] affording

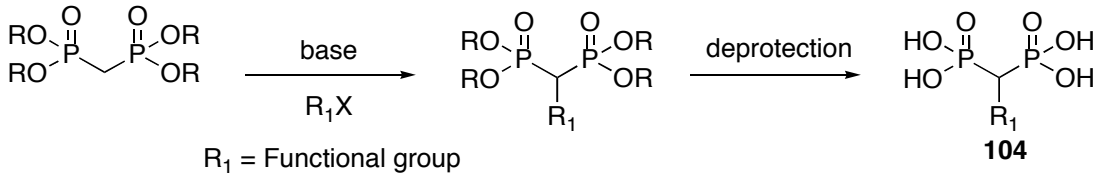
vicinal BPs in good isolated yield. This methodology is rarely used since medicinally important BPs are geminal and not vicinal. In addition, this methodology is limited to electron-deficient phenyl acetylenes (i.e., electron-withdrawing functionalities on the aryl groups).

Scheme 5.3 Palladium catalyzed bis-hydrophosphorylation of terminal alkynes



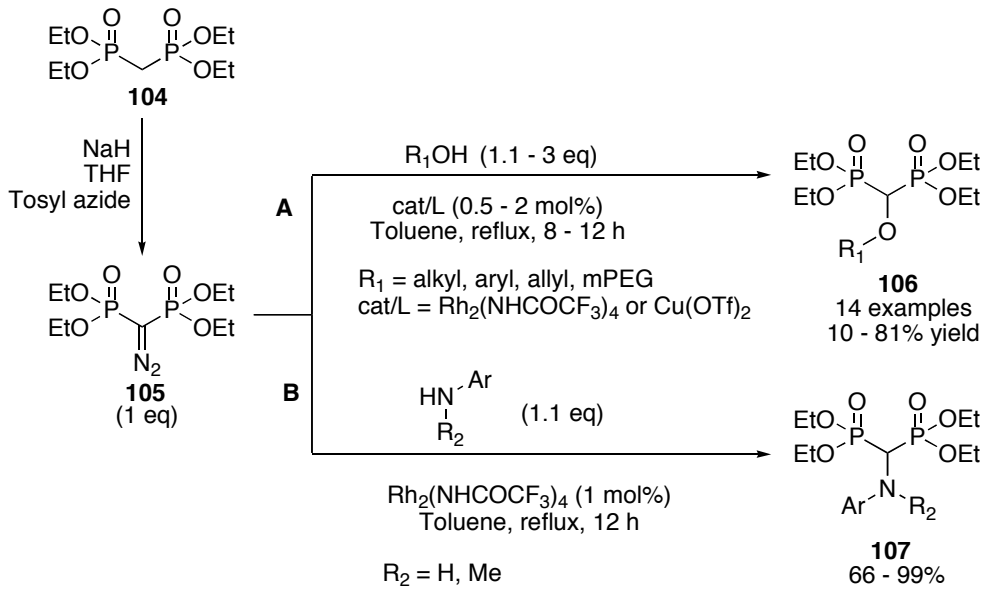
For the bone-targeting of compounds through covalent bisphosphonate modification, the alkylation approach (Scheme 5.4) can also be employed, and typically the hydroxyl group at the 1-position is not necessary (compounds **103**).[232f,232g,233a-233c,238] However, cleavage of the ester group (R) to form **103** can be problematic in complex molecules.[232f,232g,233a-233c,238]

Scheme 5.4 Functionalization of bisphosphonate precursors by alkylation



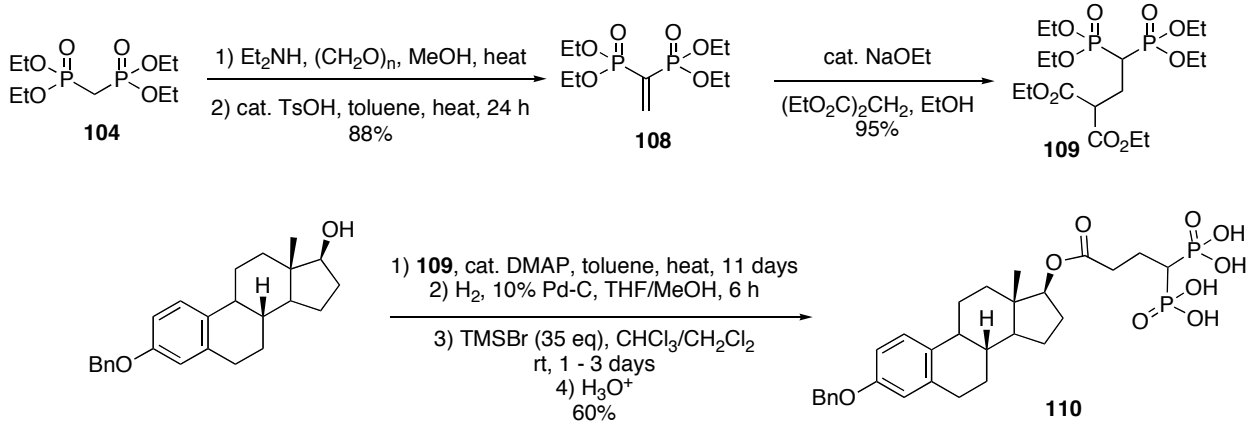
Recently, Taran and coworkers reported a facile anchoring of BPs moiety onto alcohols and phenols (Scheme 5.5, path **A**),[241a] as well as aromatic amines (Scheme 5.5, path **B**)[241b] through a copper or rhodium carbenoid mediated O-H or N-H insertion reaction. Overall, the copper-catalyzed O-H insertion and the rhodium-catalyzed N-H insertion reactions of tetraethyl diphosphonodiazomethane[241a,241b] (**105**) was successful, affording the desired products **106** and **107** in moderate to good yields.[241d,241e]

Scheme 5.5 Metal carbenoid mediated OH and NH insertion

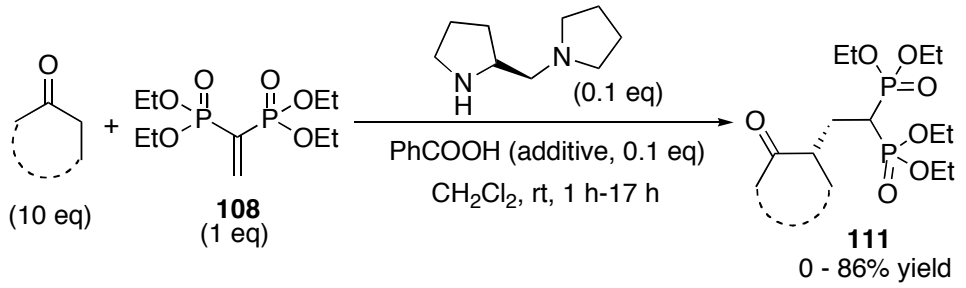


The tetraethyl vinylidenebisphosphonate, **108**, was found to be an interesting starting material for the preparation of BPs.[242] Gallagher identified **108** as a key intermediate for the preparation of bisphosphonate-steroid conjugates derivatives of oestradiol (Scheme 5.6).[232h,232f] The steroidal estrogenic units are known to be osteoclast inhibitors that regulate the circuit of cytokine action which controls bone remodeling,[243] thus **110** was prepared using this methodology.

Scheme 5.6 Gallagher's bisphosphonate conjugate

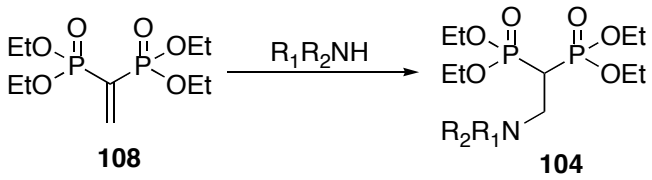


A highly diastereo- and enantioselective method for the preparation of chiral cyclic γ-keto *gem* bisphosphonates **111** was recently described,[242a] involving the Michael addition reaction of cyclic ketones to vinyl bisphosphonate **108**, catalyzed by (*S*)-(+)-1-(2-pyrrolidinyl)-pyrrolidine and benzoic acid (Eq. 5.1). The procedure gave the products **111** in yields up to 86% and the values obtained for *ee* and *dr* are up to 99% and (*cis*/*trans*) > 1:99, respectively.



(Eq. 5.1)

Increasing interest in the nitrogen-containing bisphosphonates resulted in the development of different strategies for their syntheses. The standard route to 2-aminoethylidene-1,1-bisphosphonates **112** exploits the Michael-type addition of amines or amides to tetraethyl vinylidenebisphosphonate **108** by the method elaborated by Hutchinson and Thornton (Eq. 5.2).[242b]

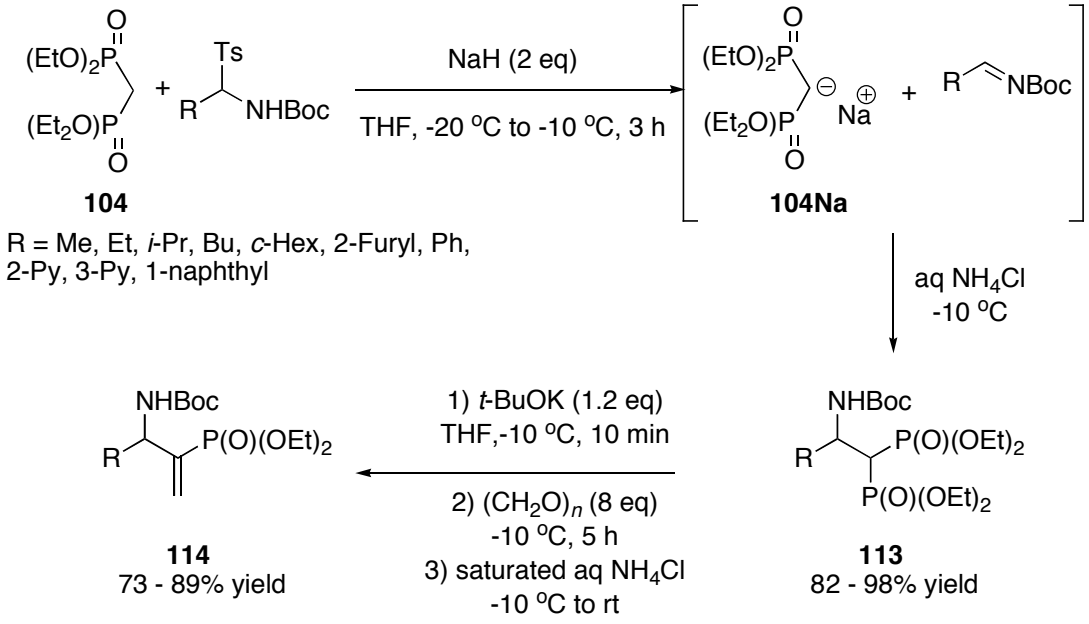


(Eq. 5.2)

A one-pot access to substituted *N*-Boc-2-aminoethylidene-1,1-bisphosphonate derivatives (Scheme 5.7, **113**) from available (albeit expensive) tetraethyl methylenebisphosphonate (**104**) and *N*-Boc-α-amidoalkyl-*p*-tolylsulfones was developed by Gajda et al.,[244] leading to the formation of the aza-Morita-Baylis-Hillman-type adducts, which are valuable synthetic

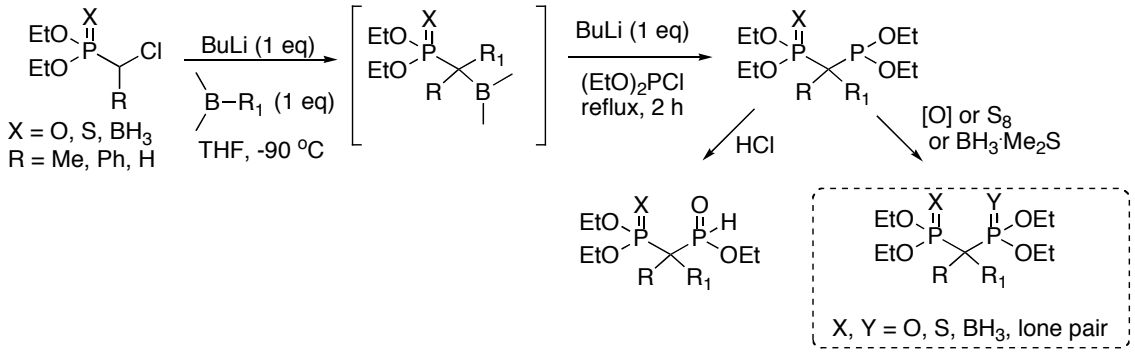
intermediates.[245] The reaction was general and a number of diverse alkyl, aryl, or heteroaryl substituted BPs **113** were obtained in this manner. The BPs **113** are also versatile synthetic intermediates for further transformations, including selective Boc group deprotection, conversion to free aminobisphosphonic acids, and direct synthesis of the aza-Morita-Baylis-Hillman-type adducts **114**.[245]

Scheme 5.7 Preparation of *N*-Boc-2-aminoethylidene-1,1-bisphosphonates

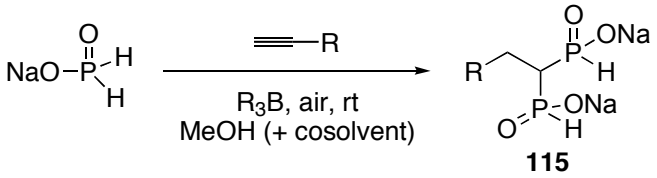


Finally, in 2008, the Montchamp group reported, a facile synthesis of symmetrically and differentially substituted 1,1-bisphosphorus compounds based on the reaction of phosphorus carbenoids with organoboranes,[108a] followed by reaction with phosphorus electrophiles. These recent results have promise for the preparation of various bisphosphorus compounds using this B-C to P-C-C homologation (Scheme 5.8).[108]

Scheme 5.8 Bisphosphorus compounds through reactions with organoboranes



The Merck method is undoubtedly the most commonly employed for the preparation of commercial BPs, but a new methodology using milder conditions is needed to further expand the variety of accessible BPs. The introduction of bis-*H*-phosphinate opens up possibilities for the preparation of important pharmaceutical bis-*H*-phosphinate conjugates. Herein, we investigate the formation of these 1,1-bis-*H*-phosphinates **115** (Eq. 5.3),[12,54] via organoborane-initiated radical reaction. Their conversion to the corresponding phosphonic acids,[12,54] as well as to the corresponding phosphine-borane ligands was also achieved.[12c] In collaboration with TCU Professor Jeffery Coffer, some bisphosphonates were prepared for testing in bone tissue engineering and drug delivery application.[246]



(Eq. 5.3)

5.2 Radical reaction of hypophosphite salts with alkynes

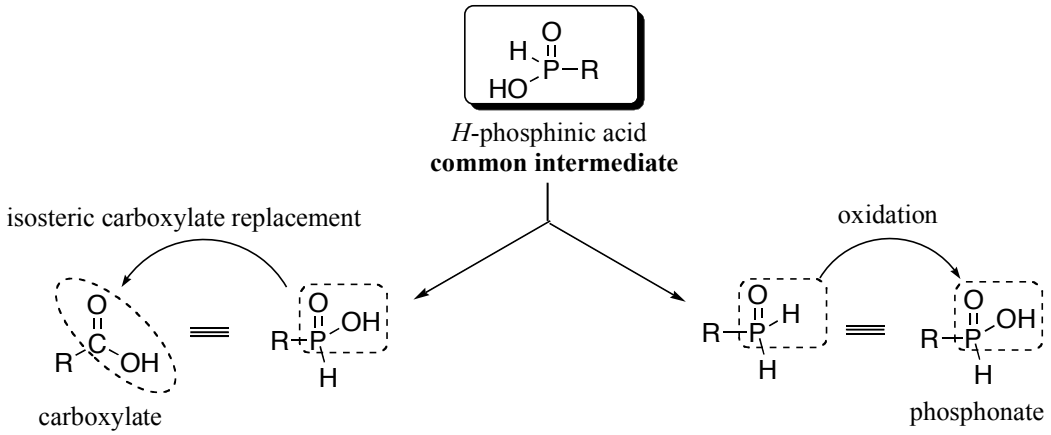
Our group recently reported a novel and general approach toward *H*-phosphinate derivatives based on the room-temperature radical addition of hypophosphorous compounds to alkenes (Chapter I, Section 1.1.1.9, Scheme 1.7).[52] Compared with previously reported syntheses, our milder conditions considerably expanded the scope of *H*-phosphinates in terms of

functional group tolerance on the alkene and hypophosphorous reagent.[52] Since then, we have studied the reaction of alkynes with sodium hypophosphite under similar conditions and discovered the formation of the 1-alkyl-1,1-bis-*H*-phosphinates **115** (Eq. 5.3).

5.2.1 The 1,1-bis-*H*-phosphinates as precursors to therapeutic bisphosphonates

Among a large number of therapeutic molecules, organophosphorus compounds have found multiple uses in medicinal chemistry. In the Montchamp laboratory, one of the aims is the synthesis and application of *H*-phosphinic acids as synthetic intermediates for the preparation of medicinal compounds. Potential applications include the treatment of various disorders of the central nervous system (GABA analogs), cancer chemotherapy (PALA analogs), and for bone and other diseases (BPs). The phosphoryl functionality (P(O)-OH) of phosphinic acids is used as an isosteric carboxylate replacement for the GABA carboxylate, while the phosphinylidene functionality (P(O)-H) is used as the precursor phosphonyl group for bisphosphonates (Scheme 5.9). As shown in Scheme 5.9, oxidation is the final step that leads to BP compounds from *H*-phosphinic acids. This conversion proceeds under mild conditions and thus should tolerate various functonalities.[237a] Furthermore, bis-*H*-phosphinic acids might be used as prodrugs of the biologically active phosphonates since there is evidence that oxidation of the phosphinylidene group (P(O)-H) into the acid (P(O)-OH) can occur *in vivo*.[4a] Perhaps, *H*-phosphinic acid being more lipophilic than the phosphonic acids would be more easily absorbed than highly charged BPs. If this turns out to be true for 1,1-bis-*H*-phosphinic acids, an unprecedented way to increase the oral bioavailability of bisphosphonates would be discovered.

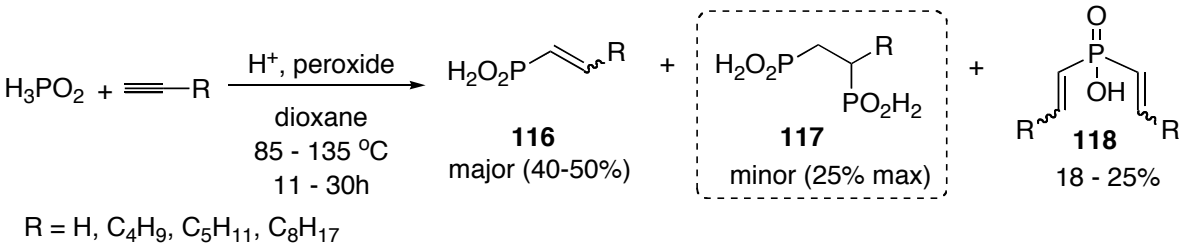
Scheme 5.9 *H*-phosphinic acid as bioreplacements



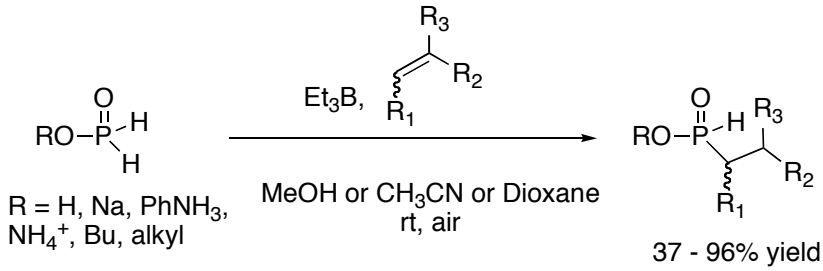
5.2.2 Reaction conditions

As mentioned in Chapter I (see section 1.1.1.9), Nifant'ev reported a methodology for the preparation of bisphosphinates,[50] target molecules that are only one oxidation step away from bisphosphonates (Scheme 5.10). The thermal radical addition of H_3PO_2 with terminal alkynes bearing alkyl chain (or simply acetylene) is initiated by various peroxides (e.g. *t*-BuOOBu-*t*) and performed at high temperature. Under the reported conditions, the alkenyl-*H*-phosphinic acids **116** are always the major products (*trans*/*cis* = 2/1). 1,2-Bis-*H*-phosphinic acids **117** are formed in minor amounts, even under forcing conditions, along with disubstituted products **118**. As might be expected, the radical addition of hypophosphorous derivatives to unsaturated compounds is sensitive to both steric and electronic factors.

Scheme 5.10 Nifant'ev methodology



Previously reported conditions for the radical addition of hypophosphorous acid or sodium hypophosphite required harsh conditions. After studying alternative conditions, the Montchamp group determined that triethylborane and oxygen allowed the reaction to proceed efficiently at room temperature, under neutral conditions (Eq. 5.4).[52] These milder conditions provided the desired monosubstituted phosphinic acid. The results prompted the study of alkynes as substrates under organoborane/air and room-temperature conditions.[12,54]



(Eq. 5.4)

As a model study, the reaction of sodium hypophosphite with 1-hexyne was investigated using Et_3B/air to promote radical formation (Scheme 5.11).[54] The results are summarized in Table 5.1.[12a] Methanol was initially selected as solvent because sodium hypophosphite has no significant solubility in other common organic solvents at room temperature. The 1,1-bis-*H*-phosphinate **115** was directly collected as a white solid. The 1,1-bis-*H*-phosphinate disodium salt precipitated spontaneously from the reaction mixture, thereby allowing easy isolation. This convenient reaction can be conducted easily on large scales. The final product **115** was always obtained as the major product (the remaining filtrate contains some unreacted starting material, sodium hypophosphite and alkyne, along with small amounts of the 1,2-disubstituted isomer **120** and, in some cases, traces of the alkenyl intermediate **118**). The only 1,1-bis-*H*-phosphinate derivatives reported in the literature are the unsubstituted ethyl and isopropyl esters of the parent acid,[247] which were obtained from $Cl_2PCH_2PCl_2$.[248]

Scheme 5.11 Preparation of 1,1-bis-*H*-phosphinate disodium salts

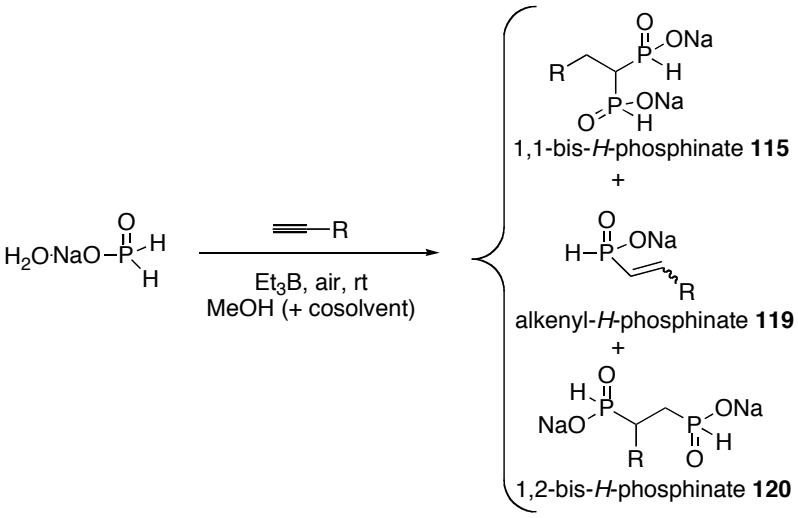
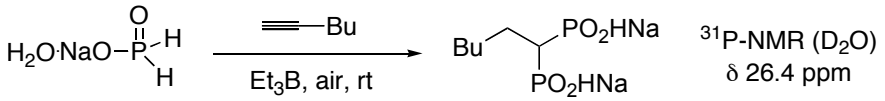


Table 5.1 Influence of reaction conditions on the yield of hexyl-1,1-bis-*H*-phosphinate[a]



entry	NaH_2PO_2 equiv	Solvent	Isolated yield[b]
1	2.5	MeOH	13
2[c]	2.5[c]	MeOH[c]	0[c]
3	2.5	MeOH/acetone (5:1)	44
4	6.0	MeOH	52
5	6.0	MeOH/H_2O (5:1)	23
6	6.0	MeOH/CH_3CN (5:1)	27
7	6.0	MeOH/acetone (5:1)	57
8	6.0	MeOH/DMF (5:1)	67
9	6.0	MeOH/dioxane (5:1)	72
10	6.0	THF/H_2O (2:1)	0
11	10.0	MeOH	62
12	10.0	MeOH/dioxane (5:1)	65

[a]Reactions were conducted in a flask open to air at room temperature, using Et_3B (1 equiv) in hexane (1 M) in reagent-grade solvent. Unless otherwise noted, the concentration of 1-hexyne before addition of Et_3B was 0.2 M. [b]After filtration and washing with cold methanol. [c]Concentration was 0.1 M.

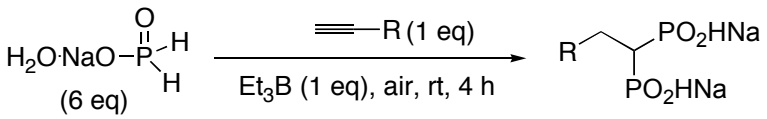
As observed in Table 5.1,[8a] under the conditions used with alkenes,[52] only a small amount of precipitate formed (entry 1). As expected, decreasing the concentration lowered the yield further (entry 2) because of both a less-efficient chain reaction and an increased solubility of the product which impedes its recovery. Addition of a cosolvent significantly increases the yield

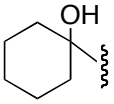
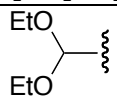
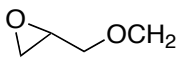
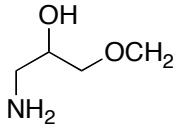
(entry 3). Since 2.5 equivalents of NaH_2PO_2 was optimum for reaction with olefins and because bis addition is required with alkynes, increased amounts of hypophosphite were tried. Not surprisingly, this resulted in a significant improvement (compare entry 11 with entry 4 and entry 1). Various co-solvents were also tried. Water (entry 5) and acetonitrile (entry 6) were unsatisfactory, whereas acetone (entry 7), DMF (entry 8), or dioxane (entry 9) afforded good yields of 1,1-bis-*H*-phosphinate. At this point, raising the amount of sodium hypophosphite had little effect (entry 12 versus 9). Therefore, the conditions in entry 9 appeared nearly optimum.

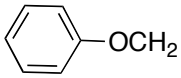
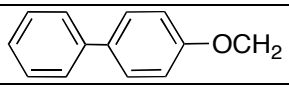
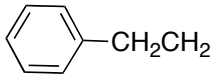
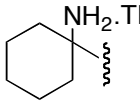
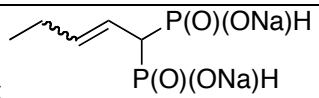
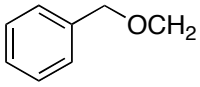
5.2.3 Scope of the reaction

A variety of terminal alkyne substrates were then studied as radical-reaction partners (Table 5.2).[12] All alkynes react to give the corresponding 1,1-bis-*H*-phosphinate which always precipitated out of the reaction mixture. Initially, the addition was investigated using unoptimized conditions (i.e., reaction performed in MeOH instead of MeOH/Dioxane, 5:1) (method A, Table 5.2). Reaction in methanol generally afforded lower yields than when dioxane was employed as a cosolvent (method B, Table 5.2, entry a versus b). A variety of functional groups are tolerated. Although the yields were sometimes low, the reaction is convenient to run even on a large scale and does not require specific precautions. Gas chromatographic analysis of the filtrate after low-yielding reactions shows that the alkyne starting material remains in significant quantity.[12a] Thus, a "recycling" strategy was developed to increase conversion: after the first run, the filtrate was concentrated, taken up in the solvent, and more NaH_2PO_2 and Et_3B were added. For example, using this method, epoxy-alkyne (Table 5.2, entry 18) yields the bisphosphinate in 24% yield in the first run and in 61% yield in the second run, for a 85% overall yield (method C, Table 5.2). The alkynes bearing an amino group were poor substrates, even when the reaction was performed in acidic medium (Table 5.2, entries 23-26).

Table 5.2 Scope of alkyne radical hydrophosphinylation



Entry	R	Method[a]	Isolated yield (%)[b]
1a	CH_2OH	A	20
1b		B	52
1c		C	61
2a	$CH_2CH_2CH_2OH$	A	25
2b		B	64
3a		A	46
3b		B	78
4a		A	39
4b		B	87
5a	Me_3S	A	33
5b		B	41
6a	CH_2Cl	B	20
6b		C	47
7	CH_2CH_2OTs	C	48
8	CH_3	D	74
9	Bu	C	72
10a	Hex	B	70
10b		C	89
11a	Oct	A	48
11b		B	64
11c		C	76
12a	*t*-Bu	A	39
12b		B	46
13a	CO_2Et	A	40
13b		B	60
14a	CH_2OAc	B	39
14b		C	56
15	$CH_2CH_2CO_2H$	B	69
16a		B	24
16b		C	38
17a	CH_2OCH_3	A	51
17b		B	47
18a		A	24
18b		B	61
18c		C	85
19		B	40

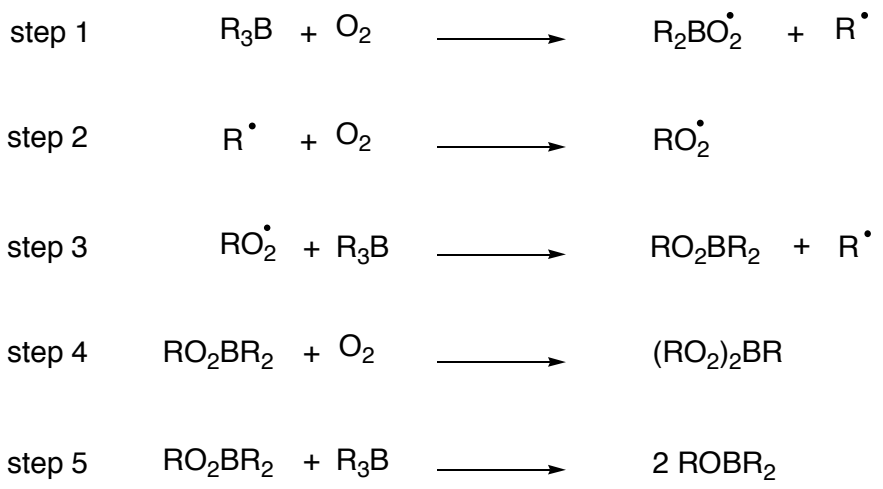
20a 20b		B C	57 79
21a 21b		B C	71 86
22a 22b		B C	21 61
23a 23b	$CH_2NH_2.HCl$[c]	B C	14 42
24a 24b	$CH_2NH_2.TFA$	B C	12 14
25a 25b	$CBz_2NCH_2CH_2$	A B	22 48
26		B C	14 14
27[d]	Product: 	B	93
28a 28b		B C	11 47

[a] Reactions were conducted in a flask open to air at room temperature, using reagent-grade solvent(s) with NaH_2PO_2 (6 equiv) and Et_3B (1 equiv, 1 M in hexane). Method A: MeOH. Method B: MeOH/dioxane (5:1). Method C: after a run conducted, as in Method B, the filtrate is concentrated and redissolved in the solvent mixture along with NaH_2PO_2 (6 equiv), and Et_3B is added. The yield corresponds to the combined yield after both runs. Method C: the propyne gas was bubble for 4 h and isolated yield calculated according to the amount of NaH_2PO_2 used. For additional details, see the Supporting Information. [b] 1,1-Bis-*H*-phosphinates were isolated by simple filtration after washing with cold methanol in >95% purity. [c] 2 equivalents of Et_3B were used. [d] ring-opening of the cyclopropylacetylene.

5.2.4 Proposed mechanistic pathways

Scheme 5.13 represents possible mechanistic pathways, leading to the formation of three products: disodium 1,1-bis-*H*-phosphinate (**115**), sodium alkenyl-*H*-phosphinate (**119**) and disodium 1,2-bis-*H*-phosphinate (**120**). Organoboranes are well precedented in the literature as excellent source of free radicals.[249] They are known to form radicals even at low temperatures[249a-249h] in the presence of oxygen. The radical chain is initiated by autooxidation of triethylborane in the presence of air (Scheme 5.12).[249] The mechanism is believed to proceed through the formation of a free alkylperoxy radical capable of attacking the boron with displacement of an alkyl radical (Scheme 5.12, step 3).[249a] The peroxide formed in step 3 may either react with another molecule of oxygen (Scheme 5.12, step 4) or undergo an intermolecular redox reaction (Scheme 5.12, step 5) with another molecule of trialkylborane.

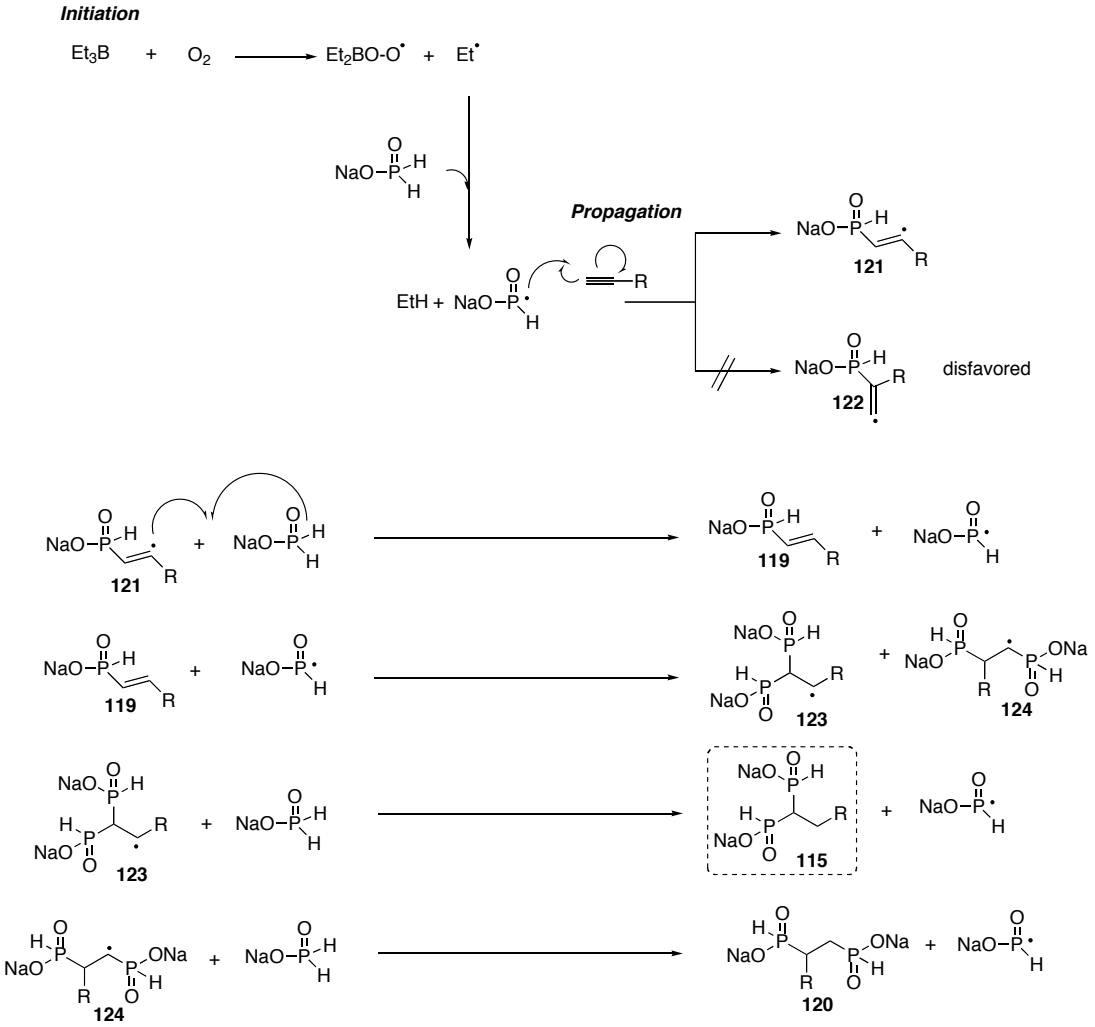
Scheme 5.12 Trialkylborane autooxidation



Further reaction with sodium hypophosphite generates an electrophilic hypophosphite radical that reacts with the alkyne, potentially generating two isomeric radicals, **121** and **122** (Propagation, Scheme 5.13). Being the more substituted radical, **121** is considered as the most stable of the two isomers. Compounds synthesized from intermediate **122** were never observed in the crude mixture, however, compound **119** could be detected.

When sodium hypophosphite was used as starting material, only compound **115** was observed. However, if anilinium hypophosphite is used as starting material, compound **1120** was produced as the major product. Properties of sodium versus anilinium clearly affect the outcome of the reaction.

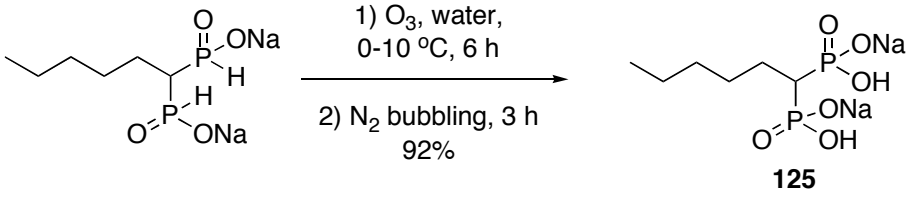
Scheme 5.13 Postulated mechanism for the radical reaction of sodium hypophosphite to terminal alkynes



5.2.5 Oxidative conversion of 1,1-bis-*H*-phosphinate into bisphosphonate

As mentioned before, oxidation of a phosphinylidene moiety can be accomplished under mild conditions and should therefore be compatible with highly functionalized molecules.[4a] *H*-Phosphinic acids have been converted into phosphonates through a variety of methods.[26b,26c,91a,91c,96,250] Since the P(V)-P(III) tautomerism of the phosphinylidene group (Chapter I, Scheme 1.1) is catalyzed by non-neutral conditions, the acids are more reactive toward oxidation than the corresponding neutral salts. However, we found ozonolysis to be a

practical method to directly convert the 1,1-bis-*H*-phosphinate disodium salts into the corresponding phosphonate **125** (Eq. 5.5). The hexyl-1,1-bis-phosphonate **125** was recently shown by Szajnman and co-workers to have significant activity on *Trypanosoma cruzi* farnesyl pyrophosphate synthase (K_i = 0.47 μM; IC_{50} = 5.67 μM).[251] Other reagents can also be employed (H_2O_2, NaOCl, Br_2), but depending on the substrate and the oxidizer, variable amounts of phosphate can be formed through P-C bond cleavage making ozonolysis the most convenient method.



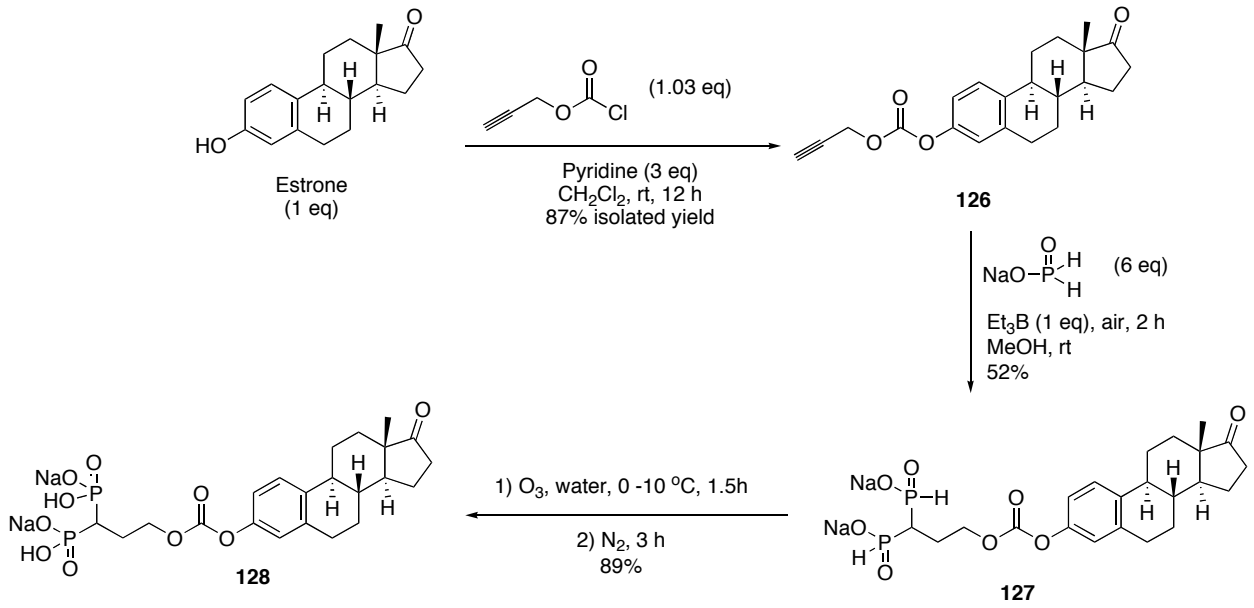
125 (Eq. 5.5)

5.2.6 Preparation of the bisphosphinate-prodrug and bisphosphonate drug-conjugates

5.2.6.1 Steroid conjugates synthesis

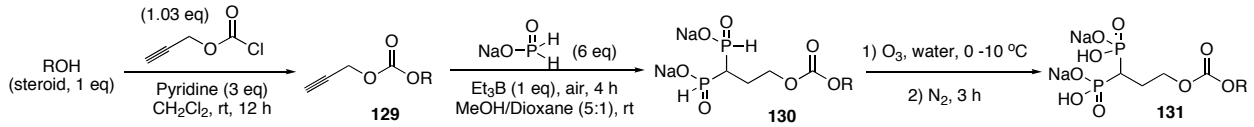
Bisphosphonate-steroid conjugates[232h] have been proposed to direct hormones to the bone for the treatment of osteoporosis and to decrease the problems associated with hormone replacement therapy in breast cancer, for example. We applied our methodology for the synthesis of such conjugate. The efficiency of our methodology is demonstrated by the synthesis of the estrone-bisphosphinate (Scheme 5.14).[12c,54] Estrone reacted with propargyl chloroformate to form the carbonate **126** in a nearly quantitative yield. Reaction with NaH_2PO_2 then afforded 1,1-bis-*H*-phosphinate **127** as a white solid. Finally, oxidation with ozone produced the bisphosphonate-estrone conjugate **128**.

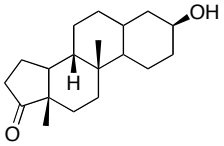
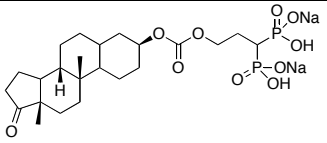
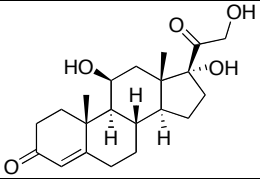
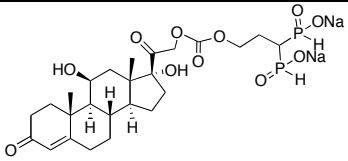
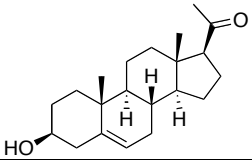
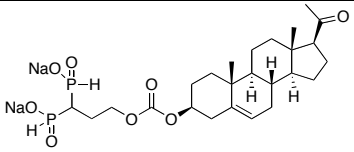
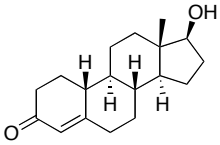
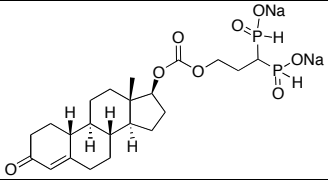
Scheme 5.14 Preparation of estrone-bisphosphonate conjugate



Our synthesis led to the desired bisphosphonate (**128**) in good yield (> 42% overall yield), in two steps and in a single day. The literature syntheses of steroid-bisphosphonate conjugates are representative of several problems with current methodologies, such as time-consuming multistep sequences, relatively harsh conditions, and necessary manipulation of the methylenebisphosphonate synthon (Scheme 5.6).[232h,232f] Satisfied by the preliminary results, a series of steroid conjugates was prepared (Table 5.3).[12c] Epiandrosterone (Entry 1), hydrocortisone (Entry 2), pregnenolone (Entry 3), and nandrolone (Entry 4) were converted into their corresponding 1,1-bis-*H*-phosphinates in moderate to good isolated yields. The oxidation step afforded the desired BPs in moderate to excellent isolated yield.

Table 5.3 Synthesis of steroid conjugates[a]



Entry	ROH	Isolated yield, %[b]	Product	Isolated yield, %	
		129	130	130[c]	131
1		90		48	79
2		86		85	97
3		99		86	47
4		87		56	- [d]

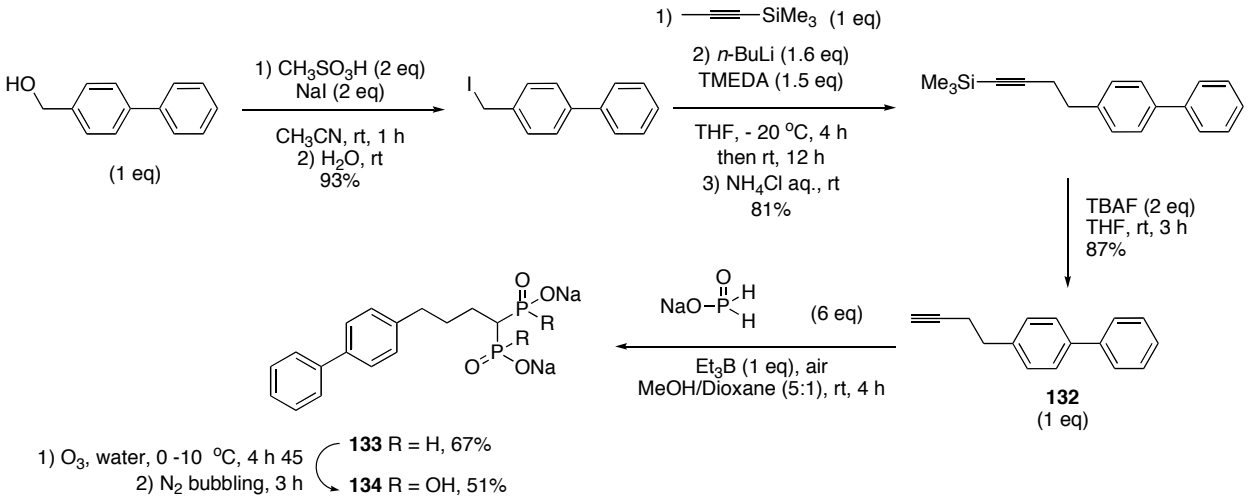
[a] See experimental section for details of the procedures. [b] Isolation by extractive work-up. [c] Yield of bis-*H*-phosphinate sodium salt were determined after filtration of the heterogenous solution obtained. The solid was rinsed several times with cold methanol and dried overnight under vacuo over P_2O_5. [d] not available.

5.2.6.2 Synthesis of Squalene Synthase inhibitor

Some bisphosphonates are also inhibitors of the cholesterol biosynthesis,[232i] and therefore, approach to these compounds are of interest. Scheme 5.15 illustrates our synthesis of (4-biphenyl-4-yl-1-phosphono-butyl)-phosphonic acid **134**, a potent inhibitor of squalene synthase (IC_{50} = 0.7 nM).[232i] Alkyne **132** reacted under our standard conditions to afford the corresponding 1,1-bis-*H*-phosphinate **133**. Oxidation afforded inhibitor **134**. The present reaction has potential for the preparation of BP libraries from terminal alkyne precursors.

As mentioned earlier, an intriguing possibility would be if *in vivo* oxidation of the 1,1-bis-*H*-phosphinate could take place, since these compounds would then act as bisphosphonate prodrugs.

Scheme 5.15 Synthesis of squalene synthase inhibitor

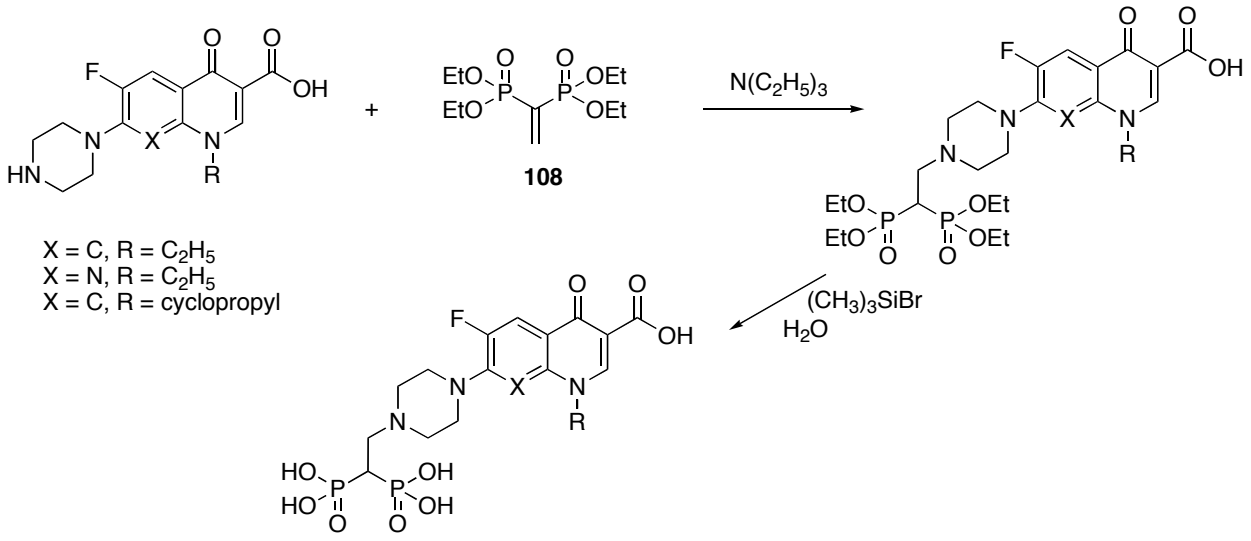


5.2.6.3 Synthesis of a bisphosphinate fluoroquinolone conjugate

BPs great potential to accumulate in bone matrix hydroxyapatite makes them useful as carriers for cytotoxic or antibacterial substances, increasing the concentration of the drug in bone tissue. The introduction of a bisphosphonate moiety into pharmacologically active molecules, such as fluoroquinolone antibacterial drugs, may enhance their ability to bind to a site, which is usually difficult to treat clinically.[252]

Few methods for the preparation of bisphosphonates conjugated to fluoroquinolone have been reported.[240,254] In most cases, the conjugates are synthesized in good to excellent yields through the Michael addition of the amine moiety of the fluoroquinolone to the ethenylidenebisphosphonate **108** (Scheme 5.16).[254b]

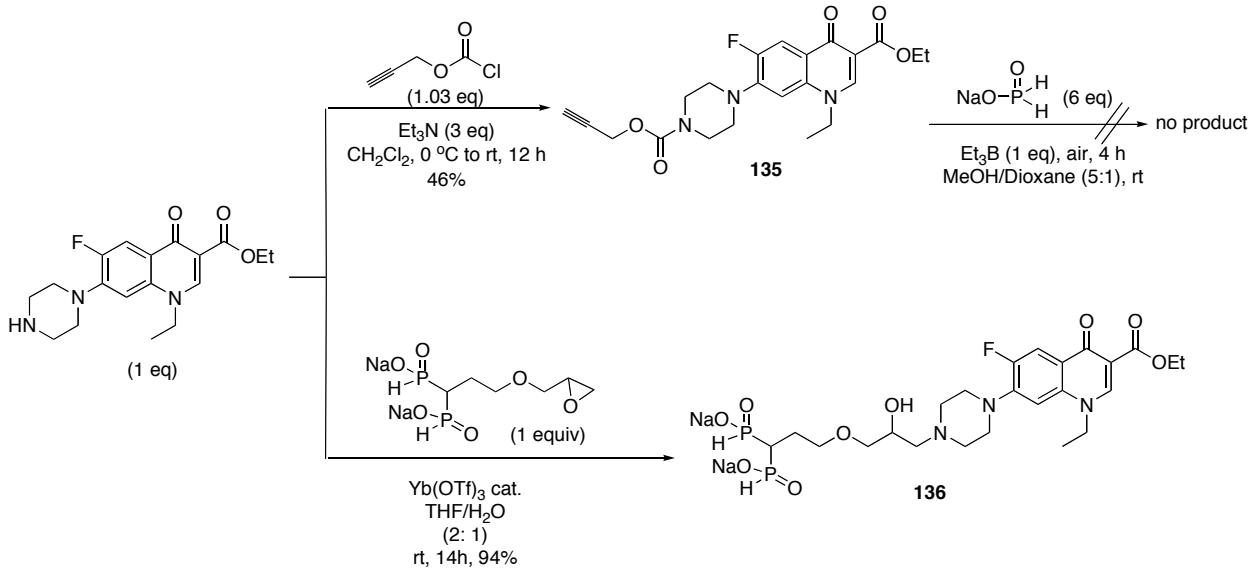
Scheme 5.16 Synthesis of bis-phosphonoethyl derivatives of fluoroquinolone antibacterials



They are generally safe agents, active orally and parenterally, and have a broad antimicrobial spectrum that includes many frequently encountered pathogens. In this process, norfloxacin was selected as a representative starting material for the synthesis of a conjugate (Scheme 5.17).[12c]

Norfloxacin-bisphosphinate **136** was prepared by tethering of the fluoroquinolone ethyl ester[253] to the disodium 3-oxiranylmethoxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 18) via epoxide ring-opening catalyzed by ytterbium triflate ($Yb(OTf)_3$; 2.5 mol%). The reaction proceeds at room temperature in a THF/water solvent mixture which solubilizes the bisphosphinate and the fluoroquinolone ethyl ester. The desired conjugate was obtained in excellent yield (94%) after work-up.

Scheme 5.17 Synthesis of the bisphosphinate fluoroquinolone conjugate



Interestingly, the epoxide ring-opening did not occur when norfloxacin (free COOH) was added to the bisphosphinate even after heating at 100 °C for four days (reaction performed in DMF, under nitrogen). On the other hand, organoborane-radical reaction methodology did not lead to the product when norfloxacin-propargylcarbonate **135** was used as starting material, likely due to the presence of the basic nitrogen of **135** that inhibits the formation of the ethyl radical.

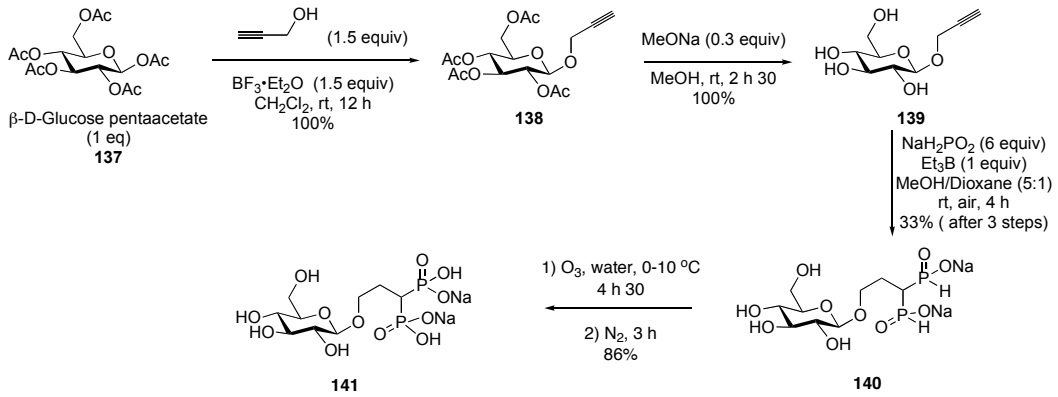
5.2.6.4 Synthesis of the carbohydrate conjugates

The role of carbohydrates in tumor progression, metastasis and anti-tumor drug development is prominent. It is now well known that oligosaccharides found on cell surfaces play key roles in many diverse recognition and adhesion processes both in physiological and pathological states. In particular, changes in glycosylation are often encountered in disease states. Also, cancer cells frequently display glycans at different levels or with fundamentally different structures than those observed on normal cells.

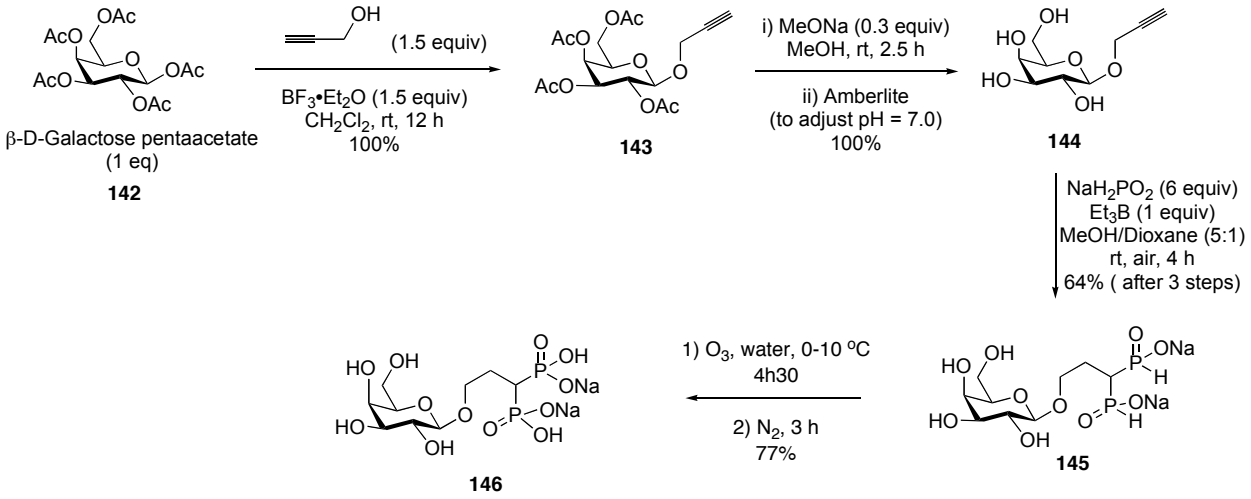
A collaborative project with TCU Professor Jeffery Coffer has been initiated to prepare the recognition component of biocompatible calcified nanoporous silicon sensor arrays.[246] Given the prevalence of glycoproteins on cell surfaces, various BPs-carbohydrate conjugates were prepared for bone tissue engineering and drug delivery.[246c] Evaluating the biocompatibility of calcium phosphate coated silicon nanowires (CaP/SiNWs), and bisphosphonate modified CaP/SiNWs composites is a valuable part of designing new effective orthopedic biomaterials if a permanent semiconducting conduit for bone regeneration is desired.[246c]

Our methodology provided three carbohydrate conjugates (Schemes 5.18-5.20, compounds **140**, **145**, and **151**). First, the peracetylated carbohydrates (**137**, **142**, and **148**) were successfully converted into their propargyl derivatives (**138**, **143**, and **149**) in excellent yields. Then, deprotection of the acetate esters using sodium methoxide afforded the unprotected carbohydrates quantitatively (**139**, **144**, and **150**).[255] The organoborane-catalyzed radical reaction of **139**, **144**, and **150** led to the formation of 1,1-bis-*H*-phosphinate compounds (**140**, **145**, and **151** respectively), which precipitated out of the crude mixture as white solids. All the compounds were purified by washing the precipitates with cold methanol. Finally, the corresponding bisphosphonate conjugates of **140** and **145** were synthesized using the ozonolysis method.

Scheme 5.18 Synthesis of the β-D-glucopyranosyl-1,1-bis-phosphonate[246c]

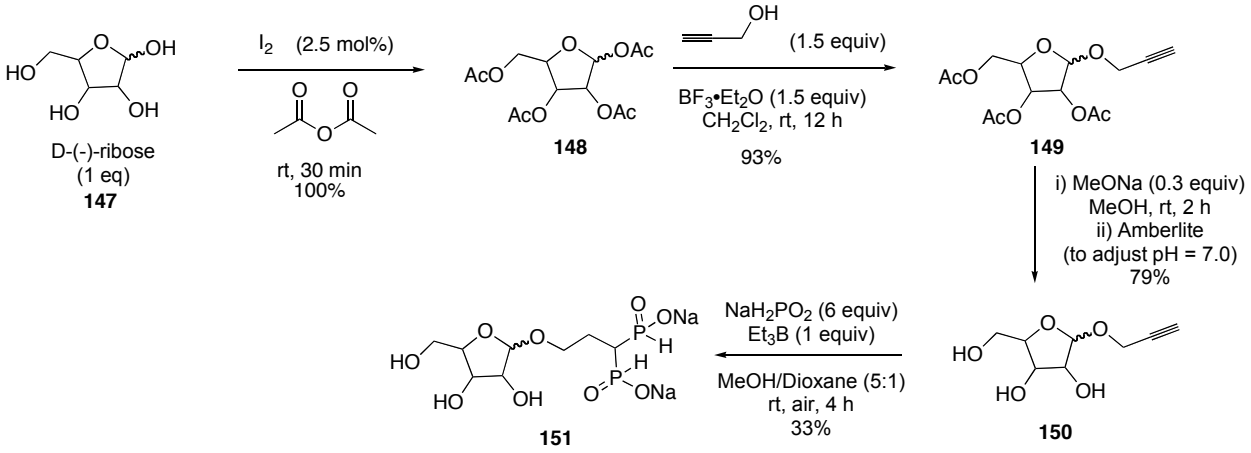


Scheme 5.19 Synthesis of the β-D-galactopyranosyl-1,1-bis-phosphonate



In the case of ribose (Scheme 5.20), the peracetylated compound (**148**) was not commercially available. Kartha and Field have demonstrated that iodine is an efficient promoter for acyl transfer reactions in carbohydrates,[256] which was applied to the acetylation of the D-(-)-ribose.

Scheme 5.20 Synthesis of the D-ribofuranosyl-1,1-bis-phosphinate



Disodium [(2,3,4,6-tetra-*O*-hydroxyl-*β*-D-glucopyranosyl)propyl]-1,1-bisphosphonate **141** was coupled to the calcified SiNW surface.[246c] It was observed that glucose sensitively improves the cytocompatibility of the nanowire vector, when compared to Alendronate (Figure 5.2).[246c]

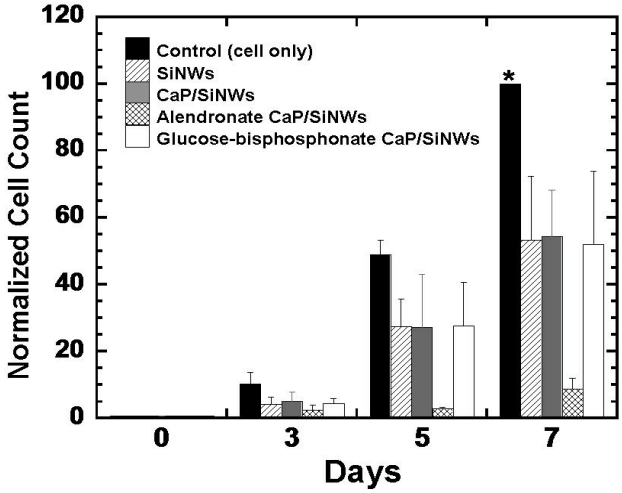
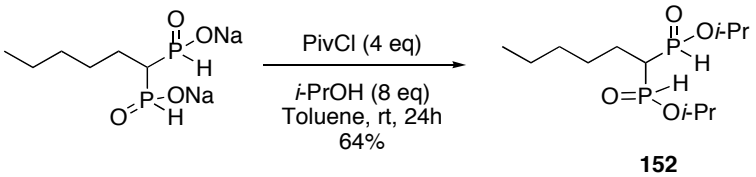


Figure 5.2. Graph of mouse stromal cell proliferation. Demonstration of the noncytotoxic behavior of SiNWs, CaP/SiNWs, and glucose-bisphosphonate CaP/SiNWs, as well as the cytotoxic behavior of alendronate CaP/SiNWs. All cell counts were normalized with respect to the number of cells in the control group after 7 days proliferation (100 %).

5.2.7 Direct esterification of 1,1-Bis-*H*-phosphinates

The esterification of a 1,1-bis-*H*-phosphinate was briefly studied. The direct esterification of the sodium salt with PivCl/*i*-PrOH delivered the corresponding ester (**152**) as a mixture of stereoisomers in 64% yield (Eq. 5.6).



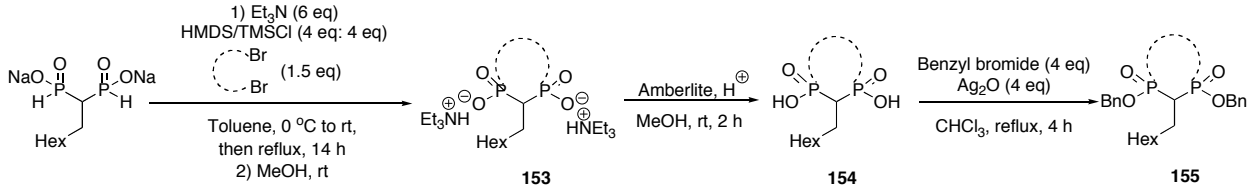
(Eq. 5.6)

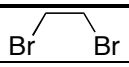
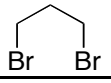
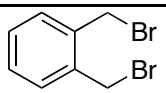
5.2.8 Bisphosphonate extractants

Phosphorus-based extractants are of particular importance, especially for the separation of cobalt from nickel.[257] In the 1950s, the solvent extraction process was applied to the recovery of uranium from sulfuric acid liquors produced in the leaching of uranium ores using extractants such as di(2-ethylhexyl) phosphoric acid (DEHPA).[257a] Presently, more than 40 reagents are available for use in hydrometallurgy, of which at least a dozen are in everyday use. It is known that P,P'-dialkyl methylenebisphosphonic acids are powerful metal extraction reagents exhibiting a strong affinity for a variety of metal ions, especially lanthanides and actinides.[257c] While the affinity of *gem*-bisphosphonic acids is generally high for most metal ions because of their relative high acidity and ability to form six-membered chelate rings, the selectivity is often low. Introducing a cyclic structure into *gem* bisphosphonic acids might enhance metal selectivity while retaining high extraction efficiency. Towards this end a new class of heterocyclic *gem*-bisphosphonic acid extraction reagents were synthesized (Table 5.4).

Cyclic bisphosphonic amino salts **153** were prepared with hexamethyldisilazane (HMDS), trimethylsilylchloride (TMSCl), and a dibromo electrophile. After refluxing for 14 hours, the reaction mixture was quenched with cold MeOH. Compounds **153** were acidified in the presence of amberlite beads at room temperature, in methanol (reaction monitored by ^{31}P NMR). Simple filtration of the reaction mixture and evaporation of the volatiles afforded compounds **154** which were directly esterified into the corresponding **155** esters. Products **155** were isolated after purification by column chromatography.

Table 5.4 Synthesis of bisphosphonate extractants[a]



Entry	Electrophile	^{31}P NMR yield, %[b]			Isolated yield, %[c]
		153	154	155	
1		100	44	55	35
2		100	68	67	52
3		100	64	88	54

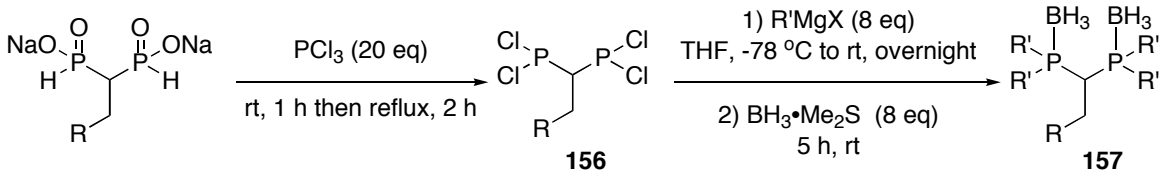
[a] See experimental section for details. [b] Yield was determined by integration of all the signals. [c] Isolated by column chromatography over silica gel. The compounds were incredibly polar.

5.2.9 1,1-Bis-*H*-phosphinates, precursors of bisphosphine-borane ligands

Organophosphorus compounds have found some importance as catalyst ligands (Chapter I).[1,258] Since the efficiency and the selectivity of the catalyst mainly rely on the structure of the ligand, there is a great interest in the design and the synthesis of new ligands. The preparation of bisphosphine-borane ligands from alkyl-1,1-bis-*H*-phosphinate is herein described (Table 5.5). The preparation was conducted by treating the alkyl-1,1-bis-*H*-phosphinate with an excess of PCl_3.[259] The corresponding alkyl-1,1-bis-phosphonous dichloride (**156**) was obtained after distillation, under nitrogen, in low to moderate yield (Table 5.5). The compounds **156** appeared to be quite stable in absence of air and moisture, and can be easily handled at room temperature. Even though the reaction can be conducted in toluene, superior results were obtained without any solvent. Finally, the synthesis of the bisphosphine ligands **157** was carried out in dry THF, under nitrogen. The quadruple substitution with the appropriate Grignard reagent led to the desired bisphosphines which was directly protected by using BH_3•Me_2S to give the corresponding borane complexes **157** (Table 5.5).

It is worth mentioning that, in the case where the alkyl chain carried an acetate (Table 5.5, entry 3), the deprotection of the hydroxyl group occurred during the substitution reaction.

Table 5.5 Synthesis of bisphosphine-borane ligand[a]



Entry	R	^{31}P NMR yield, %	R'MgX	^{31}P NMR yield, %[b]	Isolated[c] yield, %
		156		**157**	
1a	Bu	25	PhMgBr	75	10
1b			*i*-PrMgCl	98	48
1c			cyclohexyl-MgCl	100	10
2a	Hex	47	PhMgBr	100	
2b			*i*-PrMgCl	100	
3a	CH_2OAc	38	PhMgBr[d]	100	53[e]
3b			*i*-PrMgCl[d]	100	

[a] See experimental section for details of the procedures. [b] All yields are crude ^{31}P NMR percentages, calculated from the integration of all phosphorus peaks. [c] Isolation by column chromatography over silica gel. [d] deprotection of the hydroxy group occurred during the reaction. [e] R = CH_2OH.

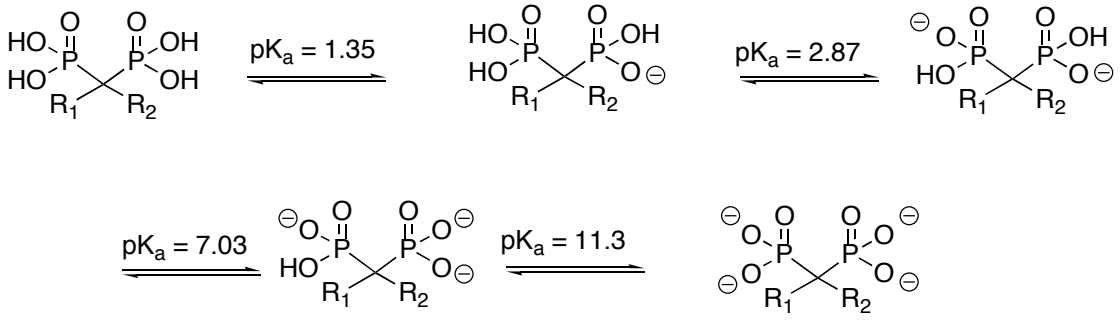
As noticed, the isolated yields were low in some cases. Purification of the products proved to be quite difficult. After several failed purification attempts, it was determined that the phosphine-borane was hydrolytically unstable. Although optimization of the reaction conditions is needed, these preliminary results are quite promising in terms of formation of the bisphosphine-borane from 1,1-bis-*H*-phosphinates.

5.2.10 Physical properties: pK_a measurements of the 1,1-bis-*H*-phosphinate

Features, such as changing the nature of the ionizable group, changing electronegativity, size, and hydrophobicity of the substituents, can influence the transport of a drug across cell membranes. These features can also affect its preferential degradation or activation in the neoplastic or virus-infected cells, and can contribute to the overall efficiency of the drug. The

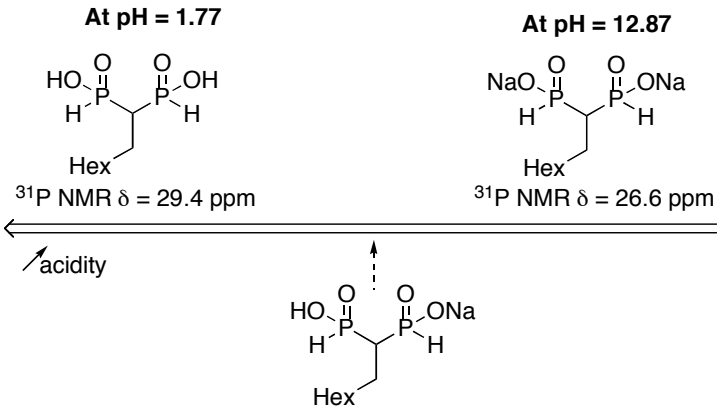
ionization of BPs is essential for activity and therapeutic utility (bone binding), but also important for adverse reactions and drug interactions. The ionization data for BPs are known, and are presented in Scheme 5.21.[260]

Scheme 5.21 Bisphosphonate Ionization[260b]



We decided to measure the ionization of the 1,1-bis-*H*-phosphinate. The results are represented in Scheme 5.22. The measurements were performed with octyl-1,1-bis-*H*-phosphinate. The latter was placed in solution in deionized water (pH of the solution = 5.95). The pH of the solution was adjusted to 0.95 by addition of 1M HCl aq. Surprisingly, titration with 0.1M NaOH gave only one pK_a value (pK_a = 3.5) out of two expected. Therefore, the second pK_a must be above 11. Also, we were interested in the effect of the pH on the ^{31}P NMR chemical shifts. It was observed that at pH > 12, the disodium 1,1-bis-*H*-phosphinate shift is upfield (^{31}P NMR in H_2O, δ_{ppm} 26.6), whereas at pH < 2, the corresponding diacid was formed with a peak shifted downfield (^{31}P NMR in H_2O, δ_{ppm} 29.4). These observations suggested that at the average value of the recorded pH, which correspond to a pH = 7.32, the ^{31}P-NMR chemical shift has a value of 28 ppm, representing the monoacid bisphosphorus compound. This data suggests that at physiological pH, the 1,1-bis-*H*-phosphinate may be under this form.

Scheme 5.22 Octyl-1,1-bis-*H*-phosphinate ionization and effect on ^{31}P NMR shift



In conclusion, we have developed a simple and practical approach to a new class of organophosphorus compounds under mild radical conditions. Through oxidation via ozonolysis, these 1,1-bis-*H*-phosphinates can be converted into biologically important 1,1-bisphosphonates. An unprecedented broad variety of functional groups is tolerated and previously unknown compounds have been synthesized, most of them by using inexpensive starting materials. The high efficiency of our methodology, as well as a very practical experimental procedure, compensate for the moderate yields obtained. Another advantage is the ease of the isolation of the product. An intriguing possibility would be if *in vivo* oxidation of the 1,1-bis-*H*-phosphinates can take place because these compounds would then act as novel bisphosphonate prodrugs.

Chapter Six: Palladium-catalyzed hydrophosphinylation reactions of terminal alkynes

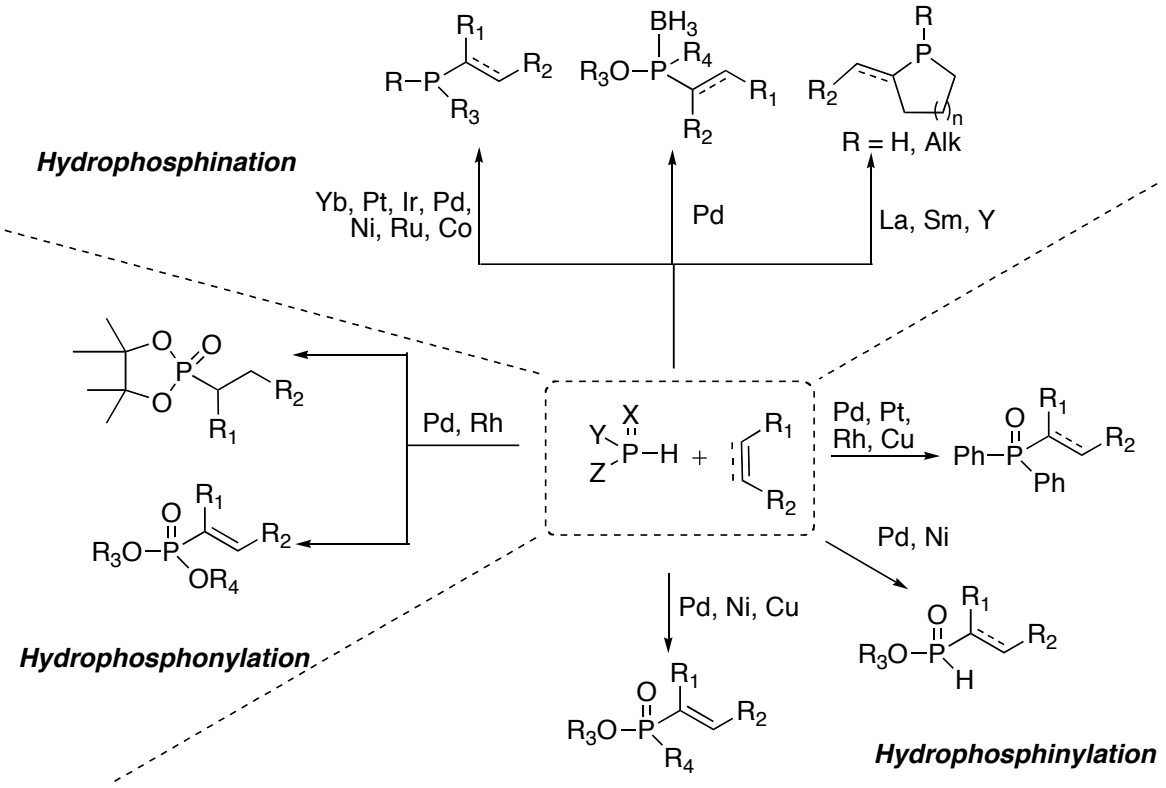
6.1 Introduction

The metal-catalyzed addition of phosphorus compounds across carbon-carbon multiple bonds has emerged as the subject of intensive research not only due to highly atom economical features, but also because of the wide availability of the starting materials. This transformation offers an efficient strategy for the synthesis of organophosphorus derivatives.

Classic methods of promoting the addition reaction for P-C bond formation include radical or base-catalyzed reaction, and to lesser extent, the use of acid-catalysis and thermal activation with activated alkenes.[261-264] Through metal catalysis,[261] significant advances on the selectivity and rate of the reaction have been achieved. Catalytic P-C bond formation by transition-metal is an increasingly active field. The addition of P(III) compounds (hydrophosphination) and P(V) compounds (hydrophosphinylation and hydrophosphonylation)[261e] to a variety of unsaturated substrates has been examined as viable routes to phosphines,[149c,149d,262,265,266] tertiary phosphine-boranes,[267] phosphonates,[88,89,268] tertiary phosphine oxides,[269] phosphinates,[69,70] and *H*-phosphinates[56-58] (Scheme 6.1). For example, addition of phosphines(PH_3, RPH_2, R^1R^2PH) to carbon-carbon multiple bonds is a valuable process for the construction of P-C bonds, from both the economical and the environmental point of view.[265,266]

In pioneering studies, Tanaka reported the metal-catalyzed hydrophosphonylation reactions through addition of *H*-phosphonates to terminal alkynes (Chapter I, Section 1.2.2.1, Scheme 1.13).[88,89]

Scheme 6.1 Metal-catalyzed additions of phosphorus compounds to unsaturated substrates

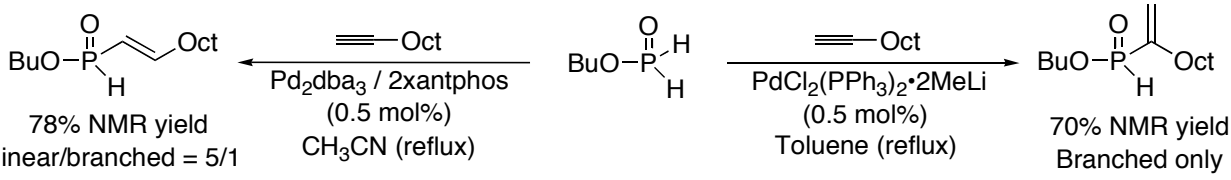


The methodology was extended by other groups,[268] but with dienes and alkenes, the reaction is limited to the pinacol-*H*-phosphinate.[89] The latter fact is a significant limitation because pinacol phosphonate esters require harsh conditions for cleavage.[89] Therefore, the overall approach may not grant substantial advantages over the classical Arbuzov or Michaelis-Becker phosphonate syntheses. Few literature examples of metal-catalyzed *H*-phosphinate P-H bond activation has been reported. Examples were only reported by Tanaka,[69] Han,[70] and by Zhao[269f] on the reaction of phenyl-*H*-phosphinate esters with alkynes (Scheme 1.11) using palladium, nickel, or copper catalysts. Excellent regioselectivity was achieved. However, in all these cases,[69,70,263,269] only aryl-*H*-phosphinate esters (e.g., phenyl-*H*-phosphinate esters) were employed, and these substrates are rather special (i.e., these substrates do not undergo transfer hydrogenation).

The plausible reason for more facile insertion into P-H bonds is probably due to the aromatic π-system which makes the position benzylic-like, similarly to benzylic C-H bonds which are more activated toward metallation.

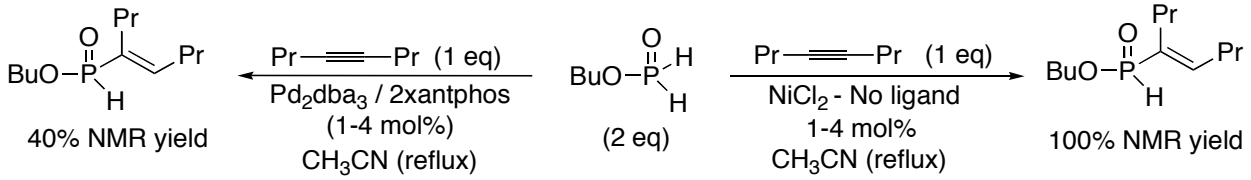
Currently, there is still no general catalytic addition of *H*-phosphinates to unsaturated hydrocarbons. Hydrophosphinylation of hypophosphorous compounds (which possess two P-H bonds) are highly prone to transfer hydrogenation reactions. Montchamp and coworkers overcame the reductive pathway (Scheme 1.8) and a vast array of synthetically versatile monosubstituted *H*-phosphinates were prepared, using both homogeneous (Eq. 1.20)[56,58] and heterogeneous catalysts (Eq. 1.21).[57] Terminal and some internal alkenes, as well as internal and terminal alkynes, participate successfully in the reaction with H_3PO_2, AHP and alkyl phosphinates.[56] The reaction occured in the presence of low catalyst loading of Pd_2dba_3/xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) (1 mol% or less).[56] In the case of terminal alkynes, depending on ligand and solvent choice, good regioselectivity for the linear *vs* the branched isomers of alkenyl-*H*-phosphinates was reported (Scheme 6.2).[56]

Scheme 6.2 Regioselectivity on addition to terminal alkynes from Ref. 56



In order to expand the scope of the reaction to access alkenyl-*H*-phosphinates directly, the Montchamp group developed a high-yielding nickel-catalyzed reaction using inexpensive $NiCl_2$ (0.5-4 mol%) under ligandless conditions (but alkenes give yields only around 70%) (Scheme 6.3).[58]

Scheme 6.3 Ni *vs* Pd catalysis in hydrophosphinylation of 4-octyne with alkyl phosphinates



Regioselectivity was only good with sterically and electronically biased alkynes. With terminal alkynes, poorer regiocontrol was observed when compared to the alternative Pd-catalyzed reaction.

Additionally, a number of one-pot transformations were described to prepare other organophosphorus compounds (phosphonates, disubstituted phosphinates, phosphonothioic acids, and tertiary phosphine oxides) in order to illustrate the synthetic flexibility that *H*-phosphinate esters offer.[58] Both Pd- and Ni-catalyzed hydrophosphinylations were conducted in minutes, using microwave irradiation.[58] The products were usually obtained in high yield.

The Pd-catalyzed addition of phosphinates $(RO)P(O)H_2$ to terminal alkynes, provided good regioselectivity. Nonetheless, it was still desirable to explore the scope of this transformation to other unsaturated partners and to improve the regiocontrol. We addressed these issues in the present study and the results will be discussed in the following section.[270]

6.2 Results and Discussion

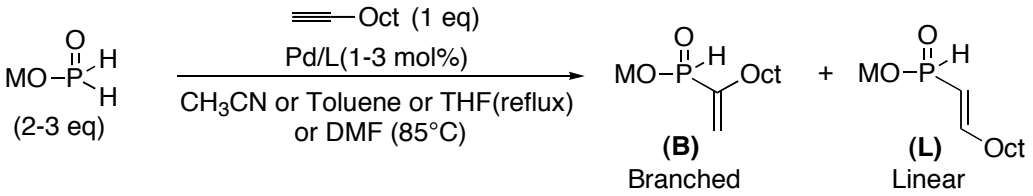
Our initial approach to this project consisted of investigating the optimum catalytic systems in order to achieve this regiocontrol. Various ligands and catalysts combinations were screened, as well as different hypophosphorous acid derivatives ($ROP(O)H_2$, R=H, $PhNH_3$, alkyl) in the hydrophosphinylation of 1-decyne. The results are listed in Table 6.1.

Using alkylphosphinates, a good regiocontrol for the formation of the branched isomer over the linear was achieved (entries 1-6). The best result was obtained using a TFA salt of an aminosilicate as esterifying agent[20] and Pd_2dba_3/dppf as catalyst in toluene (entry 1, branched/linear = 16/1). However, the previous result, where the branched isomer was obtained exclusively using $PdCl_2(PPh_3)_2$•MeLi (Scheme 6.2),[56] was not reproducible (entry 7). Instead, a ratio of 4/1, favoring the branched alkenyl-*H*-phosphinate was obtained.

On the other hand, when using Pd_2dba_3/xantphos in CH_3CN (entry 16), good regiocontrol was achieved, providing the linear isomer in a 10/ 1 ratio. In this case, the regioselectivity was improved when compared to the previous results (linear/branched = 5/1, Scheme 6.2).[56] In this case (entry 16), using Pd_2dba_3/xantphos with alkyl phosphinate $EtOP(O)H_2$ prepared *in situ* in CH_3CN by the aminosilicate methodology (entry 16) instead of using directly the stock solution of $BuOP(O)H_2$ in CH_3CN prepared from the alkoxysilane as in the previously reported conditions[56] is apparently responsible for the regioselectivity improvement.

While Pd_2dba_3/xantphos in CH_3CN gave better regioselectivity in favor of the linear isomer (entry 16), Pd_2dba_3/xantphos in toluene (entries 8, 13, and 28) favored the formation of the branched product. Furthermore, comparison of entries 9 and 17 shown that the solvent seems to reverse the regioselectivity.

Table 6.1 Regioselectivity study in the Pd-catalyzed hydrophosphinylation of 1-decyne



Entry	M	Method[a]	Solvent	Catalyst	RatioB/L	NMR Yield, % (Isolated Yield,%)
1	Et	A	Tol	Pd_2dba_3,dppf	16/1	100 (100)
2	Bu	B	Tol	Pd_2dba_3, DBFphos	14/1	63
3	Bu	B	Tol	Pd_2dba_3, dppf	13/1	100[b]
4	Et	B	Tol	Pd_2dba_3, dppf	16/1	100[b]
5	Et	B	Tol	$PdCl_2$dppf•CH_2Cl_2	12/1	100[b]
6	Bu	B	Tol	$PdCl_2$dppf•CH_2Cl_2	8/1	100[b]
7	Bu	B	Tol	$PdCl_2(PPh_3)_2$•2MeLi	4/1	72
8	Bu	B	Tol	Pd_2dba_3, xantphos	3/1	97
9	Et	B	Tol	$PdCl_2$, xantphos	2.8/1	45
10	Bu	B	Tol	$PdCl_2$, xantphos	2.5/1	86
11	Bu	B	CH_3CN	$PdCl_2(PPh_3)_2$•2MeLi	2/1	100
12	Bu	B	CH_3CN	$PdCl_2(PPh_3)_2$	2/1	93
13	Et	B	Tol	Pd_2dba_3, xantphos	1/0	10
14	Bu	B	DMF	Pd_2dba_3, xantphos	1/0	4
15	Bu	B	THF	$PdCl_2(PPh_3)_2$•2MeLi	1/0	6
16	Et	A	CH_3CN	Pd_2dba_3, xantphos	1/10	99 (99)
17	Bu	B	CH_3CN	$PdCl_2$, xantphos	1/7.2	100[b]
18	Bu	B	CH_3CN	Pd_2dba_3, xantphos	1/3.8	100[b]
19	Bu	B	CH_3CN	Pd_2dba_3,DPEphos	1/2.3	100
20	Bu	B	CH_3CN	Pd_2dba_3, dppf	1/1.75	86
21	Bu	B	CH_3CN	Pd_2dba_3,DBFphos	1/1.5	80
22	$PhNH_3$	C	CH_3CN	$PdCl_2$, xantphos	4/1	54[c] (33)
23	H	C	DMF	$PdCl_2$, xantphos	3.2/1	-[d]
24	H	C	DMF	Pd_2dba_3, xantphos	2.5/1	100
25	H	C	CH_3CN	Pd_2dba_3, dppf	1/0	10
26	$PhNH_3$	C	CH_3CN	Pd_2dba_3, xantphos	1/0	14[c]
27	H	C	Toluene	Pd_2dba_3, dppf	1/0	100[c](9)
28	H	C	Toluene	Pd_2dba_3, xantphos	2/1	100[c] (< 5)
29	H	C	CH_3CN	Pd_2dba_3, xantphos	1/1.7	19
30	H	C	CH_3CN	$PdCl_2$, xantphos	1/1.4	17
31	$PhNH_3$	C	DMF	Pd_2dba_3, xantphos	-	-[d]
32	$PhNH_3$	C	DMF	$PdCl_2$, xantphos	-	-[d]
33	H	C	DMF	Pd_2dba_3, dppf	-	0

[a] Method A: 3 eq H_3PO_2, 3 eq $(RO)_3Si(CH_2)_3NH_2$, 3 eq TFA, 1 eq alkyne, 1 mol% Pd/L. Method B: 3 eq Stock solution $ROP(O)H_2$ (0.5 M), 1 eq alkyne, 1-3 mol% Pd-L; Method C: 2 eq H_3PO_2 or AHP, 1 eq alkyne, 1 mol% Pd/L; [b] Inseparable mixture of product and $RO)_2P(O)H$; [c] Heterogeneous mixture, therefore the NMR are yields unreliable; [d] Mixture of products.

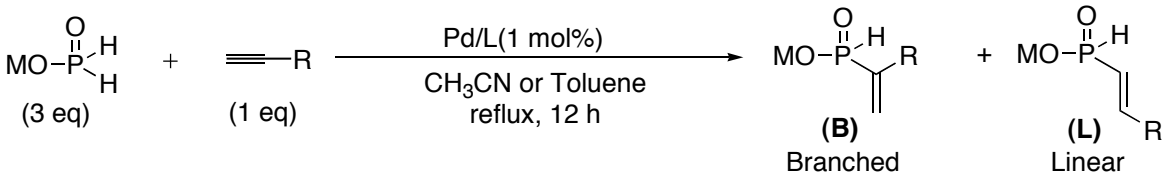
According to these results, the choice of the solvent, and to a lesser extent the ligand, appeared to be the key factor. The best ligands were dppf[42] and xantphos. Additionally, the use of aminosilicates to prepare *in situ* the alkyl phosphinate $ROP(O)H_2$ (Method A) was crucial in the isolation of pure products as the silicate by-products were eliminated by a simple acidic workup, and the diethylphosphite $(EtO)_2P(O)H$ by-product was removed in vacuo.

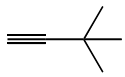
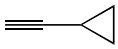
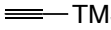
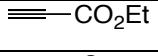
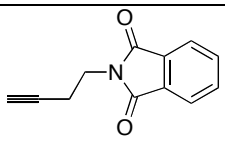
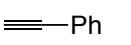
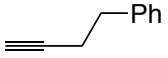
With respect to method B (use of a stock solution of $BuOP(O)H_2$ prepared from tetrabutoxysilane $(BuO)_4Si$ and H_3PO_2), attempts at purifying the products by chromatography on silica gel were not successful, due to the inability to separate the by-products dialkylphosphites from the alkenyl-*H*-phosphinates.

The use of H_3PO_2 or AHP did not give good results (entries 22-33). In general, the yields were low and/or the reactions were not selective (various unidentified products were obtained). When the reactions were performed in toluene, the mixture were not homogeneous and false NMR yields were measured (entries 27-28). In these particular cases, a thick and viscous jellylike substance was formed in the reaction mixture, so that only the supernatant was analyzed. The best result, in terms of conversion, was obtained in DMF with H_3PO_2, (branched/linear = 2.5/1, entry 24), the regioselectivity was not satisfactory.

To further extend the scope of the reaction, we investigated the reactivity of various terminal alkynes with $ROP(O)H_2$ (R = Bu, Et) and the results are summarized in the table 6.2.[270]

Table 6.2 Reactivity of terminal alkynes in the hydrophosphinylation reaction

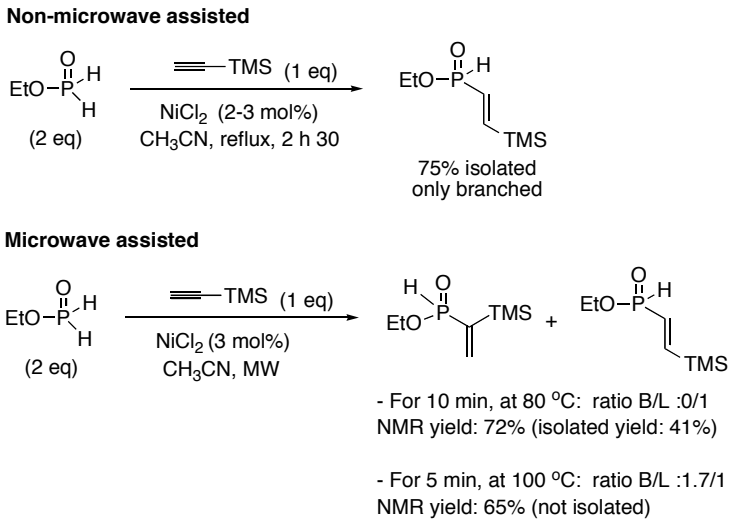


Entry	Alkyne	$MOP(O)H_2$ M =	Method for $MOP(O)H_2$[a]	Solvent	Catalyst	Ratio B/L	NMR yield[b], % (Isolated Yield, %)
1a		Et	A	CH_3CN	Pd_2dba_3/xantphos	1/10	100 (90)
1b		Et	A	toluene	Pd_2dba_3/dppf	2/1	100
1c		Bu	B	CH_3CN	Pd_2dba_3/xantphos	1/6.7	100 (87)
1d		Bu	B	toluene	Pd_2dba_3/dppf	2.6/1	100 (95)
2a		Et	A	CH_3CN	Pd_2dba_3/xantphos	1/4	100
2b		Et	A	toluene	Pd_2dba_3/dppf	1/0	100 (100)
2c		Bu	B	CH_3CN	Pd_2dba_3/xantphos	1/1	77 (66)
2d		Bu	B	toluene	Pd_2dba_3/dppf	1/0	100 (81)
3a		Et	A	CH_3CN	Pd_2dba_3/xantphos	0/1	100 (96)
3b		Et	B	toluene	Pd_2dba_3/dppf	1/0	41
4		Et	A	CH_3CN	Pd_2dba_3/xantphos	0/1	27[d]
5a		Et	A	CH_3CN	Pd_2dba_3/xantphos	1/5	100
5b		Et	A	toluene	Pd_2dba_3/dppf	11/1	100
5c		Bu	B	CH_3CN	Pd_2dba_3/xantphos	1/2	100 (67)
5d		Bu	B	toluene	Pd_2dba_3/dppf	10/1	100 (87)
6a		Et	A	CH_3CN	Pd_2dba_3/xantphos	0/1	100 (92)
6b		Et	A	toluene	Pd_2dba_3/dppf	6/1	100
6c		Bu	B	CH_3CN	Pd_2dba_3/xantphos	1/1	56
6d		Bu	B	toluene	Pd_2dba_3/dppf	-[e]	-
7a		Et	A	CH_3CN	Pd_2dba_3/xantphos	1/7	100
7b		Et	B	toluene	Pd_2dba_3/dppf	9/1	100

[a] Method A: 3 eq H_3PO_2, 3 eq $(RO)_3Si(CH_2)_3NH_2$, 3 eq TFA, 1 eq alkyne, 1 mol% Pd/L. Method B: 3 eq Stock solution $ROP(O)H_2$ (0.5 M), 1 eq alkyne, 1 mol% Pd-L; [b] Yields were determined by ^{31}P NMR analysis of the crude reaction mixtures and integration of all the resonance signals; [c] No product formed, only starting material with $(EtO)_2P(O)H$ by-product; [d] Inseparable mixture of product and $(RO)_2P(O)H$; [e] Mixture of products.

Moderate (in that case, the products were not isolated) to good regioselectivity was achieved. Depending on the nature of the terminal alkyne substituents (i.e., electronic, steric), and in general, the use of aminosilicates (Method A) gave slightly better results when compared to Method B (use of a stock solution of $BuOP(O)H_2$ prepared from tetrabutoxysilane $(BuO)_4Si$ and H_3PO_2). As expected, in all the cases, Pd_2dba_3/xantphos in CH_3CN provided the linear over the branched, whereas Pd_2dba_3/dppf in toluene provided the branched as major isomer. As exemplified in entry 1, poor regiocontrol was obtained for the synthesis of the branched isomer (entries 1b and 1d, branched/linear : less than 3/1). On the other hand, Pd_2dba_3/xantphos provided in good regioselectivity the linear product (entries 1a and 1c, branched/linear : 6.7/1 and 1/10 respectively). In sharp contrast, when the *tert*-butyl group is substituted by a cyclopropyl group (entry 2), the trend seems to be inverted, and a good regioselectivity toward the branched isomer was observed (entries 2a/2c versus entries 2b/2d). When compared to the Ni-catalyzed hydrophosphinylation (Scheme 6.4),[58] improvement in terms of regioselectivity and yield was observed with Pd for a terminal alkyne bearing a trimethylsilyl group (entry 3). However, the NMR yield of the branched isomer was low (only 41%, entry 3d).

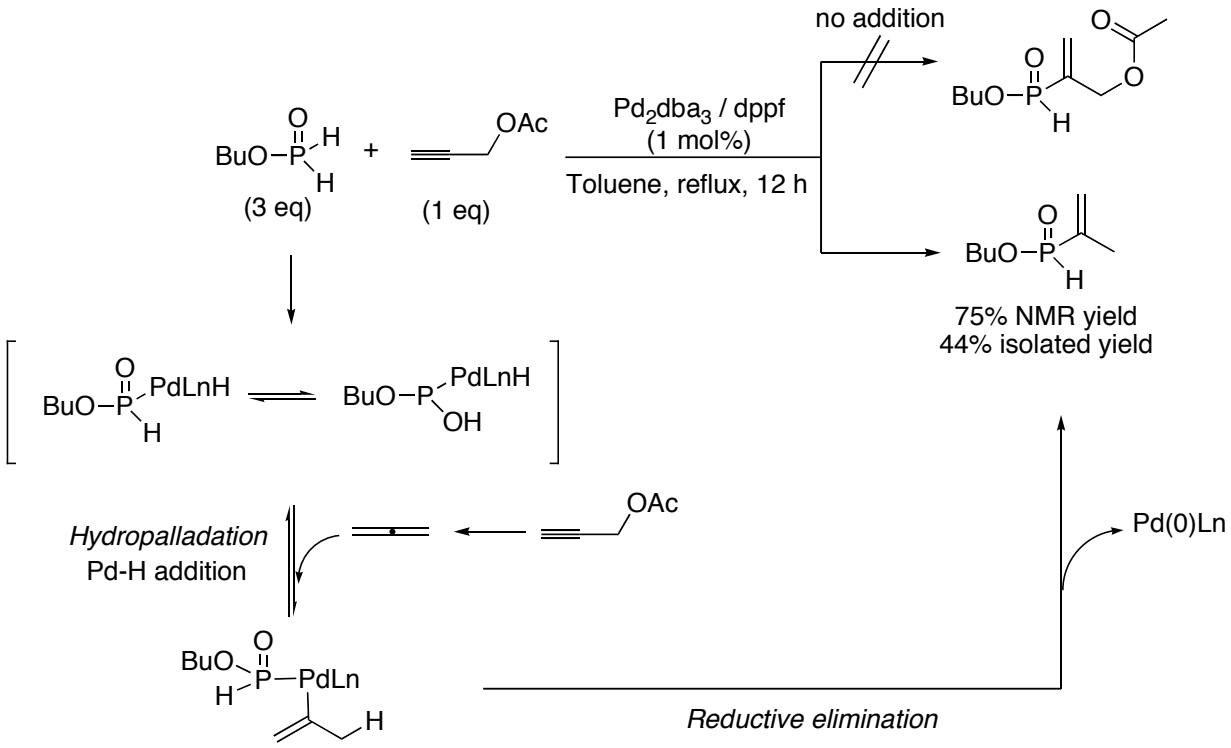
Scheme 6.4 Ni-Catalyzed hydrophosphinylation of alkynes from Ref. 54



A nitrogen-containing compound (Table 6.2, entry 6) can also be employed as substrate. Finally, direct comparison between entry 7 and the previous reports[56,58] indicates that the methodology is competitive to the Ni-catalyzed addition.

Propargyl acetate did not afford the expected compound (Scheme 6.5). Instead, a Pd-catalyzed reduction of propargylic acetate occurred, presumably forming an allene intermediate which became the partner for the hydrophosphinylation reaction, and afforded the methyl-vinyl derivative in 44% isolated yield.

Scheme 6.5 Palladium-catalyzed hydrophosphinylation of propargyl acetate



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 room temperature for 20-30 min before reaction. Triethylammonium hypophosphite was prepared according to the method described by Stawinski *et al*,[21] ammonium hypophosphite was prepared as described by Frost *et al*.[24e] Anilinum hypophosphite[20,28] was prepared as previously described. Alkyl phosphinates[20,56] was 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).[58] 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, and diisopropylamine were distilled under N_2 from CaH_2 and stored under N_2 over activated 4Å or 3Å molecular sieves. Anhydrous alcohols were dried over activated 3Å molecular sieves, and stored under N_2. 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. 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 purchased from Aldrich, Strem Chemicals. Triphenylmethanol was purchased from TCI, N,O-bis(trimethylsilyl)acetamide was purchased from Gelest, Inc., borane-*N,N*-diisopropyl-ethylamine complex was purchased from

Aldrich, borane-methyl sulfide complex was purchased from Alrdich.

Purification. Radial chromatography was carried out with a Harrison Associates Chromatotron, using 1, 2, or 4 mm layers of silica gel 60 PF254 containing gypsum. 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, or in potassium permanganate stain (3g $KMnO_4$, 20g K_2CO_3, 5 mL 5% aq. NaOH, 300 mL deionized H_2O) followed by heating.

NMR Data. ^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 standard tetramethylsilane (Me_4Si, $\delta = 0.00$ 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). 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,[19] 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. Isolated yields are sometimes significantly lower because *H*-phosphinate

esters are highly polar compounds and hydrolytically labile.

High Resolution Mass Spectrometry. Mass spectrometry was provided by the Mass Spectrometry Facility of the University of South Carolina.

General X-Ray Structure Information. Crystal data were collected with a Bruker SMART 1000 diffractometer using graphite monochromated molybdenum radiation (λ = 0.7107 Å). Crystals were attached to glass fibers using paratone oil and data were collected at -60^{o}C. The data were processed using SAINT and corrected for absorption.[165,166] Structures were solved by direct methods using the SHELXS-97 program and refined via full-matrix least squares.[165,166]

Chapter Two – Section 2.2[109]

Trityl *H*-Phosphinic Acid 31 (Eq. 2.1). A mixture of triphenylmethanol (100 g, 384 mmol), aqueous H_3PO_2 (845 mmol) and toluene (770 mL) was prepared at room temperature. The resulting mixture was heated at reflux under N_2 for 12 h, with continuous water-removal using a Dean-Stark trap. The reaction was monitored by ^{31}P NMR. The reaction mixture was concentrated in vacuo, the residue was partitioned between CH_2Cl_2 and H_2O, the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was washed several times with EtOAc, afforded the *H*-phosphinic acid (44 g, 37%) as a white powder by simple vacuum filtration. Mp 207-210 °C. IR (KBr) 3420.4 (OH), 3086.5-3021.8 (CH), 1180.0 (P=O), 980.4 (P-OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.48 ($^{1}J_{PH}$ = 572 Hz, 1H), 7.3-7.1 (m, 15H, Ar*H*); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 57.1,

126.5, 127.6, 128.5, 128.6, 129.7, 130.6 (d, $^{2}J_{PCC}$ = 28 Hz), 140.1(d, $^{3}J_{PCCC}$ = 13 Hz); ^{31}P NMR d 40.9 (d, $^{1}J_{PH}$ = 572 Hz); HRMS (FAB) calcd. for $C_{19}H_{17}O_2P$, (M) 308.0966, found 308.0959.

Tritylphosphonic Acid 32 (Eq. 2.2). Ozone was bubbled into a solution of trityl-*H*-phosphinic acid (500 mg, 1.62 mmol) in MeOH (25 mL), at 0 ºC. After 3 h, the ice bath was removed and N_2 was bubbled into the reaction mixture for 2 h. The white precipitate (triphenylmethane) was removed *via* centrifugation. The filtrate was concentrated in vacuo, and the residue partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc (3x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford **32** (431 mg, 82 %) as a white solid. Mp 248-250 °C. IR (KBr) 2800.0 (OH), 1142.6 (P=O), 965.7 (P-OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26-7.18 (m, 15H, Ar*H*), 4.12 (bs, 2H, O*H*); ^{13}C NMR δ 61.2 (d, $^{1}J_{PC}$ = 141 Hz), 127.3, 128.2, 130.5 (d, $^{3}J_{PCCC}$ = 7 Hz), 141.2 (d, $^{2}J_{PCC}$ = 5 Hz); ^{31}P NMR δ 32.7 (s); HRMS (ESI) calcd. for $C_{19}H_{17}O_3P$, (M-H) 323.0837, found 323.0843. Crystals of **32** were obtained from MeOH.

Trityl phosphonothioic acid 33 (Scheme 2.4). A solution of **31** (462 mg, 1.5 mmol) in anhydrous THF (15 mL) under N_2, was treated with BSA (1.85 mL, 7.5 mmol) at rt for 1 h. Sulfur (96 mg, 3 mmol) was then added at rt and the mixture stirred for 1 h. After addition of MeOH (15 mL), the mixture was stirred for 2 h, then concentrated in vacuo. The residue was diluted in MeOH, giving a heterogeneous mixture. A precipitate was separated from the yellowish filtrate *via* centrifugation (10 min, 1000*g*). The filtrate was concentrated in vacuo, affording **33** (510 mg, 100%) as a pale yellowish solid. Mp 84-89 °C. IR (KBr) 3327.5 (OH), 3174.6 (OH), 949.8 (P-OH), 700.1 (P=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.33-7.10 (m, 15H,

Ar*H*), 6.69 (bs, 2H, O*H*); ^{13}C NMR δ 126.9, 127.9, 129.0, 129.7, 131.1 (d, $^{3}J_{PCCC}$ = 6 Hz), 144.5 (d, $^{2}J_{PCC}$ = 5 Hz); ^{31}P NMR δ 92.5 (s); HRMS (ESI) calcd. for $C_{19}H_{17}O_2PS$, (M-H) 339.0609, found 339.0616. Crystals of **33** were obtained from toluene/CH_2Cl_2/MeOH (6:3:1).

Trityl boranophosphonic acid 34 (Scheme 2.5). A solution of **31** (308 mg, 1 mmol) in anhydrous THF (15 mL) was treated with BSA (1.23 mL, 5 mmol) at rt for 1 h, under N_2. A solution of BH_3•Me_2S (1 mL, 2.0 M solution in THF) was then added at rt, and the resulting mixture stirred for 1 h. After addition of MeOH (15 mL), the mixture was stirred for 2 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O and the organic phase was washed with H_2O (3x 15 mL). The combined aqueous layers were concentrated in vacuo, affording **34** (319 mg, 99%) as a white powder. Mp 119-122 °C. IR (KBr) 3421.1 (OH), 3173.9 (OH), 2356.3 (BH), 1040.4 (PO_2H), 702.0 (P-B) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.36-7.11 (m, 15H, Ar*H*), 6.7 (bs, 2H, O*H*), 2.59 (bq, *J* = 7 Hz, 2H, CH_2), 1.10 (bt, *J* = 7 Hz, 3H, CH_3) ; ^{13}C NMR δ 125.9, 127.5, 131.5 (d, $^{3}J_{PCCC}$ = 4 Hz), 146.2; ^{31}P NMR δ 108.1 (bs). HRMS (ESI) calcd. for $C_{27}H_{39}BNO_2P$, (M-) 321.1216, found 321.1216. Crystals of **34** were obtained from CH_2Cl_2/EtOH.

Trityl boranophosphonic acid diisopropylethylamine salt 35 (Scheme 2.5). **31** (481 mg, 1.56 mmol) in anhydrous THF (20 mL) was treated with BSA (1.92 mL, 5 mmol) for 1 h at rt under N_2. A solution of *i*-Pr_2NEt•BH_3 (543 µL, 3.12 mmol) was then added at rt. After 1 h, conc. NH_4OH in MeOH (20 mL, 1:1, v/v) was added, stirring continued for 1 h, then the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O, and the organic phase was washed with H_2O (3x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo, affording **35** (660 mg, 94%) as a white

powder. Mp 104-107 °C. IR (KBr) 3440.2 (OH), 3379.3 (NH), 2371.5 (BH), 2329.7 (PO_2), 1105.1 (C-N),1032.8 (P-OH), cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46-7.11 (m, 15H, Ar*H*), 3.53 (sept, J = 7 Hz, 2H, C*H*(CH_3)$_2$), 2.83 (q, J = 7 Hz, 2H, CH_2), 2.35 (s, OH), 1.26-1.21 (m, 15H, CH_3); ^{13}C NMR δ 12.2, 41.7, 53.0, 66.1 (d, $^1J_{PC}$ = 29 Hz), 126.0, 127.5, 131.5 (d, $^3J_{PCCC}$ = 5 Hz), 144.8; ^{31}P NMR δ 109 (q, J_{PB} = 133 Hz); HRMS (ESI) calcd. for $C_{27}H_{39}BNO_2P$, (M-) 321.1216, found 321.1224. Crystals of **35** were obtained from toluene/CH_2Cl_2/MeOH (6:3:1).

Diseleno tritylphosphinic acid 36 (Scheme 2.6). Under N_2 atmosphere, elemental selenium (257 mg, 3.25 mmol) was added to a solution of trityl *H*-phosphinic acid (400 mg, 1.3 mmol) in freshly distilled toluene (10 mL), at rt. Et_3N (0.55 mL, 3.89 mmol) was then added dropwise to the solution *via* syringe and the reaction mixture was stirred at reflux for 7 h. After this time, the mixture was cooled down to rt and stirred for 10 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and 2 M aqueous HCl. The aqueous layer was extracted with $CHCl_3$ (3x) and the combined organic extracts were dried over $MgSO_4$ and concentrated to afford a yellowish-white powder. MeOH was added to the obtained powder, giving a heterogeneous mixture from which the insoluble solid was separated from the solution by vacuum filtration, affording **36** (281 mg, 28%) as a bright yellow powder. Mp: 180-190 ºC (decomposition); ^1H NMR (300 MHz, DMSO-d_6) δ 7.29-7.20 (m, 15H, Ar*H*), 3.80 (bs, 2H, O*H*); ^{13}C NMR (75.45 MHz, DMSO-d_6) δ 21.69, 125.9, 128.8, 129.6, 138.0; ^{31}P NMR (121.47 MHz, DMSO-d_6) δ 39.0 (s); 38.8 (s); IR (KBr, cm^{-1}) 3415.1 (OH), 1166.0 (P=O), 976.5 (P-OH); HRMS (ESI) calcd. for $C_{38}H_{32}O_4P_2Se_2$, (M-H) 769.0059, found 769.0068. Crystals obtained from: toluene

Dimethyl tritylphosphine-borane 37 (Scheme 2.8). PCl_3 (15.5 mL, 177.4 mmol) was slowly added to trityl *H*-phosphinic acid (5.5 g, 17.7 mmol) under N_2 atmosphere, at rt. The reaction

mixture was stirred at rt for 1 h, then at reflux for 2 h. After cooling down to rt, excess PCl_3 and $POCl_3$ was evaporated in vacuo, affording the tritylphosphonous dichloride as a fluffy solid. The tritylphosphonous dichloride (1.7 g, 5 mmol) was dissolved in distilled THF (16 mL) and the solution placed at -78 ºC. CH_3MgCl (3.0 M solution in THF, 6.7 mL, 20 mmol) was added dropwise *via* syringe and the reaction mixture stirred at rt for 12 h. Then, BH_3•Me_2S (2.0 M in solution in THF, 10 mL, 20 mmol) was added at rt and the mixture stirred for 4 h. The reaction was quenched by addition of deionized water at 0 ºC. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine (1x), dried over $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (100% toluene), affording **37** (848 mg, 15%) as a white powder. Crystals suitable for X-ray diffraction were obtained by room temperature evaporation of the powder dissolved in toluene/CH_2Cl_2 (5:1). Mp: 147-149 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.2 (m, 15H, Ar*H*), 1.30 (s, 3H, C*H*3), 1.27 (s, 3H, C*H*3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 14.20 (d, $^1J_{PC}$ = 36 Hz), 59.34 (d, $^1J_{PC}$ = 25 Hz), 127.5 (d, $^4J_{PCCCC}$ = 2 Hz), 128.3, 130.6 (d, $^3J_{PCCC}$ = 5 Hz), 142.3; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ 27.7 (dm, J_{PB} = 33 Hz); ^{11}B (NMR) -32.2 (bs); IR (KBr, cm^{-1}) 2327 (B-H), 701 (P-B).

Phenyl tritylphosphinic acid 39 (Scheme 2.9). To a solution of phenyl *H*-phosphinic acid (20.14 g, 0.142 mol) in distilled toluene (100 mL) was added BSA (70 mL, 0.284 mmol) dropwise at rt, under N_2 atmosphere. The reaction mixture was stirred at reflux for 1 h 45. Then, a solution of trityl chloride (39.58 g, 0.142 mol) in toluene (100 mL) was added to the reaction mixture and the resulting mixture stirred for an additional 13 h at rt. The reaction was quenched with MeOH, the solvent removed in vacuo, and the residue was washed several times with EtOAc and the precipitate vacuum-filtered, giving **39** (53.5 g, 98%) as a white powder. Single

crystals obtained from slow evaporation of a toluene/ CH_2Cl_2/ MeOH (5:1:1). Mp: 282-284 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H, Ar*H*), 7.28-7.26 (m, 8H, Ar*H*), 7.18-7.11 (m, 3H, Ar*H*), 7.09-7.04 (m, 5H, Ar*H*); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 63.92 (d, $^1J_{PC}$ = 94 Hz), 127.0, 127.6 (d, $^1J_{PC}$ = 13 Hz), 127.9, 131.4 (d, $^3J_{PCCC}$ = 6 Hz), 131.8, 133.5, 133.8 (d, $^2J_{PCC}$ = 9 Hz), 141.3; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ 45.5 (s); IR (KBr, cm^{-1}) 1164 (P=O), 956 (P-OH); HRMS (ESI) calcd. for $C_{25}H_{21}O_2P$, (M-H) 383.1201, found 383.1212.

Phenyl tritylphosphinic acid benzyl ester 40 (Scheme 2.10). To a solution of trityl *H*-phenylphosphinic acid (577 mg, 1.5 mmol) in $CHCl_3$ (8 mL), at rt and under N_2 atmosphere, was added benzyl bromide (0.36 mL, 3 mmol). Silver oxide (695 mg, 3 mmol) was added to the reaction mixture in 5 portions (every 30 min) and stirred at reflux for 2 h 30. After cooling down to rt, the crude mixture was filtered through celite and the filtrate was then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/ Hexanes, 2:8 then 1:0), affording **40** (569 mg, 80%) as a white powder. Single crystals for X-ray analysis were obtained from crystals grown from toluene/ CH_2Cl_2/ MeOH (5:2:1). Mp: 144-145 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.44 (m, 6H, Ar*H*), 7.41-7.31 (m, 2H, Ar*H*), 7.29-7.14 (m, 15H, Ar*H*), 7.10-7.04 (m, 2H, Ar*H*), 5.10 (dd, J_{HP}=6 Hz, *J*=12 Hz, 1H), 4.82 (dd, J_{HP}=6 Hz, J=12 Hz, 1H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 64.6 (d, $^1J_{PC}$= 102 Hz), 66.8 (d, $^2J_{POC}$= 7 Hz), 127.3, 127.9, 128.1 (d, $^1J_{PC}$= 85 Hz), 128.13, 128.2, 129.9, 131.5, (d, $^3J_{PCCC}$= 6 Hz), 132.2 (d, $^4J_{PCCCC}$= 3 Hz), 134.3 (d, $^2J_{PCC}$= 9 Hz), 136.8 (d, $^3J_{POCC}$= 7 Hz), 141.8 (d, $^4J_{PCCCC}$= 3 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ 43.9 (s); IR (KBr, cm^{-1}) 1214 (P=O), 1006 (P-OH); HRMS (EI$^+$) calcd. for $C_{32}H_{27}O_2P$, (M) 474.1749, found 474.1739.

Phenyl tritylphosphinic acid octyl ester 41 (Scheme 2.10). To a solution of trityl *H*-phenylphosphinic acid (577 mg, 1.5 mmol) in $CHCl_3$ (8 mL), at rt and under N_2 atmosphere, was added octylbromide (0.52 mL, 3 mmol). Silver oxide (695 mg, 3 mmol) was added to the reaction mixture in 5 portions (every 30 min) and stirred at reflux for 2 h 30. After cooling down to rt, the crude mixture was filtered through celite and the filtrate was then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/ Hexanes, 2:8 then 1:0), affording the desired product (603 mg, 81%) as a white powder. Mp: 96-97 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.46 (m, 6H, Ar*H*), 7.39-7.31 (m, 2H, Ar*H*), 7.26-7.14 (m, 17H, Ar*H*), 4.03 (dq, J_{HCOP} = 29 Hz; J = 6 Hz, 1H, OCH_2), 3.75 (dq, J_{HCOP} = 29 Hz; J = 6 Hz, 1H, OCH_2), 1.51 (m, 2H, OCH_2CH_2), 1.28-1.18 (m, 8H, CH_2), 0.88 (t, J= 6.7 Hz, 3H, CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 14.12, 22.64, 25.52, 29.04 (d, $^3J_{POCC}$= 14 Hz), 30.30 (d, $^4J_{POCCC}$= 6 Hz), 31.72, 64.11 (d, $^1J_{PC}$= 93 Hz), 65.23 (d, $^2J_{POC}$= 7 Hz), 126.7 (d, $^5J_{PCCCCC}$= 2 Hz), 127.5, 127.6, 129.9, 131.3 (d, $^3J_{PCCC}$= 6 Hz), 131.5, 131.6 (d, $^4J_{PCCCC}$= 3 Hz), 133.9 (d, $^2J_{PCC}$= 9 Hz), 141.8 (d, $^4J_{PCCCC}$= 3 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ 41.9 (s); IR (KBr, cm^{-1}) 1218.1 (P=O), 965.2 (P-OH); HRMS (EI^+) calcd. for $C_{33}H_{37}O_2P$, (M) 496.2531, found 496.2521.

Diphenyl tritylphosphine 42 (Scheme 2.11). To a yellow suspension of triphenylcarbenium tetrafluoroborate (2.5 g, 7.6 mmol) in CH_2Cl_2 (25 mL) in a Schlenk flask was added diphenylphosphine (1.3 mL, 7.6 mmol) neat via syringe. The reaction immediately turned clear and colorless and was allowed to stir overnight, after which a white precipitate had developed. Approximately 25 mL of deionized water (had been previously degassed by purging with nitrogen gas for approximately 1 hour) was then added rapidly via cannula, followed by the addition of excess of Et_3N (3.2 mL, 22.8 mmol). The clear and colorless biphasic reaction mixture was allowed to stir overnight, at which time the aqueous layer containing $[Et_3NH][BF_4]$

was removed by syringe. The methylene chloride was removed in vacuo to yield diphenyl tritylphosphine **42** (3.2 g, 99%) as a white powder. Crystals were grown at rt from CH_2Cl_2. Mp: 140-144 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.19-7.06 (m, 17H, Ar*H*), 7.04-6.99 (t, 4H, Ar*H*, ^1J =7.5 Hz), 6.77-6.72 (t, 4H, Ar*H*, ^1J=7.6 Hz); ^{13}C NMR (300 MHz, C_6D_6) δ 94.3, 126.4, 127.8, 127.9, 128.0, 129.0, 129.7, 131.1, 131.2, 134.3, 135.3, 135.5, 135.6; ^{31}P NMR (300 MHz, C_6D_6) δ 27.9; IR (nujol mull, cm^{-1}) 1594 , 1155 , 973 , 742, 699; HRMS (EI^+) calcd. for $C_{31}H_{25}P$, (M+H) 429.1772, found 429.1763.

Diphenyl tritylphosphine-borane 43 (Eq. 2.3). A toluene solution of diphenyl tritylphosphine (0.4 g, 0.93 mmol) was cooled to –78 °C and BH_3•THF (1.0 M in THF, 0.93 mL, 0.93 mmol) was added dropwise to give a clear colorless solution. The cooling bath was removed immediately and the reaction mixture was allowed to stir at room temperature, overnight. Concentration and storage at room temperature of the toluene solution afforded diphenyl tritylphosphine-borane **43** (58 mg, 14%) as colorless needles. Mp: 146-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 2H, Ar*H*, ^1J =7.3 Hz), 7.24-7.19 (m, 5H, Ar*H*), 7.15-7.14 (m, 12H, Ar*H*), 7.10 (d, 1H, Ar*H*, ^1J =2.6), 7.07-7.06 (m, 1H, Ar*H*), 6.99 (t, 4H, Ar*H*, ^1J =8.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 69.6, 125.3, 126.4, 126.5, 126.8, 127.0, 127.3, 127.5, 127.9, 128.4, 128.5, 129.9. 130.95, 131.0, 133.8, 133.9, 140.7, 142.9; ^{11}B NMR (28.88 MHz, $CDCl_3$) δ -32.4; ^{31}P NMR (300 MHz, $CDCl_3$) δ 39.6, IR (nujol mull, cm^{-1}) 3162, 2360, 1154.

Trityl phosphonic acid diethyl ester 38 (Eq. 2.4). This compound was prepared according to the literature[147] via the Arbuzov reaction of $(EtO)_3P$ with TrCl in refluxing benzene (75%). Crystals suitable for X-ray diffraction were obtained from CH_2Cl_2/toluene.

Chapter Two – Section 2.3[109]

Crystallographic Parameters. Thermal ellipsoids at 50% probability. Crystal Data for complexes **32-35**:[271] (**32**) $C_{21}H_{25}O_5P$ (M = 388.38), T = 213(2) K, Triclinic, P-1, a = 9.0901(6) Å, b = 9.7482(6) Å, c = 12.3042(7)Å, α = 94.8300(10) °, β = 108.3390(10) °, γ = 105.2350(10)°, Z = 2, Reflections Collected = 6210, Independent reflections = 4416, R (int) = 0.0143, Final R indices [I>2σ(I)] R1 = 0.0376, wR2 = 0.0996 (**33**) $C_{25}H_{29}O_4PS$ (M = 456.51), T = 213(2) K, Monoclinic, P 21/n, a = 9.5308(11) b = 18.182(2) c = 14.0754(16) β = 93.703(2)° V = 2434.1(5) $Å^3$ Z = 4, Reflections Collected = 15181, Independent reflections = 5716 [R(int) = 0.0327], Final R indices [I>2σ(I)] R1 = 0.0582, wR2 = 0.1545 (**34**) $C_{24}H_{31}BO_4P$, (M = 425.27), T = 213(2) K, triclinic, P-1, a = 9.5549(9) Å, b = 10.7293(10) Å, c = 12.7101(11) Å, α = 73.331(2)°, β = 83.598(2)° γ = 74.864(2)° V = 1204.00(19) $Å^3$ Z = 2, Reflections Collected = 10251, Independent reflections = 4322 [R(int) = 0.0229], Final R indices [I>2σ(I)] R1 = 0.0527, wR2 = 0.1462 (**35**) $C_{27}H_{39}BNO_2P$ (M = 451.37), T = 213(2) K, Monoclinic, P 21/n, a = 15.737(2) Å, b = 11.0004(16) Å, c = 15.760(2) Å, β = 111.509(2)°, Z = 4, Reflections Collected = 14562, Independent reflections = 4560 [R(int) = 0.0249], Final R indices [I>2σ(I)] R1 = 0.0382, wR2 = 0.0970.

Crystal data and data collection summary for complexes **36 - 43**

Compound	$TrPPh_2$ **42**	$TrP(BH_3)Ph_2$ **43**	$TrP(BH_3)Me_2$ **37**
Chemical Formula	$C_{31}H_{25}P$	$C_{31}H_{28}PB$	$C_{21}H_{24}PB$
Formula Weight	428.48	442.31	318.18
Crystal System	Triclinic	Monoclinic	Monoclinic
Space Group	$P\bar{1}$	P21/c	C2/c
T(K)	213(2)	213(2)	91(2)
a (Å)	7.5624(6)	10.0972(12)	15.628(3)
b (Å)	9.5470(8)	9.6955(12)	12.770(3)
c (Å)	16.9722(14)	25.197(3)	18.406(4)
α (°)	83.4720(10)	90	90
β (°)	80.541(2)	90.258(2)	103.968(3)
γ (°)	68.1580(10)	90	90
V (Å ^{3})	1120.08(16)	2466.7(5)	3564.7(13)
Z	2	4	8
Reflections collected	5755	12097	14813
Independent reflections	3965	4471	3217
Data/restraints/parameter ratio	3965 / 0/ 289	4471 / 0 / 310	3217 / 0 / 208
Unique Data (*R int*)	0.0171	0.0337	0.0617
D calc (Mg/m^3)	1.270	1.191	1.186
F(000)	452	936	1360
R indices (all data)	R1 0.0541 , wR2 = 0.1075	R1 = 0.0632 wR2 = 0.1014	R1 = 0.0630 wR2 = 0.1448
Final R indices [I > 2σ(I)]	R1 = 0.0389 wR2 = 0.0940	R1 = 0.0380 wR2 = 0.0846	R1 = 0.0462 wR2 = 0.1326
Largest difference peak and hole (e Å^{-3})	0.469 and –0.352	0.336 and –0.354	0.549 and –0.337

Compound	$TrP(O)(OH)Ph$ **39**	$TrCP(O)(Ph)OBn$ **40**	$TrP(O)(OEt)_2$ **38**
Chemical Formula	$C_{25}H_{21}PO_2$	$C_{32}H_{27}O_2P$	$C_{23}H_{25}O_3P$
Formula Weight	384.39	474.51	380.40
Crystal System	Triclinic	Monoclinic	Triclinic
Space Group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
T(K)	91 (2)	213(2)	213(2)
a (Å)	8.9847(18)	7.9196(5)	7.9521(17)
b (Å)	9.7443(19)	31.701(2)	9.2205(19)
c (Å)	12.786(3)	19.8062(13)	14.471(3)
α (°)	72.045(3)	90	85.906(4)
β (°)	72.031(3)	99.7750(10)	83.031(4)
γ (°)	78.769(3)	90	68.283(4)
V (Å ^{3})	1006.8(3)	4900.3(6)	978.0(4)
Z	2	8	2
Reflections collected	8641	47552	5687
Independent reflections	3627	9881	4305
Data/restraints/parameters	3627 / 0 /253	9881 / 0 / 631	4305 / 0/ 246
Unique Data (*R int*)	0.1037	0.0418	0.0174
D calc (Mg/m^3)	1.268	1.286	1.292
F(000)	404	2000	404
R indices (all data)	R1 = 0.0662 wR2 = 0.1370	R1 = 0.0651, wR2 = 0.1125	R1 = 0.0632, wR2 = 0.1203
Final R indices [I > 2σ(I)]	R1 = 0.0540 wR2 = 0.1250	R1 = 0.0413, wR2 = 0.0942	R1 = 0.0457 wR2 = 0.1086
Largest difference peak and hole (e Å^{-3})	0.446 and –0.444	0.349 and –0.374	0.446 and –0.343

Compound	$[TrP(O)(OH)Se]_2$ **36**
Chemical Formula	$C_{38}H_32O_4P_2Se$
Formula Weight	772.50
Crystal System	Monoclinic
Space Group	$P2_1/c$
T(K)	213(2)
a (Å)	9.0603(4)
b (Å)	22.3652(11)
c (Å)	16.9134(7)
α (°)	90
β (°)	107.035(2)
γ (°)	90
V (Å ^{3})	3276.9(3)
Z	4
Reflections collected	18998
Independent reflections	7769
Data/restraints/parameters	7769 / 2 / 423
Unique Data (*R int*)	0.0422
D calc (Mg/m^3)	1.566
F(000)	1560
R indices (all data)	R1 = 0.0864 wR2 = 0.1416
Final R indices [I > 2σ(I)]	R1 = 0.0474, wR2 = 0.1180
Largest difference peak and hole (e $Å^{-3}$)	1.757 and –0.631

Chapter Three – Section 3.2[107]

Bis(triisopropylsilyloxy)phosphine-borane 55 (Eq. 3.2). Triisopropylchlorosilane (4.27 mL, 20 mmol) was added into a flame-dried two-neck round bottom flask and cooled to 0 °C, under N_2. Then, Et_3N (2.93 mL, 21 mmol) was added dropwise and the reaction mixture was stirred for approximately 10 min at 0 °C. In a separate flame-dried three-neck round bottom flask, a solution of anilinium hypophosphite (1.54 g, 10 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, under N_2. The TIPSCl/Et_3N mixture was slowly added to the hypophosphite solution via syringe, and the temperature maintained at 0 °C for 10-15 min, at which time the reaction was allowed to warm up to room temperature and stirred for 12 h under N_2. BH_3•Me_2S (1.0 M in CH_2Cl_2, 20 mL, 20 mmol) was added dropwise at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic phases washed with brine (1 x 20 mL), dried over $MgSO_4$, and concentrated in vacuo.

The residue was purified by column chromatography over silica gel (hexanes), to afford complex **55** as a pale yellowish syrup (3.46 g, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (d, J = 417.2 Hz, 1H), 1.28-1.12 (m, 6H), 1.10 (d, J = 6.4 Hz, 36H), 0.96-0.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 17.7, 12.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 100.9 (dq, J_{PB} = 90 Hz, J_{PH} = 422 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -36.8 (dq, J_{BP} = 88 Hz, J_{BH} = 92 Hz); HRMS (EI^+) calcd for $C_{18}H_{46}BO_2PSi_2$, $(M + NH_4)^+$ 410.3211, found 410.3196.

Representative Procedure for the Preparation of the Ethoxy(trialkylsilyloxy)phosphine-borane (Table 3.1). Ethoxy(triisopropylsilyloxy)phosphine-borane 56 (Table 3.1, entry 1). Triisopropylchlorosilane (12.11 mL, 56.7 mmol) was added into a flame-dried two-neck round bottom flask and cooled to 0 ^{o}C, under N_2. Then, Et_3N (8.43 mL, 60.5 mmol) was added dropwise and the reaction mixture was stirred for approximately 10 min at 0 ^{o}C. In a separate flame-dried three-neck round bottom flask, a solution of ethyl hypophosphite (0.5 M in CH_3CN, 75.7 mL, 37.8 mmol) was cooled to 0 ^{o}C, under N_2. The mixture TIPSCl/Et_3N was slowly added to the hypophosphite solution via syringe and the reaction mixture maintained at 0 ^{o}C for 10-15 min, at which time the reaction was allowed to warm up to room temperature, then stirred for 12 h under N_2. BH_3•Me_2S (2.0 M in THF, 37.8 mL, 75.6 mmol) was added dropwise at room temperature. After 1 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between DI H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x 250 mL) and the combined organic phases washed with brine (1x 50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (petroleum ether) afforded **56** as a colorless oil (9.98 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, J = 429.9 Hz, 1H), 4.26-3.98 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.22-1.12 (m, 3H), 1.08 (d, J = 6.9 Hz, 18H), 0.90-0.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 65.1 (d, J_{POC} = 8 Hz), 17.6, 16.5 (d, J_{POCC} = 6 Hz), 12.5; ^{31}P NMR ($CDCl_3$, 121.47

MHz) δ 116.7 (dq, J_{PB} = 78 Hz, J_{PH} = 425 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -39.2 (dq, J_{BP} = 79 Hz, J_{BH} = 92 Hz); HRMS (FAB) calcd for $C_{11}H_{30}BO_2PSi$, $(M + NH_4)^+$ 282.2190, found 282.2196.

Ethoxy(*tert*-butyldimethylsilyloxy)phosphine-borane 58 (Table 3.1, entry 4). Yield: 79%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (d, J = 432.1 Hz, 1H), 3.96-3.70 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H), 0.68 (s, 9H), 0.01 (s, 6H), 0.59-0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 69.0 (d, J_{POC} = 9 Hz), 29.0, 21.8 (d, J_{POSiC} = 2 Hz), 20.1 (d, J_{POCC} = 6 Hz), 0.03 (d, J_{POSiC} = 4 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 115.7 (dq, J_{PB} = 81 Hz, J_{PH} = 430 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -39.3 (dq, J_{BP} = 76 Hz, J_{BH} = 91 Hz); HRMS (EI^+) calcd for $C_8H_{24}BO_2PSi$, $(M + NH_4)^+$ 240.1720, found 240.1722.

Ethoxy(*tert*-butyldiphenylsilyloxy)phosphine-borane 59 (Table 3.1, entry 5). Yield: 91%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J = 433.2 Hz, 1H), 7.70-7.63 (m, 4H), 7.52-7.25 (m, 6H), 4.11-3.79 (m, 2H), 1.19 (t, J = 6.9 Hz, 3H), 1.13 (s, 9H), 0.90-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.5 (d, J_{POSiC} = 3 Hz), 131.6 (d, $J_{POSiCCCC}$ = 3 Hz), 130.9 (d, J_{POSiCC} = 1 Hz), 128.3 (d, $J_{POSiCCC}$ = 3 Hz), 65.3 (d, J_{POC} = 7 Hz), 26.7, 19.8, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 114.7 (dq, J_{PB} = 89 Hz, J_{PH} = 428 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -40.2 (dq, J_{BP} = 89 Hz, J_{BH} = 89 Hz); HRMS (EI^+) calcd for $C_{18}H_{28}BO_2PSi$, $(M + NH_4 - H_2)$ 362.1877, found 362.1869.

Diethoxyphosphine-borane 57 (Eq. 3.3). 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 ^{o}C. $LiBH_4$ (1.67 g, 76.7 mmol) was then added (quickly in air) at – 78 ^{o}C and the

reaction mixture was stirred at this temperature for 10 min, then allowed to warm up to room temperature 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 **57** (8.65 g, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, J_{PH} = 444.1 Hz, 1H), 4.25-4.01 (m, 4H), 1.37 (dt, J = 7.0 Hz, 6H), 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.

Bistriisopropylthiophosphonite 60 (Eq. 3.4). Triisopropylchlorosilane (2.14 mL, 10 mmol) was placed into a flame-dried two-neck round bottom flask and cooled to 0 ^oC, under N_2. Et_3N (1.47 mL, 10.5 mmol) was then added dropwise, and the reaction mixture was stirred for approximately 10 min at 0 ^oC. In a separate flame-dried three-neck round bottom flask, a solution of anilinium hypophosphite (771 mg, 5 mmol) in CH_3CN (20 mL) was cooled to 0 ^oC, under N_2. The mixture TIPSCl/Et_3N was slowly added to the anilinium hypophosphite solution via syringe, and the reaction mixture maintained at 0 ^oC for 10-15 min, at which time the reaction was allowed to warm up to room temperature and stirred for 12 h under N_2. The reaction mixture was treated with S_8 (321 mg, 10 mmol) by direct addition into the flask at room temperature. After 4 h, the reaction mixture was concentrated under reduced pressure, and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers washed with brine (1x), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography

over silica gel (100% hexanes) afforded the desired product **60** as a pale green oil (1.17 g, 57 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 637.5 Hz, 1H), 1.30-1.18 (m, 6H), 1.10 (d, J = 6.9 Hz, 36H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 17.8, 12.6; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 39.5 (d, J = 636 Hz)); HRMS (EI^+) calcd for $C_{18}H_{43}O_2PSSi$, $(M + H)^+$ 411.2338, found 411.2345.

Typical Alkylation Procedure (Tables 3.2 & 3.3).

Neat phosphine-borane (EtO)(TIPSO)P(BH_3)H **56** or $(EtO)_2P(BH_3)H$ **57** (1 equiv, 1.89 mmol and 3.68 mmol, respectively) was placed under vacuum in a flame-dried two-neck flask, for 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 ^{o}C 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 ^{o}C. After 15 min, the electrophile (1 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 slowly allowed to reach room temperature then stirring was continued (see Tables 3.2 and 3.3 for reaction times). The reaction mixture was quenched with a saturated solution of NH_4Cl/brine, and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude mixture was purified by column chromatography over silica gel.

Ethoxy(triisopropylsilyloxy)methylphosphine-borane (Table 3.2, entry 1). Yield: 100%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17-3.97 (m, 2H), 1.51 (d, J = 8.2 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.18-1.11 (m, 3H), 1.10 (d, J = 5.6 Hz,18H), 0.95-0.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.7 (d, J_{POC} = 3 Hz), 18.8 (d, J_{PC} = 53 Hz), 17.6, 16.6 (d, J_{POCC} = 6 Hz), 12.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 132.4 (q, J_{PB} = 93 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -39.2 (dq, J_{BP}

= 95 Hz, J_{BH} = 98 Hz); HRMS (EI^+) calcd for $C_{12}H_{32}BO_2PSi$, $(M + NH_4)^+$ 296.2346, found 296.2336.

Ethoxy(triisopropylsilyloxy)octylphosphine-borane (Table 3.2, entries 2 & 3). Yields: 90-100%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.13-4.00 (m, 2H), 1.73-1.60 (m, 2H), 1.62-1.46 (m, 2H), 1.37-1.23 (m, 13H), 1.17-1.02 (m, 21H), 0.87 (t, J = 7.0 Hz, 3H), 0.75-0.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.1 (d, J_{POC} = 3 Hz), 33.1 (d, J_{PC} = 53 Hz), 32.0, 31.0 (d, J_{PCC} = 14 Hz), 29.3 (d, J_{PCCC} = 3 Hz), 22.8, 22.0, 17.7, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 12.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 135.6 (q, J_{PB} = 83 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -40.6 (dq, J_{BP} = 83 Hz, J_{BH} = 94 Hz); HRMS (EI^+) calcd for $C_{19}H_{46}BO_2PSi$, $(M + NH_4)^+$ 394.4761, found 394.3442.

Ethoxy(triisopropylsilyloxy)(1-methylpropyl)phosphine-borane (Table 3.2, entry 4). Yield: 85%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21-4.00 (m, 2H), 1.90-1.74 (m, 2H), 1.29 (t, J = 6.9 Hz, 3H), 1.20-1.13 (m, 3H), 1.12-1.03 (m, 26H), 1.02-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.6 (d, J_{POC} = 3 Hz), 33.4 (d, J_{PC} = 56 Hz), 17.7, 16.7 (d, J_{POCC} = 6 Hz), 15.7, 15.4, 12.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 139.9 (q, J_{PB} = 87 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -42.3 (dq, J_{BP} = 88 Hz, J_{BH} = 89 Hz); MS *m/e* 306 $(M\text{-}BH3)^+$, 277 $(M\text{-}Pr)^+$.

Ethoxy(triisopropylsilyloxy)geranylphosphine-borane (Table 3.2, entry 5). Yield: 80%. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.30-5.12 (m, 1H), 5.12-5.05 (m, 1H), 4.18-3.95 (m, 2H), 2.55 (dd, J = 11.2 Hz, J = 7.8 Hz, 2H), 2.14-2.02 (m, 4H), 1.78-1.61 (m, 9H), 1.28 (t, J = 6.9 Hz, 3H), 1.18-1.04 (m, 21H), 0.90-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 140.3 (d, J_{PCCC} = 12 Hz), 131.7, 124.2, 112.9 (d, J_{PCC} = 5 Hz), 63.4, 40.1, 33.6 (d, J_{PC} = 52 Hz), 26.6, 25.9, 17.8, 16.7 (d, J_{POCC} = 7 Hz), 12.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 135.6 (q, J_{PB} = 87 Hz); ^{11}B NMR ($CDCl_3$,

28.88 MHz) δ -40.0 (dq, J_{BP} = 82 Hz, J_{BH} = 89 Hz); HRMS (EI^+) calcd for $C_{21}H_{46}BO_2PSi$, $(M + NH_4)^+$ 418.3442, found 418.3432.

Ethoxy(triisopropylsilyloxy)benzyloxymethylphosphine-borane (Table 3.2, entry 6). Yield: 100%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.25 (m, 5H), 4.64 (s, 2H), 4.22-4.08 (m, 2H), 3.72 (s, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.23-1.10 (m, 3H), 1.10-1.02 (m, 18H), 0.95-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.4, 128.6, 128.2, 128.1, 75.4 (d, J_{PCOC} = 9 Hz), 69.8 (d, J_{PC} = 66 Hz), 63.8 (d, J_{POC} = 4 Hz), 17.7, 16.8 (d, J_{POCC} = 6 Hz), 12.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 124.8 (q, J_{PB} = 78 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -45.0 (dq, J_{BP} = 74 Hz, J_{BH} = 90 Hz); HRMS (EI^+) calcd for $C_{19}H_{38}BO_3PSi$, $(M + NH_4)^+$ 402.2765, found 402.2769.

Diethoxy methylphosphine-borane (Table 3.3, entry 1). Yield: 80%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.13-3.96 (m, 4H), 1.50 (d, J = 8.5 Hz, 3H), 1.32 (t, J = 7.0 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 octylphosphine-borane (Table 3.3, entry 2). Yield: 74-77%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.17-3.95 (m, 4H), 1.79-1.68 (m, 2H), 1.62-1.48 (m, 2H), 1.42-1.24 (m, 16H), 0.88 (t, J = 6.4 Hz, 3H), 0.80-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.1 (d, J_{POC} = 5 Hz), 32.0, 30.9 (d, J_{PCC} = 14 Hz), 29.9 (d, J_{PC} = 56 Hz), 29.2, 22.8, 21.7, 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 148.9 (q, J_{PB} = 86 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -42.2 (dq, J_{BP}

= 83 Hz, J_{BH} = 94 Hz); HRMS (EI^+) calcd for $C_{12}H_{30}BO_2P$, $(M + NH_4)^+$ 266.2420, found 266.2418.

Diethoxy-1-methylethylphosphine-borane (Table 3.3, entry 3). Yield: 48%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.15-3.99 (m, 4H), 1.96-1.86 (m, 1H), 1.39 (t, J = 7.0 Hz, 6H), 1.14 (dd, J = 16.7 Hz, J = 7.0 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 allylphosphine-borane (Table 3.3, entry 4). Yield: 69%. ^1H 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 = 11.7 Hz, J = 7.6 Hz, 2H), 1.31 (dt, J = 7.0 Hz, J = 2.4 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 3.3, entry 5). Yield: 25%. ^1H 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), 0.95-0.001 (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)phosphine-borane (Table 3.3, entry 6). Yield: 52%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.22-4.08 (m, 8H), 2.46 (dd, J = 20.8 Hz, J = 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_{PCP} = 137 Hz, J_{PC} = 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 ($CDCl_3$, 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 benzyloxymethylphosphine-borane (Table 3.3, entry 7). Yield: 89%. ^1H 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 = 7.0 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 ($CDCl_3$, 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-pyridylmethylphosphine-borane (Table 3.3, entry 8). Yield: 69%. ^1H 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 = 11.4 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 ($CDCl_3$, 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)phosphine-borane (Table 3.3, entry 9). Yield: 36-50%. ^1H 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.

Representative Procedure for Radical Reactions (Table 3.4).

To a solution of (EtO)(TIPSO)$P(BH_3)H$ **56** (0.793 g, 3 mmol, 1 equiv) or $(EtO)_2P(BH_3)H$ **57** (0.500 g, 3.68 mmol, 1 equiv) in a mixture of methanol (12.5 mL) and dioxane (2.5 mL) were added 1-octene (1 equiv) and triethylborane (1.0 M in hexane, 1 equiv). The solution was stirred at room-temperature in a flask open to air (6 h and 4 h, respectively). The reaction mixture was then concentrated in vacuo, and the crude directly purified by column chromatography over silica gel (hexanes/EtOAc, 100:0 to 90:10, v/v) produced the expected compounds as colorless oils.

Ethoxy(triisopropylsilyloxy)octylphosphine-borane (Table 3.4, entry 2). Yield: 67%. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.12-4.00 (m, 2H), 1.73-1.60 (m, 2H), 1.62-1.46 (m, 2H), 1.37-1.23 (m, 13H), 1.17-1.02 (m, 21H), 0.87 (t, J = 7.0 Hz, 3H), 0.75-0.05 (m, 3H); ^{13}C NMR ($CDCl_3$,

75.45 MHz) δ 63.1 (d, J_{POC} = 3 Hz), 33.1 (d, J_{PC} = 53 Hz), 32.0, 31.0 (d, J_{PCC} = 14 Hz), 29.3 (d, J_{PCCC} = 3 Hz), 22.8, 22.0, 17.7, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 12.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 135.6 (q, J_{PB} = 83 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -40.6 (dq, J_{BP} = 83 Hz, J_{BH} = 94 Hz); HRMS (EI^+) calcd for $C_{19}H_{46}BO_2PSi$, $(M + NH_4)^+$ 394.4761, found 394.3442.

Diethoxy octylphosphine-borane (Table 3.4, entry 3). Yield: 66%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17-3.95 (m, 4H), 1.79-1.68 (m, 2H), 1.62-1.48 (m, 2H), 1.42-1.24 (m, 16H), 0.88 (t, J = 6.2 Hz, 3H), 0.80-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 63.1 (d, J_{POC} = 5 Hz), 32.0, 30.9 (d, J_{PCC} = 14 Hz), 29.9 (d, J_{PC} = 56 Hz), 29.2, 22.8, 21.7, 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 148.9 (q, J_{PB} = 86 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -42.2 (dq, J_{BP} = 83 Hz, J_{BH} = 94 Hz); HRMS (EI^+) calcd for $C_{12}H_{30}BO_2P$, $(M + NH_4)^+$ 266.2420, found 266.2418.

Reaction of 57 with Carbonyl Compounds (Scheme 3.8).

Diethoxy (hydroxymethyl)phosphine-borane 61. To diethoxyphosphine-borane **57** (0.408 g, 3 mmol) in CH_3CN (5 mL) was added diisopropylethylamine (1.05 mL, 6 mmol) and paraformaldehyde (0.184 g, 6 mmol) at room temperature. 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 **61** (0.334 g, 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 ($CDCl_3$, 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 ($CDCl_3$, 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.

Diethoxy-hydroxyphenyl phosphine-borane 62 (Scheme 3.8). To diethoxyphosphine-borane **57** (0.408 g, 3 mmol) in CH_3CN (5 mL) was added diisopropylethylamine (1.05 mL, 6 mmol) and benzaldehyde (0.637 g, 6 mmol) at room temperature. The solution was stirred at reflux for 12 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 90:10, v/v) produced the expected compound **62** (0.487 g, 67%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43- 7.25 (m, 5H), 4.95 (s, 1H), 4.12- 3.96 (m, 4H), 2.74 (s, 1H, OH), 1.24 (dt, J = 14.1 Hz, J = 7.2 Hz, 6H), 1.01-0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.5 (d, J_{PCC} = 2 Hz), 128.5 (d, J_{PCCCCC} = 3 Hz), 128.3 (d, J_{PCCCC} = 2 Hz), 127.6 (d, J_{PCCC} = 4 Hz), 74.4 (d, J_{PC} = 64 Hz), 64.7 (dd, J_{POC} = 4 Hz, J_{POC} = 5 Hz), 16.7 (t, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 139.2 (q, J_{PB} = 66 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -45.6 (dq, J_{BP} = 69 Hz, J_{BH} = 79 Hz); HRMS (EI^+) calcd for $C_{11}H_{20}BO_3P$, $(M + NH_4)^+$ 260.1587, found 260.1585.

Representative Procedure for the Deprotection of the Phosphonite-Borane Complexes (EtO)(TIPSO)P(BH_3)Oct (Scheme 3.9). Neat phosphine-borane (EtO)(TIPSO)P(BH_3)Oct **63** (0.188 g, 0.5 mmol) was placed in a flame-dried two-neck flask under argon, and distilled/degassed CH_2Cl_2 (2 mL) was added. The solution was placed at -5 ^{o}C, and HBF_4•OEt_2 (0.5 mL, 2.5 mmol) was slowly added via syringe. The reaction mixture was allowed to warm to

room temperature then stirred for 12 h. The reaction mixture was concentrated in vacuo. An aqueous solution of $NaHCO_3$ was added to the residue and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (hexanes-EtOAc, 1:1, v/v) afforded the desired product **64** as a colorless oil (0.082 g, 80%).

Representative Procedure for the Deprotection of the Phosphonite-Borane Complexes (Scheme 3.9). To a 0.2 M solution of phosphinite-borane in dry dichloromethane 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 $NaHCO_3$ 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 the aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo to afford the *H*-phosphinate.

Ethyl octyl-*H*-phosphinate 64.[28,108a] 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, 0.777 g, 653 ml, 3.0 equiv) in 96 % yield (317 mg, 1.54 mmol). ^{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), 1.37 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 6.6 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 pentyl-*H*-phosphinate 67. The title compound was prepared from diethoxy pentylphosphinite-borane **66** (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 (253 mg, 1.54 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 526 Hz, 1 H), 4.01 - 4.26 (m, 2 H), 1.26 - 1.83 (m, 8 H), 1.37 (t, J = 6.9 Hz, 3 H), 0.91 (t, J = 6.5 Hz, 3 H); ^{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 isopropyl-*H*-phosphinate 69.[87] The title compound was prepared from diethoxy-1-methylethylphosphine-borane **68** (0.88 mmol, 157 mg, 1.0 equiv) and tetrafluoroboric acid diethyl ether complex (4.4 mmol, 623 mg, 5.0 equiv) in 97 % yield (116 mg, 0.85 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (d, J = 519.9 Hz, 1 H), 4.25 - 4.05 (m, 2 H), 2.01- 1.85 (m, 1 H), 1.37 (t, J = 6.9 Hz, 3 H), 1.17 (dd, J = 7.0 Hz, J = 19.6 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 47.1 (dm, J = 531 Hz).

Representative Procedure for Preparation of Borano-Phosphonates (Scheme 3.11).

Scheme 3.11, Method A. Neat $(TIPSO)_2P(BH_3)H$ **55** (507 mg, 1.29 mmol) was placed under vacuum in a flame-dried two-neck flask, during 5 min before use. Anhydrous THF (5 mL) was then added under N_2. The flask was then placed at -78 ^{o}C and deoxygenated under high vacuum for 5 min. The reaction flask was back-filled with N_2 and LiHMDS (1.0 M in THF, 2.58 mL, 2.58 mmol) was added at -78 ^{o}C. After 15 min, 1-bromooctane (0.45 mL, 2.58 mmol) was added under N_2. After the addition of the electrophile, the temperature of the solution was slowly allowed to warm to room temperature, and stirred for 10 h. The reaction mixture was quenched

with a saturated solution of NH_4Cl/brine, and extracted with EtOAc (3 x 50 mL). The combined organic layers were then dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound as a brownish viscous oil. This was dissolved in petroleum ether and filtered through a pad of silica gel. The solvent was evaporated in vacuo, giving the product **71** as a pale yellowish oil (0.227 g, 35% isolated, 88% of purity in ^{31}P NMR). A portion of this intermediate (60 mg, 0.17 mmol) was dissolved in anhydrous THF (2 mL) in a flame-dried three-neck flask, at 0 ^{o}C, under N_2. TBAF (1.0 M solution in THF, 0.83 mL, 0.83 mmol) was added via syringe at 0 ^{o}C and the reaction mixture was allowed to warm to room temperature, then stirred under N_2 for 2 h. The mixture was concentrated in vacuo and the residue partitioned between deionized water and EtOAc. The organic layer was washed with deionized water (3 x 15 mL) and the aqueous layers were combined and concentrated in vacuo to afford the boranophosphonate **72** as a colorless and viscous oil (26.3 mg, 82%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.31 (s, 1H, OH), 3.24-3.19 (m, 2H), 1.72-1.58 (m, 2H), 1.51-1.39 (m, 2H), 1.32-1.19 (m, 3H), 1.12-0.94 (m, 8H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 35.0, 32.1, 29.6, 22.8, 14.3, 13.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 108.9 (q, J_{PB} = 137 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ - 38.2 (bs); HRMS (EI^+) calcd for $C_8H_{21}BO_2P$, (M) 191.1372, found 191.1364.

Scheme 3.11, Method B. A solution of octyl-*H*-phosphinic acid **73**[53,108a] (1.0 g, 5.61 mmol) in anhydrous THF (20 mL) was treated with BSA (6.94mL, 28 mmol) at room temperature for 1 h, under N_2. A solution of BH_3•Me_2S (2.0 M in THF, 5.61 mL, 11.22 mmol) was then added at rt, and the resulting mixture stirred for 1 h. After addition of MeOH (20 mL), the mixture was stirred for an additional 2 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O and the organic phase was washed with H_2O (3x). The combined aqueous layers

were concentrated in vacuo, affording the product **73** (0.965 g, 90%) as a colorless gel. HRMS (EI^+) calcd for $C_8H_{21}BO_2P$, (M) 191.1371, found 191.1373.

Ethoxy(triisopropylsilyloxy)-(*trans*-hex-1-enyl)phosphine-borane 75 (Scheme 3.13). Triisopropylchlorosilane (4.22 mL, 19.76 mmol) was placed into a flame-dried two-neck round bottom flask and cooled to 0 ^oC, under N_2. Et_3N (2.94 mL, 21.08 mmol) was then added dropwise, and the reaction mixture was stirred for approximately 10 min at 0 ^oC. In a separate flame-dried three-neck round bottom flask, a solution of ethyl (*trans*-hex-1-enyl)phosphinate **74**[56,58] (2.87 g, 14.05 mmol) in CH_3CN (28 mL) was cooled to 0 ^oC, under N_2. The mixture TIPSCl/Et_3N was slowly added to the *H*-phosphinate solution via syringe, and the reaction mixture maintained at 0 ^oC for 10-15 min, at which time the reaction was allowed to warm up to room temperature and stirred for 14 h under N_2. BH_3•Me_2S (2.0 M in THF, 14.05 mL, 28.1 mmol) was added dropwise at room temperature. After 5 h, the reaction mixture was concentrated under reduced pressure, and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers washed with brine (1x 15 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (hexanes-toluene, 100:0 to 90:10, v/v) afforded the desired product **75** as a colorless oil (2.84 g, 54 %). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.72 (ddt, J =6.6 Hz, J = 17.3 Hz, J = 2.5 Hz, 1H), 5.81 (dd, J = 17.1 Hz, J = 6.0 Hz, 1H), 4.03 (m, 2H), 2.21 (d, J = 6.9 Hz, 2H), 1.46-1.40 (m, 2H), 1.32-1.25 (m, 10H), 1.19-1.02 (m, 15H), 0.90-0.83 (m, 8H), 0.65-0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.9 (d, J_{PCC} = 14 Hz), 124.4 (d, J_{PC} = 75 Hz), 62.4 (d, J_{POC} = 4 Hz), 34.4 (d, J_{PCCC} = 17 Hz), 31.8, 29.0, 28.0, 22.8, 17.8, 16.7, 14.3, 12.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 119.7 (q, J_{PB} =

90 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -41.5 (dq, J_{BP} = 90 Hz, J_{BH} = 92 Hz); HRMS (EI^+) calcd for $C_{19}H_{44}BO_2PSi$, $(M + NH_4)^+$ 390.3129, found 390.3119.

Ethoxy(triisopropylsilyloxy)-allyl-(1-propyl-pent-1-enyl) phosphine-borane 77 (Scheme 3.13). Triisopropylchlorosilane (7.84 mL, 36.7 mmol) was added into a flame-dried two-neck round bottom flask and cooled to 0 ^oC, under N_2. Et_3N (5.46 mL, 39.17 mmol) was then added dropwise, and the reaction mixture was stirred for approximately 10 min at 0 ^oC. In a separate flame-dried three-neck round bottom flask, a solution of ethyl (1-propyl-pent-1-enyl)phosphinate **76**[23a,56,57] (5 g, 24.48 mmol) in CH_3CN (49 mL) was cooled to 0 ^oC, under N_2. The TIPSCl/Et_3N mixture was slowly added to the *H*-phosphinate solution via syringe and the reaction mixture was kept at 0 ^oC for 10-15 min, at which time the reaction was allowed to warm up to room temperature and stirred for 14 h under N_2. BH_3•Me_2S (2.0 M in THF, 14.05 mL, 28.1 mmol) was added dropwise at room temperature. After 5 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers washed with brine (1x), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (hexanes-toluene, 100:0 to 90:10, v/v) afforded the desired product **77** as a colorless oil (5.32 g, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (dt, J = 6.9 Hz, J = 22.2 Hz, 1H), 4.05-3.95 (m, 2H), 2.25-2.12 (m, 4H), 1.58-1.40 (m, 3H), 1.31-1.25 (m, 4H), 1.22-1.14 (m, 3H), 1.09 (d, J = 8.1 Hz, 18H), 0.94 (t, J = 7.2 Hz, 6H), 0.95-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.4 (d, J_{PCC} = 21 Hz), 135.8 (d, J_{PC} = 71 Hz), 62.4, 30.7 (d, J_{PCC} = 17 Hz), 28.6 (d, J_{PCCC} = 8 Hz), 23.3, 22.3, 17.8, 16.6, 14.3 (d, J_{POCC} = 42 Hz), 12.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 124.4 (q, J_{PB} = 100 Hz); ^{11}B NMR ($CDCl_3$, 28.88 MHz) δ -

43.7 (dq, J_{BP} = 100 Hz, J_{BH} = 103 Hz); HRMS (EI) calcd for $C_{19}H_{44}BO_2PSi$, $(M - H_2 + NH_4)^+$ 390.3129, found 390.3133.

Preparation of Alkyl Phosphinates R*OP(O)H_2 by Dean-Stark Esterification (Table 3.5).[17] A mixture of H_3PO_2 (1 eq) and the corresponding alcohol (2 eq) in reagent grade cyclohexane (0.50 M relative to the amount of acid) is heated at reflux temperature using a Dean-Stark trap (prefilled with cyclohexane) for 12 to 14 h, according to the progress of the reaction (by 31P NMR analysis).

Representative Procedure for the synthesis of chiral dialkoxyphosphine-boranes (Table 3.5).

Method A (Silylation with TIPSCl) and Method C (Silylation with Et_3SiCl).

Triisopropylchlorosilane or triethylchlorosilane (1.5 eq) was added into a flame-dried two-neck round bottom flask and cooled to 0 ^oC, under N_2. Then, Et_3N (1.6 eq) was added dropwise and the reaction mixture was stirred for approximately 10 min at 0 ^oC. In a separate flame-dried three-neck round bottom flask, a freshly prepared solution of R*OP(O)H_2 (0.5 M in cyclohexane, 1 eq) was cooled to 0 ^oC, under N_2. The mixture TIPSCl or Et_3SiCl/Et_3N was slowly added to the hypophosphite solution via syringe and the reaction mixture maintained at 0 ^oC for 10-15 min, at which time the reaction was allowed to warm up to room temperature, then stirred for 12 h under N_2. The reaction mixture was treated with BH_3•Me_2S (2.0 M in THF, 2 eq) by dropwise addition at room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x 250 mL) and the combined organic phases washed with brine (1x 50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification

by column chromatography over silica gel (petroleum ether, then petroleum ether/toluene 95:5, v/v).

Method B: Silylation with BSA.

BSA (1 eq) was slowly added to a freshly prepared solution of R*OP(O)H_2 (0.5 M in cyclohexane, 1 eq) via syringe at 0 ^oC, under N_2. The reaction mixture was maintained at 0 ^oC for 1 to 2 min, at which time the reaction reached completion. The reaction mixture was treated with BH_3•Me_2S (2.0 M in THF, 2 eq) by dropwise addition at room temperature. After 1 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between deionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x 150 mL) and the combined organic phases washed with brine (1x 50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (hexanes/EtOAc, 95:5, v/v).

Triisopropylsilyloxy(1*R*,2*S*,5*R*)-(-)menthoxyphosphine-borane (Table 3.5, Entry 1, Method A). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 424.5 Hz, 1H), 4.18-3.92 (m, 2H), 2.20-2.10 (m, 2H), 1.78-1.59 (m, 4H), 1.46-1.34 (m, 2H), 1.30-1.14 (m, 3H), 1.11 (d, J = 6.6 Hz, 18H), 0.91 (dm, J = 6.9 Hz, 6H), 0.79 (dm, J = 6.6 Hz, 3H), 0.78-0.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 82.3 (d, J_{POC} = 9 Hz), 48.8 (d, J_{POCC} = 5 Hz), 43.5, 34.1, 31.8, 25.6, 23.1, 22.2, 21.2, 17.7, (d, J_{POSiC} = 3 Hz), 16.1, 12.6 (3C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 114.8 (dq, J_{PB} = 86 Hz, J_{PH} = 434 Hz).

Triisopropylsilyloxy(fenchyloxy)phosphine-borane (Table 3.5, entry 2, Method A). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, J = 428.9 Hz, 1H), 3.96 (dd, J = 12.3 Hz, J = 4.7 Hz, 1H), 1.82-

1.62 (m, 3H), 1.60-1.39 (m, 3H), 1.32-1.16 (m, 4H), 1.14-1.08 (m, 24H), 0.9 (s, 3H), 0.88-0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 92.3 (d, J_{POC} = 8 Hz), 49.5, 48.1, 41.0, 39.7, 30.3, 25.9, 21.3 (2C), 19.3, 17.6 (6C), 12.5 (3C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 174.8 (dq, J_{PB} = 100 Hz, J_{PH} = 430 Hz).

Triethylsilyloxy(fenchyloxy)phosphine-borane (Table 3.5, entry 2, Method C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 425.1 Hz, 1H), 3.74 (d, J = 15.9 Hz, 1H), 1.80-1.58 (m, 4H), 1.52-1.16 (m, 6H), 1.20-0.80 (m, 12H), 0.52 (q, J = 8.1 Hz, 9H), 0.51-0.00 (m, 3H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 116.5 (dq, J_{PB} = 99 Hz, J_{PH} = 430 Hz).

Representative Procedure for the Preparation of Chiral Phosphonite-Borane Synthons (Scheme 3.14). In a flame-dried three neck round-bottomed flask was placed Et_3N (0.86 mL, 6 mmol, 2 eq) in a freshly distilled toluene (25 mL), at – 78 ^{o}C, under N_2. PCl_3 (0.27 mL, 3 mmol, 1 eq) was added dropwise to the solution via syringe at – 78 ^{o}C, followed by a slow addition of the alcohol (2 eq of borneol or (1*R*,2*S*,5*R*)-(-)menthol; 1 eq of 1,1'-bi-2-naphthol). After 10 to 15 min, the reaction mixture was allowed to warm to rt and stirred for 2 h 30, under N_2. ^{31}P NMR analysis was used to determine if the reaction was completed. The crude mixture was filtered through celite and the collected filtrate was concentrated in vacuo to afford the crude chlorophosphite. In a flame-dried three neck round-bottomed flask was placed the crude chlorophosphite in THF (20 mL) under N_2, and this was cooled to – 78 ^{o}C. $LiBH_4$ (1.05 eq) was then added (quickly in air) at – 78 ^{o}C and the reaction mixture was stirred at this temperature for 10 min, then allowed to warm up to room temperature and stirred for 1 h 30. The reaction mixture was poured directly into a separatory funnel containing ice (2-5 g). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine (x1),

then dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes 100%, then hexanes/EtOAc, 80/20, v/v).

Bis(borneoxy)phosphine-borane 78 (Scheme 3.14). Yield: 27%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, J_{PH} = 441.3 Hz, 1H), 4.53 (dt, J = 9.6 Hz, J = 8.1 Hz, 1H), 4.42 (t, J = 9.6 Hz, 1H), 2.41-2.20 (m, 2H), 2.00-1.88 (m, 2H), 1.82-1.61 (m, 6H), 1.39-1.18 (m, 10H), 0.87 (s, 12H), 0.60-0.00 (m, 3H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 135.4 (dq, J_{PB} = 89 Hz, J_{PH} = 440 Hz).

Bis(menthoxy)phosphine-borane 79 (Scheme 3.14). Yield: 41%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, J_{PH} = 436.2 Hz, 1H), 4.26-4.10 (m, 1H), 3.97 (dq, J = 10.5 Hz, J = 4.8 Hz, 1H), 2.20-2.00 (m, 4H), 1.66 (broad d, J = 10.8 Hz, 4H), 1.56-1.00 (m, 10H), 0.99-0.88 (m, 12H), 0.82 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 83.8 (d, J_{POC} = 11.4 Hz), 80.7 (d, J_{POC} = 5.1 Hz), 48.9 (d, J_{POCC} = 5.4 Hz), 48.7 (d, J_{POCC} = 6.6 Hz), 43.8, 43.3, 34.2, 34.1, 31.8, 31.7, 25.8, 25.5, 23.2, 23.0, 22.2 (2C), 21.2 (2C), 16.2, 16.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 127.6 (dq, J_{PB} = 89 Hz, J_{PH} = 438 Hz).

1,1'-Bi-2-naphthyloxyphosphine-borane 80 (Scheme 3.14). ^{31}P NMR Yield: 100%. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 158.2 (dm, J_{PB} = 67 Hz, J_{PH} = 444 Hz).

<u>Chapter Four – Section 4.2.2</u>[83]

Representative Procedure for Cross-Coupling of Aryl Halide Substrates

To a solution of diisopropyl phosphite (4.8 mmol, 1.2 equiv) in dry CH_3CN or dry DMF (previously dried over 4 Å molecular sieves) (see Tables 1, 2, 3) (15 mL), was added an aryl or heteroaryl halide (4 mmol, 1.0 equiv), *N,N*-diisopropylethylamine (5.2 mmol, 0.9 mL, 1.3 equiv),

$Pd(OAc)_2$ (0.04 mmol, 1 mol%) and dppf (0.044 mmol, 1.1 mol%) at room temperature. The solution was heated for 24 h at reflux in CH_3CN, or at 110 ^oC in DMF, under nitrogen. After cooling to room temperature, the crude mixture was concentrated in vacuo and the residue was partitioned between de-ionized water and EtOAc, followed by extraction of the aqueous phase with EtOAc (3 x 100 mL). The organic fractions were combined and washed with brine (1 x 20 mL). Drying and concentration furnished the crude compound, which was purified by radial or column chromatography using mixtures hexanes/EtOAc, unless otherwise specified.

Diisopropyl-2-pyridylphosphonate (Table 4.1, entry 1).[194] Yield: 85%. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.81 (d, J = 4.5 Hz, 1H), 7.98 (dd, J = 7.2 Hz, J = 6.6 Hz 1H), 7.84-7.76 (m, 1H), 7.44-7.39 (m, 1H), 4.91-4.78 (m, 2H), 1.40 (d, J = 6.3 Hz, 6H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.7 (d, J_{PC} = 225 Hz), 150.1 (d, J_{PCNC} = 23 Hz), 135.8 (d, J_{PCCC} = 12 Hz), 127.5 (d, J_{PCC} = 27 Hz), 125.6, 71.1 (d, J_{POC} = 6 Hz, 2C), 23.7 (2C), 23.5 (2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 9.88 (s).

Diisopropyl-3-pyridylphosphonate (Table 4.1, entry 2). Yield: 48-61%. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.20-8.86 (m, 1H), 8.78-8.70 (m, 1H), 8.18-8.02 (m, 1H), 7.42-7.36 (m, 1H), 4.81-4.68 (m, 2H), 1.40 (d, J = 6.3 Hz, 6H), 1.26 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.8, 152.3 (d, J_{PCC} = 13 Hz), 139.4 (d, J_{PCC} = 8 Hz), 126.6 (d, J_{PC} = 190 Hz), 123.4 (d, J_{PCCC} = 12 Hz), 71.4 (d, J_{POC} = 6 Hz, 2C), 24.1 (d, J_{POCC} = 4 Hz, 2C), 23.9 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 14.4 (s); HRMS (EI^+) calcd for $C_{11}H_{18}NO_3P$, $(M)^+$ 243.1024, found 243.1022.

Diisopropyl-4-pyridylphosphonate (Table 4.1, entry 3).[273] Yield: 63%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78-8.73 (m, 2H), 7.67 (dm, J = 13 Hz, 2H), 4.82-4.70 (m, 2H), 1.40 (d, J = 6 Hz, 6H), 1.27 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 150.1 (d, J_{PCCC} = 12 Hz, 2C), 139.1 (d, J_{PC} = 187 Hz), 125.4 (d, J_{PCC} = 8 Hz), 71.9 (d, J_{POC} = 6 Hz), 24.2 (d, J_{POCC} = 4 Hz), 24.0 (d, J_{POCC} = 4 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 13.5 (s).

Diisopropyl-2-bromo-pyridyl-6-phosphonate (Table 4.1, entry 4). After purification by column chromatography over silica gel, the solid was recrystallized with hot hexanes. White crystal needles were formed after cooling to room temperature and the crystals were filtered and washed several times with cold hexanes. Yield: 30%. M.p. 92-94 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93-7.87 (m, 1H), 7.66-7.55 (m, 2H), 4.92-4.76 (m, 2H), 1.39 (d, J = 6 Hz, 6H), 1.31 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.7 (d, J_{PC} = 227 Hz), 143.0 (d, J_{PCNC} = 26 Hz), 138.4 (d, J_{PCCC} = 12 Hz), 130.7 (d, J_{PCCCC} = 3 Hz), 126.9 (d, J_{PCC} = 24 Hz), 72.5 (d, J_{POC} = 6 Hz, 2C), 24.3 (d, J_{POCC} = 4 Hz, 2C), 24.0 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 7.64 (s); HRMS (EI^+) calcd for $C_{11}H_{17}BrNO_3P$, $(M+H)^+$ 322.0208, found 322.0201.

Diisopropyl-2-pyrimidylphosphonate (Table 4.1, entry 5).[198] Yield: 62-67%. M.p. 51-57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91-8.87 (m, 2H), 7.45-7.40 (m, 1H), 5.02-4.88 (m, 2H), 1.44 (d, J = 6 Hz, 6H), 1.35 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 164.1 (d, J_{PC} = 273 Hz), 156.9 (d, J_{PCNC} = 18 Hz, 2C), 122.5 (d, J_{PCNCC} = 4 Hz), 72.4 (d, J_{POC} = 6 Hz, 2C), 24.0 (d, J_{POCC} = 4 Hz, 2C), 23.6 (d, J_{POCC} = 4 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 4.7 (s).

Diisopropyl-5-pyrimidylphosphonate (Table 4.1, entry 6). Yield: 83%. M.p. 30-32 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.25 (s, 1H), 8.97 (d, J = 7 Hz, 2H), 4.76-4.66 (m, 2H), 1.32 (d, J = 6

Hz, 6H), 1.20 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 160.8, 159.5 (d, J_{PCC} = 5 Hz), 159.3 (d, J_{PCC} = 5 Hz), 125.1 (d, J_{PC} = 192 Hz), 71.9 (d, J_{POC} = 6 Hz, 2C), 23.9 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 10.9 (s); HRMS (EI^+) calcd for $C_{10}H_{17}N_2O_3P$, $(M)^+$ 244.0977, found 244.0975.

Diisopropyl-2-pyrazylphosphonate (Table 4.1, entry 7). Yield: 97%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.02 (s, 1H), 8.64 (d, J = 16 Hz, 2H), 4.86-4.75 (m, 2H), 1.33 (d, J = 6 Hz, 6H), 1.23 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 148.9 (d, J_{PC} = 226 Hz), 147.7 (d, J_{PCC} = 26 Hz), 146.7 (d, J_{PCCNC} = 3 Hz), 145.2 (d, J_{PCNC} = 18 Hz), 72.2 (d, J_{POC} = 6 Hz, 2C), 24.0 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 4 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 7.73 (s); HRMS (EI^+) calcd for $C_{10}H_{17}N_2O_3P$, $(M)^+$ 244.0977, found 244.0977.

Diisopropyl-3-quinolinylphosphonate (Table 4.1, entry 8). Yield: 46%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (dd, J = 2 Hz, J = 5 Hz, 1H), 8.72 (dd, J = 1 Hz, J = 15 Hz, 1H), 8.16 (d, J = 9 Hz, 1H), 7.92 (d, J = 7 Hz, 1H), 7.85 (t, J = 7 Hz, 1H), 7.64 (t, J = 7 Hz, 1H), 4.84-4.72 (m, 2H), 1.43 (d, J = 6 Hz, 6H), 1.26 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.1(d, J_{PCC} = 12 Hz), 149.4, 142.9 (d, J_{PCC} = 9 Hz), 131.9, 129.7 (d, J_{PCCCC} = 1 Hz), 128.9, 127.7, 126.9 (d, J_{PCCC} = 14 Hz), 123.6 (d, J_{PC} = 189 Hz), 71.7 (d, J_{POC} = 5 Hz, 2C), 24.3 (d, J_{POCC} = 4 Hz, 2C), 24.1 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 19.3 (s); HRMS (EI^+) calcd for $C_{15}H_{20}NO_3P$, $(M)^+$ 293.1181, found 293.1181.

Diisopropyl-2-anilinylphosphonate (Table 4.2, entry 1). Yield: 70%. M.p. 46-47 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (quin, J = 7 Hz, 1H), 7.25 (q, J = 7 Hz, 1H), 6.71-6.60 (m, 2H), 5.19 (s, 2H, NH_2), 4.65 (sext, J = 7 Hz, 2H), 1.38 (t, J = 6 Hz, 6H), 1.24 (t, J = 6 Hz, 6H); ^{13}C NMR

($CDCl_3$, 75.45 MHz) δ 151.3 (d, J_{PCC} = 9 Hz), 133.7 (d, J_{PCCCC} = 2 Hz), 133.4 (d, J_{PCC} = 7 Hz), 116.5 (d, J_{PCCC} = 14 Hz), 116.3 (d, J_{PCCC} = 13 Hz), 109.3 (d, J_{PC} = 184 Hz), 70.7 (d, J_{POC} = 5 Hz, 2C), 24.2 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 20.2 (s); HRMS (EI^+) calcd for $C_{12}H_{20}NO_3P$, $(M)^+$ 257.1181, found 257.1178.

Diisopropyl-3-anilinylphosphonate (Table 4.2, entry 2).[274] Yield: 72%. M.p. 103-104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.12 (m, 3H), 6.81 (d, J = 7 Hz, 1H), 4.71-4.60 (m, 2H), 3.86 (s, 2H, NH_2), 1.36 (d, J = 6 Hz, 6H), 1.22 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 146.9 (d, J_{PCCC} = 18 Hz), 130.6 (d, J_{PC} = 190 Hz), 129.5 (d, J_{PCCC} = 17 Hz), 121.3 (d, J_{PCC} = 9 Hz), 118.6 (d, J_{PCCCC} = 3 Hz), 118.0 (d, J_{PCC} = 12 Hz), 70.7 (d, J_{POC} = 5 Hz, 2C), 24.2 (d, J_{POCC} = 6 Hz, 2C), 24.0 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 18.5 (s).

Diisopropyl-4-anilinylphosphonate (Table 4.2, entry 3). Yield: 70-92%. M.p. 113-115 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (dd, J = 9 Hz, J = 13 Hz, 2H), 6.67 (dd, J = 4 Hz, J = 9 Hz, 2H), 4.69-4.54 (m, 2H), 4.10 (s, 2H, NH_2), 1.35 (d, J = 6 Hz, 6H), 1.21 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 150.6, 133.7 (d, J_{PCC} = 11 Hz, 2C), 117.1 (d, J_{PC} = 198 Hz), 114.2 (d, J_{PCCC} = 16 Hz, 2C), 70.3 (d, J_{POC} = 5 Hz, 2C), 24.3 (d, J_{POCC} = 4 Hz, 2C), 24.0 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 19.1 (s); HRMS (EI^+) calcd for $C_{12}H_{20}NO_3P$, $(M)^+$ 257.1181, found 257.1183.

Diisopropyl-[(3-tert-butoxycarbonylamino)phenyl]phosphonate (Table 4.2, entry 4). After work-up, the solid was simply washed with Et_2O, affording the desired product as a white powder. Yield: 81%. M.p. 168-169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82-7.78 (m, 1H), 7.62 (d, J = 14 Hz, 1H), 7.48-7.37 (m, 2H), 6.78 (s, 1H, OH), 4.73-4.62 (m, 2H), 1.52 (s, 9H), 1.36 (d,

J = 6 Hz, 6H), 1.22 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.9, 139.1 (d, J_{PCCC} = 19 Hz), 130.1 (d, J_{PC} = 189 Hz), 129.1 (d, J_{PCC} = 16 Hz), 125.4 (d, J_{PCCC} = 9 Hz), 122.0 (d, J_{PCCCC} = 1 Hz), 121.9 (d, J_{PCC} = 8 Hz), 80.4, 70.7 (d, J_{POC} = 6 Hz, 2C), 28.3, 24.0 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 4 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.4 (s); HRMS (EI^+) calcd for $C_{17}H_{28}NO_5P$, $(M)^+$ 357.1705, found 357.1696.

Diisopropyl-[(4-tert-butoxycarbonylamino)phenyl]phosphonate (Table 4.2, entry 5). After purification by column chromatography over silica gel, the solid was washed with petroleum ether, affording the pure product as a white powder. Yield: 82%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (dd, J = 9 Hz, J = 13 Hz, 2H), 7.45 (dd, J = 4 Hz, J = 9 Hz, 2H), 6.67 (s, 1H, NH), 4.72-4.57 (m, 2H), 1.52 (s, 9H), 1.35 (d, J = 6 Hz, 6H), 1.20 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.7, 142.5 (d, J_{PCCCC} = 3 Hz), 133.1 (d, J_{PCC} = 11 Hz, 2C), 123.3 (d, J_{PC} = 194 Hz), 117.8 (d, J_{PCCCC} = 15 Hz, 2C), 81.2, 70.7 (d, J_{POC} = 5 Hz, 2C), 28.5, 24.3 (d, J_{POCC} = 4 Hz, 2C), 24.0 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 18.1 (s); HRMS (EI^+) calcd for $C_{17}H_{28}NO_5P$, $(M)^+$ 357.1705, found 357.1710.

Diisopropyl-1,2-methylenedioxyphenyl-4-phosphonate (Table 4.2, entry 6). Yield: 99%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (qt, J = 1 Hz, J = 8 Hz, J = 6 Hz, 1H), 7.20 (dt, J = 1 Hz, J = 13 Hz, 1H), 6.86 (qd, J = 1 Hz, J = 3 Hz, 1H), 6.01 (s, 2H), 4.68-4.61 (m, 2H), 1.35 (d, J = 5 Hz, 6H), 1.22 (d, J = 5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 150.1(d, J_{PCCCC} = 3 Hz), 147.8 (d, J_{PCCC} = 22 Hz), 127.2 (d, J_{PCC} = 11 Hz), 122.9 (d, J_{PC} = 194 Hz), 111.1 (d, J_{PCC} = 12 Hz), 108.4 (d, J_{PCCC} = 19 Hz), 101.6, 70.6 (d, J_{POC} = 6 Hz, 2C), 24.0 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.8 (s); HRMS (EI^+) calcd for $C_{13}H_{19}O_5P$, $(M)^+$ 286.0970, found 286.0972.

Diisopropyl-1,2,3-trimethoxyphenyl-5-phosphonate (Table 4.2, entry 7). Yield: 61%. M.p. 72-74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J = 13 Hz, 2H), 4.73-4.60 (m, 2H), 3.86 (s, 9H), 1.35 (d, J = 6 Hz, 6H), 1.21 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 153.2 (d, J_{PCCC} = 22 Hz, 3C), 141.3, 124.6 (d, J_{PC} = 189 Hz), 108.9 (d, J_{PCC} = 4 Hz), 108.8 (d, J_{PCC} = 4 Hz), 70.9 (2C), 56.3 (3C), 24.2 (2C), 23.8 (2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 18.3 (s); HRMS (EI^+) calcd for $C_{15}H_{25}O_6P$, $(M)^+$ 332.1389, found 332.1393.

Diisopropyl-4-nitrophenylphosphonate (Table 4.2, entry 8).[186,275] Yield: 60%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (dd, J = 3 Hz, J = 9 Hz, 2H), 8.01 (dd, J = 8 Hz, J = 13 Hz, 2H), 4.82-4.71 (m, 2H), 1.40 (d, J = 6 Hz, 6H), 1.25 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 150.1(d, J_{PCCCC} = 3 Hz), 137.4 (d, J_{PC} = 188 Hz), 132.9 (d, J_{PCC} = 11 Hz, 2C), 123.3 (d, J_{PCCC} = 15 Hz, 2C), 71.8 (d, J_{POC} = 6 Hz, 2C), 24.1 (d, J_{POCC} = 4 Hz, 2C), 23.9 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 13.9 (s).

Diisopropyl-1-naphthylphosphonate (Table 4.2, entry 9). Yield: 86%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, J = 8 Hz, 1H), 8.30 (dd, J = 6 Hz, J = 15 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.62-7.48 (M, 3H), 4.79-4.67 (m, 2H), 1.41 (d, J = 6 Hz, 6H), 1.14 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.6 (d, J_{PCC} = 9 Hz), 133.7 (d, J_{PCCC} = 13 Hz), 133.5 (d, J_{PCCCC} = 3 Hz), 132.8 (d, J_{PCCC} = 11 Hz), 128.8 (d, J_{PCCCC} = 1 Hz), 127.2, 127.1, 126.4, 126.3 (d, J_{PC} = 183 Hz), 124.6 (d, J_{PCC} = 17 Hz), 71.1 (d, J_{POC} = 5 Hz, 2C), 24.3 (d, J_{POCC} = 4 Hz, 2C), 23.9 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.8 (s); HRMS (EI^+) calcd for $C_{16}H_{21}O_3P$, $(M)^+$ 292.1228, found 292.1124.

Diisopropyl-phenylphosphonate (Table 4.2, entry 10).[186,275] Yield: 47-93%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (dd, J = 7 Hz, J = 13 Hz, 2H), 7.53-7.49 (m, 1H), 7.47-7.40 (m, 2H), 4.75-4.63 (m, 2H), 1.37 (d, J = 6 Hz, 6H), 1.22 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 132.1, 131.7 (d, J_{PCC} = 10 Hz, 2C), 130.0 (d, J_{PC} = 188 Hz), 128.4 (d, J_{PCCC} = 15 Hz, 2C), 70.7 (2C), 24.1 (d, J_{POCC} = 4 Hz, 2C), 23.8 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 17.6 (s).

Diisopropyl-4-hydroxyphenylphosphonate (Table 4.2, entry 11). Yield: 27-76%. M.p. 125-127 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.79 (s, 1H, OH), 7.64 (dd, J = 9 Hz, J = 13 Hz, 2H), 7.02-6.99 (m, 2H), 4.71-4.56 (m, 2H), 1.36 (d, J = 6 Hz, 6H), 1.23 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 161.9 (d, J_{PCCCC} = 3 Hz), 133.9 (d, J_{PCC} = 12 Hz, 2C), 117.9 (d, J_{PC} = 198 Hz), 116.1 (d, J_{PCCC} = 16 Hz, 2C), 71.2 (d, J_{POC} = 5 Hz, 2C), 24.2 (d, J_{POCC} = 4 Hz, 2C), 24.0 (d, J_{POCC} = 4 Hz, 2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 19.9 (s); HRMS (EI^+) calcd for $C_{12}H_{19}O_4P$, $(M)^+$ 258.1021, found 258.1022.

Diisopropyl-4-methylbenzoylphosphonate (Table 4.3, entry 1). Yield: 44%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14-8.09 (m, 2H), 7.94-7.86 (m, 2H), 4.77-4.66 (m, 2H), 3.95 (s, 3H), 1.38 (d, J = 6 Hz, 6H), 1.23 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 166.4, 135.0 (d, J_{PC} = 187 Hz), 133.4 (d, J_{PCCCC} = 3 Hz), 131.8 (d, J_{PCC} = 10 Hz, 2C), 129.4 (d, J_{PCCC} = 15 Hz, 2C), 71.3 (d, J_{POC} = 5 Hz, 2C), 52.5, 24.2 (d, J_{POCC} = 4 Hz, 2C), 23.9 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 14.7 (m); HRMS (EI^+) calcd for $C_{14}H_{21}O_5P$, $(M)^+$ 300.1127, found 300.1120.

Diisopropyl-4-cyanophenylphosphonate (Table 4.3, entry 2). Yield: 57%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (dd, J = 8 Hz, J = 13 Hz, 2H), 7.78-7.73 (m, 2H), 4.82-4.67 (m, 2H), 1.40 (d, J = 6 Hz, 6H), 1.25 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.7 (d, J_{PC} = 188 Hz), 132.4 (d, J_{PCC} = 10 Hz, 2C), 132.1 (d, J_{PCCC} = 15 Hz, 2C), 118.2, 115.9 (d, J_{PCCCC} = 3 Hz), 71.8 (d, J_{POC} = 6 Hz, 2C), 24.2 (d, J_{POCC} = 4 Hz, 2C), 24.1 (d, J_{POCC} = 5 Hz, 2C); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 14.2 (s); HRMS (EI^+) calcd for $C_{13}H_{18}NO_3P$, $(M)^+$ 267.1024, found 267.1025.

Diisopropyl-4-trifluorophenylphosphonate (Table 4.3, entry 3).[276] Yield: 22%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (dd, J = 8 Hz, J = 13 Hz, 2H), 7.74-7.70 (m, 2H), 4.80-4.68 (m, 2H), 1.40 (d, J = 6 Hz, 6H), 1.25 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.6 (d, J_{PC} = 187 Hz), 133.9 (dq, J_{FC} = 33 Hz, J_{PCCCC} = 3 Hz), 132.3 (d, J_{PCC} = 10 Hz, 2C), 125.3 (d, J_{FC} = 15 Hz, 4 Hz), 123.4 (d, J_{FC} = 273 Hz), 71.5 (d, J_{POC} = 5 Hz), 24.2 (d, J_{POCC} = 4 Hz), 24.0 (d, J_{POCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 16.5 (s); ^{19}F NMR ($CDCl_3$, 282.306 MHz) δ -63.7 (s).

General Procedure for Scheme 4.3. The crude reaction mixture from the Pd-catalyzed cross-coupling was concentrated in vacuo. The residue was partitioned between concentrated aqueous HCl and $CHCl_3$. The aqueous layer was washed once with $CHCl_3$, then treated with concentrated aqueous NaOH. The resulting basic aqueous layer was extracted with $CHCl_3$ (3 X), and the combined organic layers dried with $MgSO_4$, and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 and treated with bromotrimethylsilane (2.2 equiv) at room temperature under N_2. When silylation was complete (24 - 48 h, monitored by ^{31}P-NMR), the solvent was removed in vacuo and MeOH was added. The phosphonic acids were obtained as solids either directly, or by precipitation from water/acetone or water/methanol.

Pyrazine phosphonic acid (Scheme 4.3, compound 86). Yield: 69%. M.p. 171 – 173 ^{o}C. ^{1}H NMR (D_2O, 300 MHz) δ 8.63 (bs, 1H), 8.55 (bs, 1H), 8.45 (bs, 1H); ^{13}C NMR (D_2O, 75.45 MHz) δ 152.1 (d, J_{PC} = 206 Hz), 145.2 (d, J_{PCC} = 16 Hz), 144.5, 144.2; ^{31}P NMR (D_2O, 121.47 MHz) δ 3.64 (s); HRMS (ES^+) calcd for $C_4H_5N_2O_3P$, $(M + H)^+$ 161.0116, found 161.0111.

5-Pyrimidine phosphonic acid (Scheme 4.3, compounds 88). Yield: 78%. M.p. 203 – 204 ^{o}C. ^{1}H NMR (D_2O, 300 MHz) δ (major, $PyrimP(O)(OH)_2$) 9.13 (s, 1H), 8.92 (d, J = 7 Hz, 2H), (minor, $PyrimH^+P(O)(OH)(O^-)$) 8.09 (s, 1 H), 6.84 (d, J = 13 Hz, 1 H), 5.57 (d, J = 6 Hz, 1 H); ^{13}C NMR (D_2O, 75.45 MHz) δ (major) 158.6 (d, J_{PCC} = 7 Hz), 155.7, 134.24 (d, J_{PC} = 161 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ (minor, $PyrimH^+P(O)(OH)(O^-)$) 9.34 (s) and (major, $PyrimP(O)(OH)_2$) 4.51 (s); HRMS (ES^+) calcd for $C_4H_5N_2O_3P$, $(M + H)^+$ 161.0116, found 161.0116.

2-Pyrimidine phosphonic acid (Scheme 4.3, compound 90). Yield: 89%. M.p. 207 – 208 ^{o}C. ^{1}H NMR (D_2O, 300 MHz) δ 8.97 (d, J = 5 Hz, 2H), 7.79 (dt, J = 5, 3 Hz, 1H); ^{13}C NMR (D_2O, 75.45 MHz) δ 164.1 (d, J_{PC} = 224 Hz), 157.2 (d, J_{PCNC} = 12 Hz), 123.12; ^{31}P NMR (D_2O, 121.47 MHz) δ - 1.31 (s).

3-Pyridine phosphonic acid (Scheme 4.3, compound 92). Yield: 100%. M.p. 237 – 240 ^{o}C. ^{1}H NMR (D_2O, 300 MHz) δ 8.84 (dd, J = 7, 1 Hz, 1H), 8.75 (dd, J = 7, 1 Hz, 1H), 8.71 (ddt, J = 12, 7, 1 Hz, 1H), 8.01 – 8.07 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 148.4 (d, J_{PCC} = 7 Hz), 142.37, 142.1 (d, J_{PCCC} = 15 Hz), 136.5 (d, J_{PC} = 175 Hz), 127.5 (d, J_{PCC} = 11 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 4.48 (t, J_{PCCH} = 9 Hz).

Chapter Five, Section 5.2

Representative Procedure for Radical Reaction of Sodium Hypophosphite with Alkynes-Tables 5.1 and 5.2. To a solution of $NaH_2PO_2.H_2O$ (18.0 mmol) in a mixture of methanol (12.5 mL) and dioxane (2.5 mL) were added the alkyne (3 mmol) and triethylborane (1.0 M in hexane, 3 mL, 3 mmol). The solution was stirred for 4 hours at room-temperature in a flask open to air, and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the the 1,1-bis *H*-phosphinate sodium salt in good purity (typically >95%).

Disodium hexyl-1,1-bis-*H*-phosphinate (Table 5.1, entry 9). Mp: > 250 °C (dec). ^{1}H NMR (D_2O, 300 MHz) δ 6.85 (d, $^1J_{PH}$ = 524 Hz, 2 H), 1.62-1.28 (m, 5 H), 1.20-1.10 (bs, 4 H), 0.70 (t, $^3J_{HH}$ = 6.7 Hz, 3 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 13.7, 21.6 (t, ^3JPC = 2.7 Hz), 22.0, 29.0 (t, $^2J_{PC}$ = 6.6 Hz), 31.5, 44.4 (t, $^1J_{PC}$ = 78.5 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.4 (dm, $^1J_{PH}$ = 523 Hz). HRMS (FAB) calcd. for $C_6H_{14}Na_2O_4P_2$, (M-2Na$^+$+H$^+$) 213.0446, found 213.0446.

Disodium (3-hydroxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 1). ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (d, $^1J_{PH}$ = 529.7 Hz, 2 H), 3.57 (t, $^3J_{HH}$ = 7.0 Hz, 2 H), 1.87-1.70 (m, 2 H), 1.63-1.46 (m, 1 H); ^{13}C NMR (D_2O, 75.45 MHz) δ 23.9, 41.4 (t, $^1J_{PC}$ = 77.7 Hz), 61.2 (t, $^2J_{PC}$ = 7.8 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.6 (dm, $^1J_{PH}$ = 530 Hz). HRMS (FAB) calcd. for $C_3H_8Na_2O_5P_2$, (M-2Na$^+$+H$^+$) 186.9925, found 186.9924.

Disodium (5-hydroxy-pentyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 2). ^{1}H NMR (D_2O, 300 MHz) δ 6.84 (d, $^1J_{PH}$ = 523.6 Hz, 2 H), 3.42 (t, $^3J_{HH}$ = 6.0 Hz, 2 H), 1.7- 1.4 (m, 3 H), 1.48 (bs, 4 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 20.8, 24.8, 31.0, 43.8 (t, $^1J_{PC}$ = 74.8 Hz); ^{31}P NMR

(D_2O, 121.47 MHz) δ 26.1 (dm, $^1J_{PH}$ = 525.5 Hz). Anal. calcd. for $C_5H_{12}Na_2O_5P_2$: C, 23.09; H, 4.65; O, 30.76. Found: C, 22.89; H, 4.79; O, 31.02.

Disodium (2-cyclohexyl-2-hydroxy-ethyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 3). ^{1}H NMR (D_2O, 300 MHz) δ 6.86 (d, $^1J_{PH}$ = 531.8 Hz, 2 H), 1.90-1.68 (m, 3 H), 1.33 (bs, 10 H); ^{13}C NMR (D_2O, 75.45 MHz) δ 22.0, 25.3, 31.7, 37.0, 39.4 (t, $^1J_{PC}$ = 77.2 Hz), 71.5 (t, ^2JPC = 5.8 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (dm, ^1JPH = 531.6 Hz). HRMS (FAB) calcd. for $C_8H_{16}Na_2O_5P_2$, (M-2Na$^+$+H$^+$) 255.0558, found 255.0551. Anal. calcd. for $C_8H_{16}Na_2O_5P_2 + H_2O$: C, 30.20; H, 5.70. Found: C, 30.27; H, 5.76.

Disodium (3-hydroxy-3-methyl-butyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 4). ^{1}H NMR (D_2O, 300 MHz) δ 7.00 (d, $^1J_{PH}$ = 532.0 Hz, 2 H), 1.95-1.85 (m, 3 H), 1.2 (s, 6 H); ^{13}C NMR (D_2O, 75.45 MHz) δ 28.4, 33.5, 40.6 (t, $^1J_{PC}$ = 76.9 Hz), 70.7 (t, $^2J_{PC}$ = 6.0 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 28.6 (dm, $^1J_{PH}$ = 532.0 Hz). HRMS (FAB) calcd. for $C_5H_{12}Na_2O_5P_2$, (M-2Na$^+$+H$^+$) 259.0241, found 259.0227.

Disodium (2-trimethylsilyl-ethyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 5). ^{1}H NMR (D_2O, 300 MHz) δ 6.91 (d, $^1J_{PH}$ = 524.8 Hz, 2 H), 1.67 (tt, $^2J_{PH}$ = 18.5 Hz, $^3J_{HH}$ = 6.2 Hz, 1 H), 0.77 (dt, $^3J_{HH}$ = 6.2 Hz, $^3J_{PH}$ = 17.5 Hz, 2 H), 0.00 (s, 9 H); ^{13}C NMR (H_2O, 22.635 MHz) δ -2.3, 5.7, 38.8 (t, $^1J_{PC}$ = 77.5 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 27.3 (dm, $^1J_{PH}$ = 524.2 Hz). HRMS (FAB) calcd. for $C_5H_{14}Na_2O_4P_2Si$, (M-Na$^+$+2H$^+$) 253.0191, found 253.0197. Anal. calcd. for $C_5H_{14}Na_2O_4P_2Si + H_2O$: C, 20.55; H, 5.52. Found: C, 20.75; H, 5.12.

Disodium (3-chloro-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 6). ^{1}H NMR (D_2O, 300

MHz) δ 7.06 (d, $^{1}J_{PH}$ = 5.32.4 Hz, 2 H), 3.79 (t, $^{3}J_{HH}$ = 7.0 Hz, 2 H), 2.26-2.09 (m, 2 H), 2.01-1.86 (m, 1 H); ^{31}P NMR (D_2O, 36.44 MHz) δ 23.1 (dm, $^{1}J_{PH}$ = 531.4 Hz). HRMS (ES) calcd. for $C_3H_7ClNa_2O_4P_2$, 251.9382, found 251.9387.

Disodium (4-tosyl-butyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 7). ^{1}H NMR (D_2O, 300 MHz) δ 7.67 (d, *J* = 7.0 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 6.80 (d, $^{1}J_{PH}$ = 528.9 Hz, 2 H), 3.96 (t, *J* = 6.3 Hz, 2 H), 2.28 (s, 3 H), 1.79-1.68 (m, 2 H), 1.59-1.33 (m, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.5 (dm, $^{1}J_{PH}$ = 527.5 Hz).

Disodium propyl-1,1-bis-*H*-phosphinate (Table 5.2, entry 8). ^{1}H NMR (D_2O, 300 MHz) δ 6.85 (d, $^{1}J_{PH}$ = 525 Hz, 2 H), 1.67-1.49 (m, 3 H), 1.48-1.30 (m, 1 H), 0.93 (t, $^{3}J_{HH}$ = 7.6 Hz, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.4 (dm, $^{1}J_{PH}$ = 525.0 Hz).

Disodium octyl-1,1-bis-*H*-phosphinate (Table 5.2, entry 10). ^{1}H NMR (D_2O, 300 MHz) δ 6.85 (d, $^{1}J_{PH}$ = 523.8 Hz, 2 H), 1.60-1.40 (m, 2 H), 1.39-1.25 (m, 1 H), 1.10 (bs, 10 H),), 0.68 (t, $^{3}J_{HH}$ = 6.9 Hz, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.6 (dm, $^{1}J_{PH}$ = 525.5 Hz).

Disodium decyl-1,1-bis-*H*-phosphinate (Table 5.2, entry 11). ^{1}H NMR (D_2O, 300 MHz) δ 7.00 (d, $^{1}J_{PH}$ = 524.0 Hz, 2 H), 1.70-1.60 (m, 2 H), 1.50-1.40 (m, 1 H), 1.30-1.20 (bs, 14 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 12.9, 20.9, 21.5, 28.0 (bs), 30.7, 43.7 (t, $^{1}J_{PC}$ = 76.8 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 22.5 (dm, $^{1}J_{PH}$ = 524.0 Hz). HRMS (FAB) calcd. for $C_{10}H_{22}Na_2O_4P_2$, ($M+H^+$) 315.0867, found 315.0868.

Disodium (3,3-dimethyl-butyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 12). ^{1}H NMR (D_2O, 300 MHz) δ 6.83 (d, $^{1}J_{PH}$ = 527.1 Hz, 2 H), 1.66-1.34 (m, 3 H), 0.71 (bs, 9 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 28.4, 29.7, 33.7, 40.1 (t, $^{1}J_{PC}$ = 78.5 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 27.1 (dm, $^{1}J_{PH}$ = 512.0 Hz**).** HRMS (FAB) calcd. for $C_6H_{14}Na_2O_4P_2$ (M-Na^++2 H^+) 237.0422, found 237.0412.

Disodium (2-ethyl-ethyl-ester)-1,1-bis-*H*-phosphinate (Table 5.2, entry 13). ^{1}H NMR (D_2O, 300 MHz) δ 6.86 (d, $^{1}J_{PH}$ = 531.8 Hz, 2 H), 3.99 (q, $^{3}J_{HH}$ = 6.7 Hz, 2 H), 2.60-2.40 (m, 2 H), 2.19-1.86 (m, 1 H), 1.07 (t, $^{3}J_{HH}$ = 6.7 Hz, 3 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 12.8, 26.6, 40.1 (t, $^{1}J_{PC}$ = 77.7 Hz), 61.5, 173.7; ^{31}P NMR (D_2O, 121.47 MHz) δ 23.4 (dm, $^{1}J_{PH}$ = 532.8 Hz). HRMS (FAB) calcd. for $C_5H_{10}Na_2O_6P_2$ (M+Na^++H^+) 296.9646, found 296.9646.

Disodium (3-acetyl-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 14). ^{1}H NMR (D_2O, 300 MHz) δ 6.90 (d, $^{1}J_{PH}$ = 529.8 Hz, 2 H), 4.10 (t, J = 6.9 Hz, 2 H), 1.94 (s, 3 H), 1.93-1.83 (m, 2 H), 1.72-1.55 (m, 1 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 20.5 (2C), 40.8 (t, $^{1}J_{PC}$ = 77.5 Hz), 64.2 (t, $^{2}J_{PC}$ = 7.9 Hz), 174.5; ^{31}P NMR (D_2O, 121.47 MHz) δ 25.1 (dm, $^{1}J_{PH}$ = 529.9 Hz). HRMS (ES) calcd. for $C_5H_{10}Na_2O_6P_2$ (M+H^+) 274.9826, found 274.9825.

Disodium 5,5-bis-*H*-pentanoic acid phosphinate (Table 5.2, entry 15). ^{1}H NMR (D_2O, 300 MHz) δ 6.85 (d, $^{1}J_{PH}$ = 527.1 Hz, 2 H), 2.22 (t, $^{3}J_{HH}$ = 6.4 Hz, 2 H), 1.70-1.35 (m, 5 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 20.2, 23.8 (t, $^{2}J_{PC}$ = 7.21 Hz), 33.7, 42.9 (t, $^{1}J_{PC}$ = 78.5 Hz), 178.4; ^{31}P NMR (D_2O, 121.47 MHz) δ 25.8 (dm, $^{1}J_{PH}$ = 527.5 Hz). HRMS (FAB) calcd. for $C_5H_{10}Na_2O_6P_2$ (M+H^+) 274.9826, found 274.9836.

Disodium (3,3-diethoxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 16). ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (d, $^{1}J_{PH}$ = 528.9 Hz, 2 H), 4.80 (t, J = 6.6 Hz, 1 H), 3.62 (q, J = 6.7 Hz, 2 H), 3.51 (q, J = 6.7 Hz, 2 H), 1.88-1.70 (m, 2 H), 1.65-1.55 (m, 1 H), 1.03 (t, J = 7.0 Hz, 6 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 23.1 (dm, $^{1}J_{PH}$ = 544.2 Hz). HRMS (FAB) calcd. for $C_7H_{16}Na_2O_6P_2$ ($M+Na^+$) 327.0115, found 327.0112.

Disodium (3-methoxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 17). ^{1}H NMR (D_2O, 300 MHz) δ 6.84 (d, $^{1}J_{PH}$ = 529.1 Hz, 2 H), 3.44 (t, $^{3}J_{HH}$ = 6.5 Hz, 2 H), 3.18 (s, 3 H), 1.90-1.65 (m, 2 H), 1.60-1.35 (m, 1 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 20.8, 40.3 (t, $^{1}J_{PC}$ = 76.2 Hz), 57.5, 71.0; ^{31}P NMR (D_2O, 121.47 MHz) δ 25.3 (dm, $^{1}J_{PH}$ = 529.6 Hz). HRMS (FAB) calcd. for $C_4H_{10}Na_2O_5P_2$, ($M+H^+$) 246.9877, found 246.9867.

Disodium (3-oxiranylmethoxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 18). ^{1}H NMR (D_2O, 300 MHz) δ 6.88 (d, $^{1}J_{PH}$ = 529.4 Hz, 2 H), 3.77 (dd, J = 2.0 Hz, J = 11.4 Hz, 1 H), 3.57 (t, $^{3}J_{HH}$ = 7.3 Hz, 2 H), 3.28-3.14 (m, 2 H), 2.78 (t, J = 4.0 Hz, 1 H), 2.61 (dd, J = 2.9 Hz, J = 4.4 Hz, 1 H), 1.92-1.72 (m, 2 H), 1.64-1.46 (m, 1 H); ^{13}C NMR (H_2O, 75.45 MHz) δ 21.3, 40.8 (t, $^{1}J_{PC}$ = 77.7 Hz), 45.2, 51.7, 70.3, 71.1; ^{31}P NMR (D_2O, 121.47 MHz) δ 23.3 (dm, $^{1}J_{PH}$ = 529.2 Hz). HRMS (FAB) calcd. for $C_6H_{12}Na_2O_6P_2$, ($M-2Na^+ + H^+$) 243.0187, found 243.0187.

Disodium [3-(3-amino-2-hydroxypropoxy)-propyl]-1,1-bis-*H*-phosphinate (Table 5.2, entry 19). ^{1}H NMR (D_2O, 300 MHz) broad peaks δ 6.86 (d, $^{1}J_{PH}$ = 527.1 Hz, 2 H), 4.00-3.70 (m, 1 H), 3.47 (dm, J = 35.8 Hz, 4 H), 3.02-2.81 (m, 2 H), 2.00-1.70 (m, 2 H), 1.68-1.40 (m, 1 H); ^{13}C NMR (H_2O, 75.45 MHz) broad peaks δ 21.0, 44.1 (t, $^{1}J_{PC}$ = 75.0 Hz), 50.7, 66.8, 70.9, 73.1; ^{31}P NMR (D_2O, 121.47 MHz) δ 27.9 (dm, $^{1}J_{PH}$ = 530.0 Hz). HRMS (FAB) calcd. for

$C_6H_{15}NNa_2O_6P_2$, ($M\text{-}Na^+ + 2H^+$) 306.0248, found 306.0243.

Disodium (3-phenoxy-propyl]-1,1-bis-*H*-phosphinate) (Table 5.2, entry 20). ^1H NMR (D_2O, 300 MHz) δ 7.23 (t, J = 7.6 Hz, 2 H), 7.00 (t, J = 7.6 Hz, 1 H), 6.93 (d, $^1J_{PH}$ = 529.7 Hz, 2 H), 6.90 (d, J = 7.3 Hz, 2 H), 4.10 (t, J = 7.3 Hz, 2 H), 2.12-1.94 (m, 2 H), 1.80-1.62 (m, 1 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.1 (dm, $^1J_{PH}$ = 529.9 Hz).

Disodium [3-(4-phenyl-phenoxy)-propyl]-1,1-bis-*H*-phosphinate (Table 5.2, entry 21). ^1H NMR (D_2O, 300 MHz) δ 7.57-7.53 (m, 4 H), 7.40-7.35 (m, 2 H), 7.26 (t, J = 6.2 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 2 H), 6.97 (dm, $^1J_{PH}$ = 529.7 Hz, 2 H), 4.17 (t, J = 6.9 Hz, 2 H), 2.15-2.01 (m, 2 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.1 (dm, $^1J_{PH}$ = 526.3 Hz). HRMS (ES) calcd. for $C_{15}H_{16}Na_2O_5P_2$, ($M+H^+$) 385.0346, found 385.0357.

Disodium (4-phenyl-butyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 22). ^1H NMR (D_2O, 300 MHz) δ 7.16 (bs, 5 H), 6.84 (d, $^1J_{PH}$ = 524.8 Hz, 2 H), 2.50 (t, $^3J_{HH}$ = 7.0 Hz, 2 H), 1.70-1.4 (m, 5 H); ^{13}C NMR (D_2O, 22.635 MHz) δ 21.3, 31.1, 35.4, 44.2 ((t, $^1J_{PC}$ = 77.7 Hz), 126.0, 128.7, 128.8, 142.9; ^{31}P NMR (D_2O, 121.47 MHz) δ 26.0, (dm, $^1J_{PH}$ = 527.5 Hz). HRMS (FAB) calcd. for $C_{10}H_{14}Na_2O_4P_2$, ($M+H^+$) 307.0241, found 307.0227.

Disodium (3-aminopropyl)-1,1-bis-*H*-phosphinate hydrochloride (Table 5.2, entry 23). ^1H NMR (D_2O, 300 MHz) δ 6.87 (d, $^1J_{PH}$ = 533.2 Hz, 2 H), 3.02 (t, $^3J_{HH}$ = 7.03 Hz, 2 H), 2.10-1.80 (m, 2 H), 1.66-1.43 (m, 1 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.8 (dm, $^1J_{PH}$ = 534.0 Hz). HRMS (FAB) calcd. for $C_3H_9NNa_2O_4P_2$, ($M\text{-}2Na^+ + H^+$) 186.0085, found 186.0086.

Disodium (3-aminopropyl)-1,1-bis-*H*-phosphinate trifluoroacetic acid (Table 5.2, entry 24). ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (d, $^{1}J_{PH}$ = 533.2 Hz, 2 H), 3.02 (t, $^{3}J_{HH}$ = 7.03 Hz, 2 H), 2.10-1.80 (m, 2 H), 1.66-1.43 (m, 1 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.8 (dm, $^{1}J_{PH}$ = 534.0 Hz). HRMS (ES) calcd. for $C_3H_9NNa_2O_4P_2$, ($M+H^+$) 232.9880, found 232.9880.

Disodium [*N*,*N*-(dicarbobenzyloxy)-aminobutyl]-1,1-bis-*H*-phosphinate (Table 5.2, entry 25). ^{1}H NMR (D_2O, 300 MHz) δ 6.80 (d, $^{1}J_{PH}$ = 526.8 Hz, 2 H), 2.27 (bs, 10 H), 5.11 (s, 4 H), 3.58 (t, $^{3}J_{HH}$ = 6.7 Hz, 2 H), 1.66-1.43 (m, 5 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.5 (dm, $^{1}J_{PH}$ = 526.0 Hz). HRMS (FAB) calcd. for $C_{20}H_{23}NNa_2O_8P_2$, ($M-2Na^+ + H^+$) 468.0977, found 468.0964.

Disodium (3-amino-3-cyclohexyl-ethyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 26). ^{1}H NMR (D_2O, 300 MHz) δ 6.88 (d, $^{1}J_{PH}$ = 533.8 Hz, 2 H), 2.09-1.88 (m, 2 H), 1.70-1.20 (m, 11 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.5 (dm, $^{1}J_{PH}$ = 536.1 Hz).

Disodium (pent-2-enyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 27). ^{1}H NMR (D_2O, 300 MHz) δ 6.83 (d, $^{1}J_{PH}$ = 529.8 Hz, 2 H), 5.60-5.50 (m, 1 H), 5.21-5.10 (m, 1 H), 2.00-1.82 (m, 3 H), 0.82 (t, *J* = 7.9 Hz, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 23.2 (dm, $^{1}J_{PH}$ = 518.1 Hz) and 22.6 (dm, $^{1}J_{PH}$ = 525.9 Hz).). HRMS (FAB) calcd. for $C_5H_{10}Na_2O_4P_2$, ($M+Na^+$) 264.9747, found 264.9747.

Disodium (3-benzyloxy-propyl)-1,1-bis-*H*-phosphinate (Table 5.2, entry 28). ^{31}P NMR (D_2O, 121.47 MHz) δ 25.2 (dm, $^{1}J_{PH}$ = 526.4 Hz). HRMS (FAB) calcd. for $C_{10}H_{14}Na_2O_5P_2$, ($M+H^+$) 323.0190, found 323.0191.

Disodium hexyl-1,1-bis-phosphonate (Eq. 5.5, Compound 125). Ozone was bubbled into a solution of disodium hexyl-1,1-bis-*H*-phosphinate (1.00 g, 3.88 mmol) in water (30 mL) at 0 ºC. The temperature of the solution was maintained between 0 ºC and 10 ºC during the reaction. After 6 h, the ice bath was removed and nitrogen was bubbled into the reaction mixture for 3 h to remove excess ozone. After concentration in vacuo, the residue was washed with cold methanol and dried over P_2O_5 to afford the disodium hexyl-1,1-bis-phosphonate (1.04 g, 92 %) as a white solid. ^{1}H NMR (D_2O, 300 MHz) δ 1.87-1.51 (m, 3 H), 1.41-1.31 (m, 2 H), 1.20-1.05 (m, 4 H), 0.68 (t, $^3J_{HH}$ = 7.03 Hz, 3 H); ^{13}C NMR (D_2O, 22.635 MHz) δ 12.3, 20.6, 24.3, 27.7 (t, $^2J_{PC}$ = 6.6 Hz), 29.9, 36.6 (t, $^1J_{PC}$ = 117.7 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 22.1 (s). HRMS (FAB) calcd. for $C_6H_{14}Na_2O_6P_2$, ($M-2Na^+ + H^+$) 245.0344, found 245.0354.

Representative Procedure for the Preparation of the Steroid Propargyl Carbonate (Scheme 5.14, Compound 126 and Table 5.3, Compound 129).

Esteronyl prop-2-ynyl carbonate 126 (Scheme 5.14). To a solution of estrone (1.57 g, 5.82 mmol) in CH_2Cl_2 (20 mL) at 0 ºC, was added pyridine (1.41 mL, 17.46 mmol). The solution was stirred at this temperature 5 min and propargyl chloroformate (0.58 mL, 5.99 mmol) was added dropwise. The resulting mixture was stirred overnight at room temperature and quenched by adding aqueous HCl (1 N). The solution was extracted with CH_2Cl_2 and the combined organic extracts were washed successively with saturated aq $NaHCO_3$ (3 x 100 mL) and brine (1 x 30 mL). Drying and concentration in vacuo afforded the desired compound which did not require further purification. Yield: 87%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, *J* = 8.4 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.93 (s, 1 H), 4.84 (s, 2 H), 3.01-2.75 (m, 2 H), 2.57 (s, 1 H), 2.55-1.95 (m, 7 H), 1.65-1.42 (m, 6 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 14.0, 21.8, 26.0, 26.5,

29.6, 31.7, 36.0, 38.1, 44.3, 48.1, 50.5, 56.0, 76.6, 77.0, 118.3, 121.1, 126.7, 138.1, 138.4, 149.1, 153.5, 220.7.

Epiandrosteronyl prop-2-ynyl carbonate 129 (Table 5.3, entry 1). Yield: 90%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (d, $^{4}J_{HH}$ = 2.4 Hz, 2 H), 4.59 (sp, J_{HH} = 5.3 Hz, 1 H), 2.52 (t, $^{4}J_{HH}$ = 2.3 Hz, 1 H), 2.44 (dd, $^{2}J_{HH}$ = 19.0 Hz, $^{3}J_{HH}$ = 8.5 Hz, 1 H), 2.17-1.12 (m, 21 H), 0.86 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 12.4, 14.0, 20.7, 22.0, 27.5, 28.4, 31.0, 31.7, 34.0, 35.2, 35.8, 36.1, 36.8, 44.8, 48.0, 51.5, 54.4, 55.2, 75.7, 76.8, 78.4, 154.2, 221.5. HRMS (EI^+) calcd. for $C_{23}H_{32}O_4$, 372.2301, found 372.2294.

Hydrocortisonyl prop-2-ynyl carbonate 129 (Table 5.3, entry 2). Yield: 86%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.68 (s, 1 H), 5.13 (d, *J* = 17.7 Hz, 1 H), 4.90 (d, *J* = 17.4 Hz, 1 H), 4.82-4.75 (m, 2 H), 4.49 (t, *J* = 2.7 Hz, 1 H), 2.86-2.72 (m, 1 H), 2.60-1.00 (m, 12 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 17.3, 21.2, 23.8, 31.6, 32.3, 32.9, 34.0, 35.0, 35.2, 39.5, 40.0, 47.9, 52.2, 56.0, 56.2, 68.4, 70.8, 71.1, 76.2, 77.1, 89.8, 154.7, 172.8, 200.1, 204.5.

Pregnenolonyl prop-2-ynyl carbonate 129 (Table 5.3, entry 3). Yield: 99%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.38 (bs, 1 H), 4.72 (d, *J* = 2.7 Hz, 2 H), 4.58-4.42 (m, 1 H), 2.54 (s, 1 H), 2.48-2.38 (m, 1 H), 2.14 (s, 3 H), 2.13-1.16 (m, 19 H), 1.02 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 19.4, 21.2 (2C), 22.9, 24.6, 27.8, 31.7, 31.9 (2C), 36.7, 37.0, 38.1, 38.9, 44.1, 50.0, 55.1, 56.9, 63.7, 75.9, 77.3, 78.5, 122.9, 139.4, 154.0, 209.4.

Nandrolonyl prop-2-ynyl carbonate 129 (Table 5.3, entry 4). Yield: 87%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (bs, 1 H), 4.78 (d, *J* = 2.7 Hz, 2 H), 4.57 (t, *J* = 9.0 Hz, 1 H), 2.57-1.02 (m, 21

H), 0.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 12.2, 23.4, 26.2, 26.8, 27.5, 30.8, 35.6, 36.7 (2C), 40.3, 42.7, 43.0, 49.5, 55.3, 56.0, 75.8, 76.2, 87.0, 124.9, 154.7, 166.5, 200.1.

Representative Procedure for the Preparation of the Steroid-1,1-bis-*H*-phosphinate (Scheme 5.14, Compound 127 and Table 5.3, Compound 130).

Esteronyl-1,1-bis-*H*-phosphinate conjugate 127 (Scheme 5.14). To a solution of $NaH_2PO_2.H_2O$ (1.91 g, 18.0 mmol) in a mixture of methanol (12.5 mL) and dioxane (2.5 mL) were added alkyne **126** (1.05 g, 3 mmol) and triethylborane (1.0 M in hexane, 3 mL, 3 mmol). The solution was stirred for 4 hours at room-temperature in a flask open to air and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the 1,1-bis-*H*-phosphinate sodium salt **127**. The filtrate was concentrated in vacuo and redissolved with the same mixture of methanol and dioxane. Sodium hypophosphite hydrate (18.0 mmol) and triethylborane (1.0 M in hexane, 3 mL, 3 mmol) were added and the resulting mixture was stirred again 4 hours at room-temperature. As previously, the resulting precipitate was washed several times with cold methanol, and dried over P_2O_5 to afford sodium salt **127** as a white solid. Yield: 52%. ^{1}H NMR (D_2O, 300 MHz) δ 7.21 (d, J = 8.1 Hz, 1 H), 6.89 (d, $^1J_{PH}$ = 530.4 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 1 H), 4.27 (t, J = 6.9 Hz, 2 H), 2.71 (bs, 2 H), 2.45-1.20 (m, 16 H), 0.73 (s, 3 H) ; ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (dm, $^1J_{PH}$ = 530.4 Hz). HRMS (FAB) calcd. for $C_{22}H_{28}Na_2O_8P_2$, ($M+H^+$) 529.1133, found 529.1135.

Epiandrosteronyl-1,1-bis-*H*-phosphinate conjugate 130 (Table 5.3, entry 1). Yield: 48%. ^{1}H NMR (D_2O, 300 MHz) δ 6.88 (d, $^1J_{PH}$ = 528.9 Hz, 2 H), 4.41 (bs, 2 H), 4.14 (bs, 2 H), 2.33 (dd, $^2J_{HH}$ = 19.3 Hz, $^3J_{HH}$ = 9.6 Hz, 1 H), 2.1-0.50 (m, 23 H), 0.72 (s, 3 H), 0.69 (s, 3 H); ^{13}C NMR

(D_2O, 75.45 MHz) δ 11.9, 13.7, 20.5, 21.0, 21.7, 27.2, 28.2, 30.8, 31.4, 33.7, 34.9, 35.4, 36.0, 36.5, 40.7 (t, $^1J_{PC}$ = 77.6 Hz), 44.4, 48.4, 51.1, 54.1, 67.3, 78.4; ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (dm, $^1J_{PH}$ = 529.5 Hz). HRMS (FAB) calcd. for $C_{23}H_{36}Na_2O_8P_2$, (M-2Na^++H^+) 503.1963, found 503.1975.

Hydrocortisonyl-1,1-bis-*H*-phosphinate conjugate 130 (Table 5.3, entry 2). Yield: 85%. ^{1}H NMR (D_2O, 300 MHz) δ 7.01 (d, $^1J_{PH}$ = 530.0 Hz, 2 H), 5.62 (s, 1 H), 5.06 (d, *J* = 18.2 Hz, 1 H), 4.86 (d, *J* = 18.2 Hz, 1 H), 4.35 (s, 1 H), 4.24 (t, *J* = 7.0 Hz, 1 H), 2.55-1.00 (m, 26 H), 0.71 (s, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.8 (dm, $^1J_{PH}$ = 530.0 Hz). HRMS (ESI) calcd. for $C_{23}H_{36}Na_2O_{11}P_2$, (M+$H^+$) 621.1606, found 621.1602.

Pregnenolonyl-1,1-bis-*H*-phosphinate conjugate 130 (Table 5.3, entry 3). Yield: 86%. ^{1}H NMR (D_2O, 300 MHz) δ 6.90 (d, $^1J_{PH}$ = 530.4 Hz, 2 H),5.37 (bs, 1 H), 5.40-5.35 (m, 1 H), 4.18 (t, *J* = 6.9 Hz, 2 H), 2.62 (t, *J* = 7.2 Hz, 1 H), 2.31-2.22 (m, 2 H), 2.06 (s, 3 H), 1.99-1.70 (m, 6 H), 1.63-1.51 (m, 7 H), 1.43-1.35 (m, 4 H), 1.13-1.01 (m, 3 H), 0.90 (s, 3 H), 0.46 (s, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.1 (dm, $^1J_{PH}$ = 530.8 Hz). HRMS (ESI) calcd. for $C_{25}H_{38}Na_2O_8P_2$, (M-2Na^++H^+) 529.2120, found 529.2119.

Nandrolonyl-1,1-bis-*H*-phosphinate conjugate 130 (Table 5.3, entry 4). Yield: 56%. ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (d, $^1J_{PH}$ = 531.0 Hz, 2 H), 4.45-4.32 (m, 1 H), 4.14 (t, *J* = 7.2 Hz, 2 H), 2.42-0.85 (m, 24 H), 0.65 (s, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (dm, $^1J_{PH}$ = 530.8 Hz). HRMS (ESI) calcd. for $C_{22}H_{32}Na_2O_8P_2$, (M+H^+) 533.1446, found 533.1457.

Representative Procedure for the Preparation of the Steroid-1,1-Bisphosphonate (Scheme 5.14, compound 128 and Table 5.3, compound 131).

Esteronyl-1,1-bisphosphonate conjugate 128 (Scheme 5.14). To a solution of **127** (196 mg, 0.37 mmol) in water (15 mL), at 0 ºC, was bubbled ozone. The temperature of the solution was maintained between 0 ºC and 10 ºC during the reaction. After 1.5-3 h, the ice bath was remove and nitrogen was bubbling into the reaction mixture during 3 h to remove excess ozone. After concentration in vacuo, the residue was washed with cold methanol and dried over P_2O_5 to afford the disodium 1,1-bisphosphonate as a white solid. Yield: 89%. ^{31}P NMR (D_2O, 121.47 MHz) δ 21.9 (bs).

Epiandrosteronyl-1,1-bisphosphonate conjugate 131 (Table 5.3, entry 1). Yield: 79%. ^{1}H NMR (D_2O, 300 MHz) δ 4.40 (bs, 2 H), 4.16 (t, $^3J_{HH}$ = 6.4 Hz, 2 H), 2.31 (dd, $^2J_{HH}$ = 19.6 Hz, $^3J_{HH}$ = 10.8 Hz, 1 H), 2.03-0.50 (m, 23 H), 0.70 (s, 3 H), 0.67 (s, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (bs). HRMS (FAB) calcd. for $C_{23}H_{36}Na_2O_{10}P_2$, ($M-2Na^+ + H^+$) 535.1862, found 535.1861.

Hydrocortisonyl-1,1-bisphosphonate conjugate 131 (Table 5.3, entry 2). Yield: 97%. ^{1}H NMR (D_2O, 300 MHz) δ 5.60 (s, 1 H), 5.05 (d, J = 18.5 Hz, 1 H), 4.77 (d, J = 18.5 Hz, 1 H), 4.23 (bs, 4 H), 2.80-0.98 (m, 25 H), 0.79-0.68 (m, 1 H), 0.50 (s, 3 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 20.3 (bs).

Pregnenolonyl-1,1-bisphosphonate conjugate 131 (Table 5.3, entry 3). Yield: 47%. ^{31}P NMR (D_2O, 121.47 MHz) δ 20.4 (bs).

Nandrolonyl-1,1-bisphosphonate conjugate 131 (Table 5.3, entry 4). ^{31}P NMR (D_2O, 121.47 MHz) δ 17.9 (bs).

Preparation of Squalene Synthase inhibitor 134 (Scheme 5.15).[277,278] To a vigorously stirred solution of NaI (4.53 g, 30.2 mmol) and 4-biphenylmethanol (2.79 g, 15.1 mmol) in acetonitrile (60 mL) under N_2 is added methanesulphonic acid (2.9 g, 30.2 mmol) in 15 mL of acetonitrile with a syringe at room temperature.[277] The reaction mixture was allowed to stir for 1 h, then quenched with water, and extracted with diethyl ether. The organic layer was washed with 10% sodium thiosulphate solution and dried over anhydrous magnesium sulfate. Upon evaporation, crude iodide was obtained. This was purified by column chromatography on silica gel by eluting with hexane/EtOAc (8:2, v/v), giving the corresponding iodide compound (4.12 g, 93%). HRMS (FAB) calcd. for $C_{13}H_{11}I$, ($M+H^+$) 293.9906, found 293.9911. To a solution of trimethylsilyl propyne (1.51 mL, 10.2 mmol) in THF (20 mL), under nitrogen and at -20 °C, is added *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (1.52 mL, 10.2 mmol) and *n*-BuLi (1.6 M in hexane, 6.8 mL, 10.9 mmol). The yellowish solution was stirred at -20 °C to -15 °C for 4 h. After this time, the solution of iodide compound (2 g, 6.8 mmol) in THF (10 mL) was added to the previous solution mixture and stirred for 1 h at - 20 °C, then overnight at room temperature. The reaction mixture was quenched with aq. NH_4Cl and extracted with diethyl ether. The organic layer was washed with 1 N HCl (x1),with water (x2), with $NaHCO_3$ (x1), then with saturated NaCl (x1) and dried over anhydrous magnesium sulphate. The crude was purified by column chromatography on silica gel by eluting with hexane, giving the corresponding 4-(4-biphenyl)-1-trimethylsilyl-1-butyne in 80% yield. To a solution of 4-(4-biphenyl)-1-trimethylsilyl-1-butyne (1.8 g, 6.5 mmol) in THF (5 mL) was added a solution of TBAF (3.37 g, 12.9 mmol) in THF (13

mL) under nitrogen and the reaction mixture was stirred at room temperature for 3 h (reaction monitored by TLC).[278] After this time, 10 mL of water was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (x1) then with brine and dried over anhydrous magnesium sulfate, affording the alkyne **132** in 87% isolated yield. ^{13}C NMR (CDCl3, 75.45 MHz) δ 18.2, 32.1, 66.7, 81.4, 124.7 (2C), 124.8, 124.9 (2C), 126.4 (2C), 126.5 (2C), 137.0, 137.2, 138.6; HRMS (FAB) calcd. for $C_{16}H_{14}$, ($M+H^+$) 206.1096, found 206.1088. To a solution of $NaH_2PO_2.H_2O$ (33.5 mmol) in a mixture of methanol (23 mL) and dioxane (5 mL) were added the alkyne **132** (5.6 mmol) and triethylborane (1.0 M in hexane, 5.6 mL, 5.6 mmol). The solution was stirred for 4 h at room-temperature in a flask open to air, and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the 1,1-bis-*H*-phosphinate sodium salt **133**. The filtrate was concentrated in vacuo and redissolved with the same mixture of methanol and dioxane. Sodium hypophosphite hydrate (33.5 mmol) and triethylborane (1.0 M in hexane, 5.6 mL, 5.6 mmol) were added and the resulting mixture was stirred again 4 h at room-temperature. As previously, the resulting precipitate was washed several times with cold methanol, and dried over P_2O_5 to afford sodium salt **133** (1.43 g, 67%) as a white solid. ^1H NMR (D_2O, 300 MHz) δ 7.54-7.46 (m, 4 H), 7.38-7.32 (m, 2 H), 7.26-7.22(m, 1H), 7.25 (d, J = 7.6 Hz, 2 H), 6.85 (d, $^1J_{PH}$ = 523.6 Hz, 2 H), 2.55 (t, J = 7.0 Hz, 2 H), 1.80-1.42 (m, 5 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 26.4 (dm, $^1J_{PH}$ = 521.8 Hz). HRMS (ES) calcd. for $C_{16}H_{18}Na_2O_4P_2$, ($M-2Na^+ + H^+$) 337.0759, found 337.0760. To a solution of **133** (180 mg, 0.47 mmol) in water (15 mL), at 0 ºC, was bubbled ozone. The temperature of the solution was maintained between 0 ºC and 10 ºC during the reaction. After 4.5 h, the ice bath was remove and nitrogen was bubbling into the reaction mixture during 3 h to get rid of the excess of ozone. After concentration under vacuum, the residue was washed with cold methanol and dried over P_2O_5 to afford the disodium 1,1-bisphosphonate **134** (99 mg, 51%) as a

white solid (96% purity on ^{31}P NMR). ^{31}P NMR (D_2O, 121.47 MHz) δ 19.6 (bs).

Preparation of Fluoroquinolonyl-1,1-Bis-*H*-Phosphinate (Scheme 5.17, Compound 136). The starting material norfloxacin ethyl ester, called 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid ethyl ester, was prepared following the literature procedure.[253] To an ice-cooled mixture of norfloxacin (1.0 g, 3.13 mmol) and absolute ethanol (31.3 mL) was added dropwise $SOCl_2$ (4.37 mL, 62.6 mmol), under nitrogen. The misture was refluxed for 12.5 h and evaporated until dryness. The residue was made basic with aqueous K_2CO_3 and extracted with CH_2Cl_2. After working up, the solid was crystallized from CH_3CN, affording the corresponding norfloxacin ethyl ester in 86% isolated yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 8.10 (d, J_{HF} = 13.5 Hz, 1 H), 6.74 (d, J_{HF} = 6.6 Hz, 1 H), 4.40 (q, J = 8.1 Hz, 2 H), 4.22 (q, J = 7.5 Hz, 2 H), 3.30 – 3.20 (m, 4 H), 3.12 – 3.09 (m, 4 H), 1.55 (t, J = 7.2 Hz, 3 H), 1.42 (t, J = 7.2 Hz, 3 H), 1.23 (s, 1 H, NH). To a solution of disodium (3-oxiranylmethoxy-propyl)-1,1-bis-*H*-phosphinate (114.5 mg, 0.4 mmol) in a solvent mixture of THF/H_2O (2:1, C = 0.5 M) placed under nitrogen, was added a catalytic amount of $Yb(OTf)_3$ (2.5 mol%). After complete dissolution of the 1,1-bis-*H*-phosphinate (3 min), the norfloxacin ester was added and the reaction mixture was stirred under nitrogen, at room temperature for 14 h. After evaporation of the volatiles, the residue was partitioned between deionized H_2O and $CHCl_3$ and the organic layer was extracted several times by deionized H_2O (4 x 20 mL). The combined aqueous layer was concentrated in vacuo, affording the desired product **136** (238 mg, 94%). ^1H NMR (D_2O, 300 MHz) δ 8.54 (bs, 1 H), 7.64 (d, J_{HF} = 13.3 Hz, 1 H), 6.94 (bs, 1 H), 6.88 (d, $^1J_{PH}$ = 527.7 Hz, 2 H), 4.40-4.01 (m, 4 H), 3.68-2.80 (m, 16 H), 2.00-1.78 (m, 2 H), 1.72-1.48 (m, 1 H), 1.40-1.14 (m, 6 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 25.1 (dm, $^1J_{PH}$ = 532.4 Hz). HRMS (ES^+) calcd. for $C_{24}H_{34}FN_3Na_2O_9P_2$, ($M+H^+$) 592.1989, found 592.1990.

Synthesis of the β-D-Glucopyranosyl-1,1-Bis-Phosphonate Conjugate (Scheme 5.18).[246c]

2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 138 (Scheme 5.18). To a solution of β-D-glucopyranose pentaacetate (**137**) (5 g, 12.8 mmol, 1 equiv) in CH_2Cl_2 was added propargyl alcohol (1.12 mL, 19.22 mmol, 1.5 equiv) and BF_3•Et_2O (2.44 mL, 19.22 mmol, 1.5 equiv) and the mixture then stirred at room temperature for 12 h (reaction monitored by TLC). Powdered anhydrous K_2CO_3 (2.42 g) was added and stirring continued for 30 min. The reaction mixture was then filtered, the filtrate washed with deionized H_2O (3 x 200 mL) and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was obtained in quantitative yield (4.94 g, 12.8 mmol) as a pale yellowish syrup and used directly for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.25 (t, J = 9.3 Hz, 1H), 5.10 (t, J = 9.9 Hz, 1H), 5.02 (t, J = 7.8 Hz, 1H), 4.79 (d, J = 8.5 Hz, 1H), 4.38 (d, J = 2.3 Hz, 2 H), 4.34-4.25 (m, 1 H), 4.17-4.12 (m, 1 H), 3.78-3.72 (m, 1 H), 2.52 (t, J = 2.4 Hz, 1 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H).

2-propynyl 2,3,4,6-tetra-*O*-hydroxyl-β-D-glucopyranoside 139 (Scheme 5.18). To a solution of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **138** (4.95 g, 12.8 mmol, 1 eq) in MeOH (25 mL) was added sodium methoxide (208 mg, 3.85 mmol, 0.3 eq). The resulting mixture was stirred for 2 h 30 min (reaction monitored by TLC) then the pH of the medium was adjusted to 7.0 by addition of anhydrous Amberlite ion-exchange resin IRA-400 with the aid of paper pH indicator. The resin was removed by filtration, the filtrate concentrated under reduced pressure, affording the desired product in quantitative yield (2.80 g, 12.8 mmol). ^{1}H NMR (D_2O, 300 MHz) δ 4.44 (d, J = 7.9 Hz, 1 H), 4.27 (d, J = 1.5 Hz, 2 H), 3.72 (d, J = 2.3 Hz, 1 H), 3.56-3.48 (m, 1 H), 3.34-3.18 (m, 4 H), 3.15 (s, 4 H), 3.14-3.06 (m, 1 H).

Disodium[(2,3,4,6-tetra-*O*-hydroxyl-β-D-glucopyranosyl)-propyl]-1,1-bis-*H*-phosphinate 140 (Scheme 5.18). To a solution of $NaH_2PO_2 \bullet H_2O$ (8.14 g, 76.8 mmol, 6 eq) in a mixture of methanol (21.5 mL) and dioxane (4.5 mL) were added the propargyl-β-D-glucopyranoside **139** (2.80 g, 12.8 mmol, 1 eq) and triethylborane (1.0 M in hexane, 12.8 mL, 12.8 mmol). The solution was stirred for 4 h at room-temperature in a flask open to air, and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the 1,1-bis-*H*-phosphinate sodium salt as a white solid (1.51 g, 33%). Mp: > 250 °C (dec). ^{1}H NMR (D_2O, 300 MHz) δ 6.88 (d, $^1J_{PH}$ = 530.0 Hz, 2 H), 4.32 (d, J = 7.9 Hz, 1 H), 3.90 (q, J = 9.9 Hz, 1 H), 3.75-3.62 (m, 2 H), 3.57-3.50 (m, 1 H), 3.35-3.07 (m, 4 H), 1.92-1.72 (m, 2 H), 1.69-1.56 (m, 1 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 97.3, 71.1 (2C), 68.4, 65.0 (2C), 54.6, 35.7 (t, $^1J_{PC}$ = 79.9 Hz), 16.9; ^{31}P NMR (D_2O, 121.47 MHz) δ 23.2 (dm, $^1J_{PH}$ = 513.6 Hz); HRMS (ES^+) calcd for $C_9H_{18}Na_2O_{10}P_2$, (M + H) 395.0249, found 395.0239.

Disodium[(2,3,4,6-tetra-*O*-hydroxyl-β-D-glucopyranosyl)-propyl]-1,1-bis-phosphonate 141 (Scheme 5.18). To a solution of **140** (677 mg, 1.72 mmol) in deionized water (15 mL), at 0 °C, was bubbled ozone. The temperature of the solution was maintained between 0 °C and 10 °C during the reaction. After 4 h 30, the ice bath was removed and nitrogen was bubbling into the reaction mixture during 3h to remove excess ozone. After concentration under vacuum, the residue was washed with cold methanol and dried over P_2O_5 to afford the disodium 1,1-bis-phosphonate **141** (630 mg, 86%) as a white solid. Mp: > 250 °C (dec). ^{1}H NMR (D_2O, 300 MHz) δ 4.32 (d, J = 7.9 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.78-3.48 (m, 3 H), 3.50-3.07 (m, 4 H), 2.03-1.77 (m, 3 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 102.7, 75.9, 73.3, 69.8, 62.8, 54.3, 35.5 (t, J_{PC} = 122.8

Hz), 28.9 (d, J_{PCC} = 141.53 Hz), 17.0 (d, J_{PCCC} = 92.6 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 20.82 (s); HRMS (ES^+) calcd for $C_9H_{18}Na_2O_{12}P_2$, (M + H) 427.0147, found 427.0145.

Synthesis of the β-D-Galactopyranosyl-1,1-Bis-Phosphonate Conjugate (Scheme 5.19).

2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside 143 (Scheme 5.19). To a solution of β-D-galactopyranose pentaacetate (**142**) (5 g, 12.8 mmol, 1 eq) in CH_2Cl_2 was added propargyl alcohol (1.12 mL, 19.22 mmol, 1.5 eq) and BF_3•Et_2O (2.44 mL, 19.22 mmol, 1.5 eq) and the mixture then stirred at room temperature for 12 h (reaction monitored by TLC). Powdered anhydrous K_2CO_3 (2.42 g) was added and stirring continued for 30 min. The reaction mixture was then filtered, the filtrate washed with water (3 x 200 mL) and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was obtained in quantitative yield (4.93 g, 12.8 mmol) as a pale yellowish syrup and used directly for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41 (broad d, J = 2.4 Hz, 1 H), 5.26 (dd, J = 2.1 Hz, J = 10.2 Hz, 1 H), 5.22 (d, J = 2.1 Hz, 1 H), 5.10 (d, J = 2.1 Hz, 1 H), 4.40 (d, J = 2.3 Hz, 2 H), 4.24-4.12 (m, 3 H), 2.48 (t, J = 2.3 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.00 (s, 3 H).

2-propynyl 2,3,4,6-tetra-*O*-hydroxyl-β-D-galactopyranoside 144 (Scheme 5.19).[255b] To a solution of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **144** (2.78 g, 7.20 mmol, 1 eq) in MeOH (25 mL) was added sodium methoxide (117 mg, 2.16 mmol, 0.3 eq). The resulting mixture was stirred for 2 h 30 min (reaction monitored by TLC) then the pH of the medium was adjusted to 7.0 by addition of anhydrous Amberlite ion-exchange resin IRA-400 with the aid of paper pH indicator. The resin was removed by filtration, the filtrate concentrated under reduced pressure, affording the desired product in quantitative yield (1.57 g, 7.20 mmol). ^{1}H NMR (D_2O,

300 MHz) δ 4.37 (d, J = 7.9 Hz, 1 H), 4.28 (t, J = 2.1 Hz, 2 H), 3.73 (d, J = 3.5 Hz, 1 H), 3.60-3.42 (m, 4 H), 3.36-3.30 (m, 1 H), 2.75 (t, J = 2.7 Hz, 1 H).

Disodium[(2,3,4,6-tetra-*O*-hydroxyl-β-D-galactopyranosyl)-propyl]-1,1-bis-*H*-phosphinate 145 (Scheme 5.19). To a solution of $NaH_2PO_2 \bullet H_2O$ (3.36 g, 31.7 mmol, 6 eq) in a mixture of methanol (21.5 mL) and dioxane (4.5 mL) were added the propargyl-β-D-glucopyranoside **144** (1.57 g, 5.28 mmol, 1 eq) and triethylborane (1.0 M in hexane, 5.3 mL, 5.28 mmol). The solution was stirred for 4 h at room-temperature in a flask open to air, and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the the 1,1-bis-*H*-phosphinate sodium salt as a white solid (2.93 g, 64%). Mp: > 250 °C (dec). ^{1}H NMR (D_2O, 300 MHz) δ 6.87 (d, $^1J_{PH}$ = 530.3 Hz, 2 H), 4.25 (d, J = 7.8 Hz, 1 H), 3.90 (q, J = 10.2 Hz, 1 H), 3.80-3.31 (m, 7 H), 2.01-1.80 (m, 2 H), 1.78-1.56 (m, 1 H); ^{13}C NMR (H_2O, 22.635 MHz) δ 97.3, 71.2 (2C), 68.5, 64.8 (2C), 56.1, 35.8 (t, $^1J_{PC}$ = 80.0 Hz), 15.8; ^{31}P NMR (D_2O, 121.47 MHz) δ 23.3 (dm, $^1J_{PH}$ = 542.6 Hz); HRMS (ES^+) calcd for $C_9H_{18}Na_2O_{10}P_2$, ($M + H^+$) 395.0249, found 395.0246.

Disodium[(2,3,4,6-tetra-*O*-hydroxyl-β-D-galactopyranosyl)-propyl]-1,1-bis-phosphonate 146 (Scheme 5.19). To a solution of **145** (500 mg, 1.27 mmol) in deionized H_2O (15 mL), at 0 °C, was bubbled ozone. The temperature of the solution was maintained between 0 °C and 10 °C during the reaction. After 4 h 30, the ice bath was removed and nitrogen was bubbling into the reaction mixture during 3 h to remove excess ozone. After concentration under vacuum, the residue was washed with cold methanol and dried over P_2O_5 to afford the disodium 1,1-bis-phosphonate **146** (564 mg, 77%) as a white solid. Mp: > 250 °C (dec). ^{1}H NMR (D_2O, 300 MHz)

δ 4.31 (d, J = 8.2 Hz, 1 H), 3.89-3.39 (m, 4 H), 3.36-3.00 (m, 3 H), 2.63-2.50 (m, 1 H), 1.97-1.75 (m, 3H); ^{31}P NMR (D_2O, 121.47 MHz) δ 20.2 (bs).

Synthesis of the Ribofuranosyl-1,1-Bis-Phosphonate Conjugate (Scheme 5.20, Compound 151). At room temperature, iodine (0.150 g, 0.6 mmol) is added to a stirred suspension of D-(-)-ribose (3.0 g, 20 mmol) in acetic anhydride (15 mL). The reaction mixture rapidly began to warm up and the sugar started to go into solution. A dark amber colored solution was obtained and the reaction was followed by TLC until completion. The reaction mixture was poured into a separating funnel containing sodium thiosulfate, CH_2Cl_2, and crushed ice and was shaken thoroughly. The colorless organic layer thus obtained was then transferred to another separating funnel containing aqueous sodium carbonate. The residual aqueous layer in the first separting funnel was then extracted with CH_2Cl_2 (x2) and the combined organic layers were washed with sodium carbonate to neutrality, then dried over magnesium sulfate and concentration in vacuo affording the compound **148** as a colorless syrup in quantitative yield (6.4 g, 20 mmol). To a solution of **148** (3 g, 9.42 mmol, 1 eq) in CH_2Cl_2 was added propargyl alcohol (0.82 mL, 14.1 mmol, 1.5 eq) and BF_3•Et_2O (1.79 mL, 14.1 mmol, 1.5 eq) and the mixture then stirred at room temperature for 12 h (reaction monitored by TLC). Powdered anhydrous K_2CO_3 (1.45 g) was added and stirring continued for 30 min. The reaction mixture was then filtered, the filtrate washed with water (3 x 30 mL) and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue **149** (2.76 g, 93%) was obtained as a pale orange syrup and used directly for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40-5.36 (m, 1 H), 5.22-5.18 (m, 1 H), 5.09-5.04 (m, 1 H), 4.36-4.25 (m, 3 H), 4.01 and 3.81 (AB part of ABX system, J = 5.2 Hz, 5.2 Hz, J = 12.9 Hz, 2 H), 2.15-2.05 (3s, 9 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 20.7 (3C), 54.8, 63.8, 75.1 (3C), 77.5, 78.7, 103.1, 169.8

(3C). To a solution of **149** (2.76 g, 8.76 mmol, 1 eq) in MeOH (29 mL) was added sodium methoxide (142 mg, 2.63 mmol, 0.3 eq). The resulting mixture was stirred for 2 h (reaction monitored by TLC) then the pH of the medium was adjusted to 7.0 by addition of anhydrous Amberlite ion-exchange resin IRA-400 with the aid of paper pH indicator. The resin was removed by filtration, the filtrate concentrated under reduced pressure, affording the desired product **150** (1.30 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.11-5.01 (m, 2 H), 4.52-4.20 (m, 3 H), 4.01-3.68 (m, 3 H), 3.46 (s, 3 H), 2.57 (s, 1 H). To a solution of $NaH_2PO_2 \bullet H_2O$ (3.38 g, 31.9 mmol, 6 eq) in a mixture of methanol (23 mL) and dioxane (4 mL) were added **150** (1 g, 5.31 mmol, 1 eq) and triethylborane (1.0 M in hexane, 5.3 mL, 5.31 mmol). The solution was stirred for 4 h at room-temperature in a flask open to air, and then filtered. The precipitate was washed several times with cold methanol and dried in vacuo over P_2O_5 to afford the the 1,1-bis-*H*-phosphinate sodium salt **151** as a white solid (636 mg, 33%). ^{1}H NMR (D_2O, 400 MHz) δ 7.04 (d, $^{1}J_{PH}$ = 530.0 Hz, 2 H), 4.22-3.61 (m, 8 H), 2.10-1.92 (m, 2 H), 1.82-1.68 (m, 1 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 23.2 (dm, $^{1}J_{PH}$ = 527.5 Hz).

Diisopropyl hexyl-1,1-bis-*H*-phosphinate (Eq. 5.6, Compound 152). To a suspension of hexyl-1,1-bis-*H* phosphinate (500 mg, 1.94 mmol) in toluene (25 ml) under N_2 was added trimethylacetyl chloride (0.86 mL, 7.76 mmol) and isopropyl alcohol (1.19 mL, 15.52 mmol) at room temperature. The resulting solution was stirred for 24 h then concentrated in vacuo. The residue was partitioned between EtOAc and H_2O, the organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated, and purified by silica gel chromatography (100 % EtOAc, v/v, EtOAc/MeOH 1:1) to afford the ester (359 mg, 62 %) as a colorless oil: ^{1}H NMR (D2O, 300 MHz) δ 7.30 (dm, 2 H), 4.70 (bs, 2 H), 2.30-1.40 (m, 9 H), 1.35 (bs, 12 H), 0.90 (bs,

3 H); ^{13}C NMR (D2O, 75.45 MHz) δ 14.1, 22.3, 23,4, 24.3, 28.6 (t, $^{3}J_{PC}$ = 6.9 Hz), 31.7, 39.7 (t, $^{1}J_{PC}$ = 84.3 Hz), 50.4; ^{31}P NMR (D_2O, 121.47 MHz) δ 29.76 (dm, $^{1}J_{PH}$ = 568.7 Hz), 29.78 (dm, $^{1}J_{PH}$ = 568.7 Hz), 30.29 (dm, $^{1}J_{PH}$ = 565.9 Hz), 31.38 (dm, $^{1}J_{PH}$ = 569.1 Hz). HRMS (FAB) HRMS (FAB) calcd. for $C_{12}H_{28}O_4P_2$, ($M+H^+$) 299.1541, found 299.1536.

General Procedure for the Preparation of Bisphosphonate Dibenzyl Esters Extractants (Table 5.4, Compound 155). To a solution of disodium octyl-1,1-bis-*H*-phosphinate (1.0 g, 3.5 mmol, 1 eq) in freshly distilled toluene (35 mL), were added Et_3N (2.92 mL, 21.0 mmol, 6 eq), HMDS (1.82 mL, 8.74 mmol, 2.5 eq), TMSCl (1.10 mL, 8.74 mmol, 2.5 eq), and the alkyl dihalide (3.84 mmol, 1.1 eq) at 0 °C, under N_2. The reaction mixture was allowed to warm up to room temperature, then stirred at reflux for 14-16 h. After this time, the reaction mixture was cooled and quenched by addition of cold MeOH (20 mL). (^{31}P NMR of the crude, compounds **153**: entry 1, δ 47.8 ppm; entry 2, δ 38.9 ppm; entry 3, δ 34.1 ppm). The crude mixture was concentrated by rotary evaporation (40 °C, 0.5 mmHg) [*Note: extensive foaming took place*] and the solid washed several times with $CHCl_3$. The solid **153** (1.0 g) was put in suspension in MeOH (15-20 mL) with approximately 5 g of Amberlite and stirred vigorously at room temperature, in a flask open to air for 1 - 2 h depending on the nature of **153**. The solid dissolved as the reaction proceed and after filtration and evaporation of the volatiles, a clear amber syrup was obtained. (^{31}P NMR of the crude, compounds **154**: entry 1, δ 56.05 ppm; entry 2, δ 48.2 ppm; entry 3, δ 42.3 ppm). To a solution of **154** (1 eq) in $CHCl_3$ (10 mL), at rt and under N_2 atmosphere, was added benzylbromide (4 eq). Silver oxide (4 eq) was added to the reaction mixture in 5 portions (every 30 min) and stirred at reflux. After cooling down to rt, the crude mixture was filtered through celite and the filtrate was then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/ Hexanes, 1:9 then 1:0; then

EtOAc/MeOH, 8:2), affording **155** as a pale creme powder.

Dibenzyl hexyl-(ethyl)-1,1-bis-phosphonate 155 (Table 5.4, entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.22 (m, 10 H), 5.20-4.82 (m, 4 H), 2.20-1.76 (m, 4 H), 1.60-1.40 (m, 1 H), 1.38-1.00 (m, 12 H), 0.94-0.78 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) broad peaks δ 14.4 (2C), 22.9 (2C), 24.1, 29.2 (2C), 31.9 (2C), 35.1, 66.9 (2C), 128.4-128.8 (10C), 136.0 (2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 57.6 (bs), 58.3 (bs), 59.3 (bs), 60.3 (bs).

Dibenzyl hexyl-(propyl)-1,1-bis-phosphonate 155 (Table 5.4, entry 2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.22 (m, 10 H), 5.20-4.90 (m, 4 H), 2.20-1.00 (m, 17 H), 0.89-0.85 (m, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 50.4 (bs), 51.1 (bs), 51.5 (bs), 51.9 (bs).

Dibenzyl hexyl-(*o*-xylylene)-1,1-bis-phosphonate 155 (Table 5.4, entry 3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-6.86 (m, 14 H), 5.22-4.90 (m, 4 H), 3.50-3.12 (m, 4 H), 2.00-1.08 (m, 13 H), 0.92-0.78 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) broad peaks δ 14.3 (2C), 22.8 (3C), 29.1 (2C), 29.5, 29.8, 30.1 (d, J_{PC} = 86.0 Hz, 2C), 31.9 (2C), 37.3 (t, J_{PC} = 87.8 Hz), 66.9 (d, J_{POC} = 23.6 Hz, 2C), 127.9 (2C), 128.4 (4C), 128.7 (6C), 130.9 (2C), 136.3 (2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 43.8 (bs), 38.9 (bs), 43.8 (bs), 45.8 (bs).

Representative Procedure for the Synthesis of Bisphosphonous Dichloride (Table 5.5, Compound 156). A three-necked flask fitted with reflux condenser was charged with the disodium alkyl-1,1-bis-*H*-phosphinate salt (5.0 g, 0.019mol). PCl_3 (34 mL, 0.388 mmol) was added slowly at 0 ºC under N_2 and the resulting solution was stirred vigorously at room temperature for 1 h, refluxed for 2 h, and then left overnight at rt. The disodium salt dissolved

slowly while a precipitate was formed. The remaining solution was filtered under N_2, the excess of PCl_3 was distilled from the filtrate, and the residue was distilled cautiously under vacuum.

Hexyl-1,1-bisphosphonous dichloride (Table 5.5, entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.77 (m, 1 H), 2.22-2.04 (m, 2 H), 1.71-1.58 (m, 2 H), 1.44-1.10 (m, 4 H), 0.92 (t, $^3J_{HH}$ = 7.3 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 187.2 (s).

Octyl-1,1-bisphosphonous dichloride (Table 5.5, entry 2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02-3.80 (m, 1 H), 2.86-2.72 (m, 1 H), 2.22-2.12 (m, 2 H), 1.75-1.58 (m, 2 H), 1.49-1.10 (m, 9 H), 0.92 (t, $^3J_{HH}$ = 7.3 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 187.3 (s).

(3-acetoxypropyl)-1,1-bisphosphonous dichloride (Table 5.5, entry 3). The representative procedure was followed but in this case, after removing the excess of PCl_3 by distillation, the residue was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37 (m, 2 H), 3.00 (m, 1 H), 2.61-2.49 (m, 4 H), 2.10 (bs, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 185.0 (s).

Representative Procedure for the Preparation of Bisphosphine-Boranes (Table 5.5, Compound 157). To a cooled solution (-78 ºC) of alkyl-1,1-bisphosphonous dichloride **156** (0.69 mmol, 1 eq) in anhydrous THF (2 mL), under N_2, was added dropwise RMgCl (5.52 mmol, 8 eq). The mixture was allowed to gradually warm up to r.t. and stirred overnight. The conversion of the reaction was checked by ^{31}P NMR. BH_3•Me_2S (2.76 mL, 5.52 mmol, 2.0 M in THF) was added carefully and the remaining solution was stirred for additional 5 h, then concentrated under vacuum. The residue was partitioned between EtOAc and water (water was added carefully). The organic phase was separated and the aqueous layer extracted with EtOAc.

Combined organic extracts were washed successively with water and brine, dried over $MgSO_4$ and concentrated. A purification by chromatography over a silica gel column (100 % toluene) afforded the adduct **157** as a white solid.

Bisphosphine-borane (Table 5.5, entry 1a). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.5 (s).

Bisphosphine-borane (Table 5.5, entry 1b): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (m, 4 H), 2.16 (tt, $^{2}J_{PH}$ = 12.9 Hz, $^{3}J_{HH}$ = 4.7 Hz, 1 H), 2.04-1.84 (m, 2 H), 1.60-1.46 (m, 2 H), 1.38-1.20 (bm, 24 H), 0.89 (t, $^{3}J_{HH}$ = 6.4 Hz, 3 H), 0.49 (br qd, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 49.1 (s).

Bisphosphine-borane (Table 5.5, entry 1c): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (t, $^{2}J_{PH}$ = 12.9 Hz, 1 H), 2.10-1.10 (m, 52 H), 0.90 (t, $^{3}J_{HH}$ = 6.7Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.4 (s).

Bisphosphine-borane (Table 5.5, entry 3a): ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.5 (s).

Bisphosphine-borane (Table 5.5, entry 3b): ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 48.9 (s).

Chapter Six, Section 6.2

Representative Procedure for Table 6.1 - Method A. Ethyl (1-hexyl-vinyl) phosphinate (entry 1). To a mixture of concentrated H_3PO_2 (0.396 g, 6 mmol, 3 eq) and 3-aminopropyltriethoxysilane (1.33 g, 6 mmol, 3 eq) in toluene (12 mL) were added 1-decyne (0.36 mL, 0.28 g, 2 mmol, 1 eq) and trifluoroacetic acid (0.460 mL, 0.68 g, 6 mmol, 3 eq). After

stirring for 5 min at rt, Pd_2dba_3 (0.0092g, 0.01 mmol, 1 mol% Pd) and dppf (0.112 g, 0.02 mmol) were added and the reaction mixture was heated at reflux for 12 h. At this point the reaction is not homogeneous because the silicates get polymerized forming sticky gels at the bottom of the flask. After cooling to rt, ^{31}P NMR of the reaction mixture revealed the formation of the products at 28.9 ppm (branched isomer) and 24.2 ppm (linear isomer) in a ratio of 16/1. The mixture was then diluted with EtOAc and washed successively with 2 M aqueous HCl (1 x). The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine. Drying over $MgSO_4$ and concentration under reduced pressure afforded the products along with 10-20% of diethyl phosphite $(EtO)_2P(O)H$, which was eliminated under reduced pressure (0.1 mmHg, 40°C, 12 h). The pure product was then obtained as a mixture of isomers in the form of light yellow oil (0.463 g, 100%).

Ethyl (1-hexyl-vinyl) phosphinate (major isomer, 94%) (Table 6.1, entry 1).[57] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J_{HP} = 549 Hz, 1 H), 5.95 (d, J_{HP} = 5 Hz, 1H), 5.91 (d, J_{HP} = 71 Hz, 1H), 4.03-4.24 (m, 2H), 2.18-2.38 (m, 2H), 1.45-1.63 (m, 2H), 1.38 (td, J = 6 Hz, J = 2 Hz, 3H), 1.17-1.4 (m, 6H), 0.89 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 141.8 (d, J_{PC} = 118 Hz), 128.9 (d, J_{PCC} = 14 Hz), 62.3 (d, J_{POC} = 6 Hz), 31.9, 30.7 (d, J_{PCCC} = 12 Hz), 29.4 (d, J_{PCCCC} = 7 Hz), 28.0 (d, J_{PCCCCC} = 5 Hz), 22.8, 16.4 (d, J_{POCC} = 7 Hz), 14.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 30.62 (dm, J_{PH} = 553 Hz).

Ethyl (*trans*-oct-1-enyl) phosphinate (major isomer, 88%) (Table 6.1, entry 16).[56,57] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, J_{HP} = 549 Hz, 1 H), 6.81 (ddt, J = 24 Hz, J = 17 Hz, J = 7 Hz, 1H), 5.79 (dd, J = 24 Hz, J = 17 Hz, 1H), 4.3-4.24 (m, 2H), 2.19-2.33 (m, 2H), 1.4-1.55 (m, 2H), 1.38 (t, J = 6 Hz, 3H), 1.18-1.4 (m, 6H), 0.89 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45

MHz) δ 155.3 (d, J_{PCC} = 5 Hz), 119.7 (d, J_{PC} = 131 Hz), 61.9 (d, J_{POC} = 6 Hz), 34.4 (d, J_{PCCC} = 20 Hz), 32.0, 29.4 (d, J_{PCCCCC} = 8 Hz), 27.8, 22.8, 16.4 (d, J_{POCC} = 7 Hz), 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.81 (dm, J_{PH} = 554 Hz).

Ethyl (1-*tert*-butyl-vinyl) phosphinate (major isomer, 90%) (Table 6.2, entry 1a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, J_{HP} = 553 Hz, 1 H), 6.74 (dd, *J* = 21 Hz, *J* = 17 Hz, 1H), 5.62 (dd, *J* = 23 Hz, *J* = 17 Hz, 1H), 4.82-3.94 (m, 2H), 1.32 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 162.3, 115.5 (d, J_{PC} = 136 Hz), 60.3 (d, J_{POC} = 6 Hz), 35.1 (d, J_{PCC} = 17 Hz), 28.7 (3C), 16.8 (d, J_{POCC} = 6 Hz), 14.2; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 33.6 (dm, J_{PH} = 548 Hz).

Butyl (*trans*-*tert*-butyl-1-enyl) phosphinate (major isomer, 87%) (Table 6.2, entry 1c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, J_{HP} = 555 Hz, 1 H), 6.84-6.62 (m, 1H), 5.78-5.56 (m, 1H), 4.14-4.01 (m, 2H), 1.70 (quint, *J* = 7 Hz, 2H), 1.41 (sext, *J* = 8 Hz, 2H), 1.08 (s, 9H), 0.94 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 164.5 (d, J_{PCC} = 5 Hz), 114.8 (d, J_{PC} = 131 Hz), 65.8 (d, J_{POC} = 6 Hz), 32.6 (d, J_{PCCC} = 7 Hz), 28.7, 28.5 (3C), 18.9, 13.7; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 25.3 (dm, J_{PH} = 557 Hz).

Ethyl (1-cyclopropyl-vinyl) phosphinate (Table 6.2, entry 2b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J_{HP} = 554 Hz, 1 H), 5.91 (d, *J* = 24 Hz, 1H), 5.65 (d, *J* = 47 Hz, 1H), 4.22-4.08 (m, 2H), 1.65-1.52 (m, 1H), 1.39 (t, *J* = 7 Hz, 3H), 0.85 (dm, *J* = 7 Hz, 2H), 0.65 (dm, *J* = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 143.4 (d, J_{PC} = 120 Hz), 125.5 (d, J_{PCC} = 14 Hz), 62.0 (d, J_{POC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz), 11.2 (d, J_{PCC} = 18 Hz), 7.2 (d, J_{PCCC} = 4 Hz), 6.6 (d, J_{PCCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 29.2 (dqq, J_{PH} = 554 Hz, *J* = 24 Hz, *J* = 9 Hz).

Butyl (1-cyclopropyl-vinyl) phosphinate (Table 6.2, entry 2d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (d, J_{HP} = 553 Hz, 1 H), 5.88 (d, J = 24 Hz, 1H), 5.70 (d, J = 47 Hz, 1H), 4.18-4.01 (m, 2H), 1.72 (quint, J = 6 Hz, 2 H), 1.62-1.50 (m, 1H), 1.42 (sext, J = 7 Hz, 1 H), 0.96 (t, J = 7 Hz, 3 H), 0.84 (dm, J = 7 Hz, 2 H), 0.64 (dm, J = 9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 143.5 (d, J_{PC} = 127 Hz), 125.4 (d, J_{PCC} = 14 Hz), 65.7 (d, J_{POC} = 7 Hz), 32.5, 18.8, 13.5, 11.2 (d, J_{PCC} = 5 Hz), 7.2, 6.6; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 27.9 (dqq, J_{PH} = 553 Hz, J = 25 Hz, J = 9 Hz).

Ethyl (*trans*-2-trimethylsilyl-vinyl) phosphinate (Table 6.2, entry 3a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J_{HP} = 551 Hz, 1 H), 7.13 (dd, J = 37 Hz, J = 21 Hz, 1H), 6.28 (ddd, J = 32 Hz, J = 21 Hz, J = 1.5 Hz, 1H), 4.01 (q, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.0 (d, J_{PCC} = 3 Hz), 136.9 (d, J_{PC} = 118 Hz), 64.2 (d, J_{POC} = 6 Hz), 18.5 (d, J_{POCC} = 6 Hz), 0.0 (3C); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 23.7 (dqt, J_{PH} = 551 Hz, J = 30 Hz, J = 9 Hz).

Butyl [N-(4-butyl)phthalimidyl-vinyl]phosphinate (Table 6.2, entry 2d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J_{HP} = 561 Hz, 1 H), 7.85 (dd, J = 5 Hz, J = 3 Hz, 2H), 7.72 (dd, J = 5 Hz, J = 3 Hz, 2H), 5.99 (d, J = 26 Hz, 1H), 5.88 (d, J = 49 Hz, 1 H), 4.12-3.96 (m, 2H), 3.71 (t, J = 7 Hz, 2 H), 2.33 (dt, J = 13 Hz, J = 8 Hz, 2 H), 1.80-1.56 (m, 4H), 1.40 (sext, J = 8 Hz, 2 H), 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 168.5 (2C), 141.5 (d, J_{PC} = 119 Hz), 134.1, 129.4 (d, J_{PCCC} = 14 Hz), 123.3, 66.2 (d, J_{POC} = 7 Hz), 37.6, 32.5 (d, J_{POCC} = 6 Hz), 28.2, 25.3 (d, J_{PCC} = 6 Hz), 18.9, 13.7; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 28.2 (dm, J_{PH} = 563 Hz).

Ethyl (*trans*-styryl)phosphinate (Table 6.2, entry 7a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.48 (m, 2H), 7.46-7.38 (m, 3H), 7.35 (d, J_{HP} = 562 Hz, 1 H), 6.40 (d, J = 22 Hz, 1H), 6.37 (d, J

= 5 Hz, 1H), 4.24-4.19 (m, 2H), 1.41 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 149.9 (d, J_{PCC} = 7 Hz), 134.7 (d, J_{PCCC} = 21 Hz), 130.9, 129.2, 128.1, 116.6 (d, J_{PC} = 133 Hz), 62.3 (d, J_{POC} = 6 Hz), 16.7 (d, J_{POCC} = 7 Hz); ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 25.6 (dm, J_{PH} = 561 Hz).

Butyl (1-methyl-vinyl) phosphinate (Scheme 6.5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J_{HP} = 550 Hz, 1 H), 5.99-5.81 (m, 2H), 4.22-3.98 (m, 2H), 1.96 (d, J = 14 Hz, 3 H), 1.70 (quint, J = 7 Hz, 2H), 1.42 (sext, J = 7 Hz, 2H), 0.94 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.3 (d, J_{PC} = 120 Hz), 129.6 (d, J_{PCC} = 14 Hz), 66.4 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 18.8, 16.8 (d, J_{PCC} = 13 Hz), 13.6; ^{31}P NMR ($CDCl_3$, 36.441 MHz) δ 25.6 (dm, J_{PH} = 548 Hz).

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VITA

Yamina Belabassi was born on September 27, 1976, in Perpignan, France. She is the daughter of Mohamed El Habib Belabassi and Zoula Belabassi. She received her Master of Science degree with a major in Organic and Biomolecular Chemistry from Université des Sciences et Techniques de Montpellier, France, *magna cum laude*, in 2003.

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ABSTRACT

CARBON-PHOSPHORUS BOND FORMATION
NEW METHODOLOGIES FOR THE PREPARATION OF ORGANOPHOSPHORUS COMPOUNDS OF BIOLOGICAL INTEREST

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The work presented in this dissertation deals with the development of new methodologies for P-C bond formation as well as synthesizing biologically relevant organophosphorus compounds. A distinct emphasis is given to the important synthetic targets, the *H*-phosphinates. A review of relevant literature is provided in Chapter 1.

Chapter 2 describes the synthesis and structural analyses, of triphenylmethyl-containing phosphorus compounds. For the first time, both phosphonothioic and boranophosphonic acids have been characterized by single X-ray diffractometry.

The third chapter details the preparation and the reactivity of phosphine-borane complexes. Novel dialkoxyphosphine-borane complexes were introduced, both as general synthetic intermediates for the preparation of *H*-phosphinates or disubstituted phosphinic acids, and as boranophosphonate precursors. Related to this chemistry, silylation of an *H*-phosphinate intermediate can also be conducted and the resulting phosphonite protected with borane. This allows the temporary protection of the sensitive P-H group, so that manipulations of the alkyl chain might be conducted.

In chapter 4, the palladium-catalyzed cross-coupling reaction of dialkylphosphites with aryl and heteroaryl halides is presented. An efficient, versatile and economically attractive alternative to the original Hirao cross-coupling by using only 1 mol% (or less) $Pd(OAc)_2$/dppf is

described. Moreover, first example of palladium-catalyzed P-C bond formation between activated aryl chlorides and a phosphite are herein reported.

Chapter 5 focuses on the free-radical hydrophosphinylation of alkynes. The triethylborane-initiated radical addition of sodium hypophosphite to terminal alkyne affords the previously unknown 1,1-bis-*H*-phosphinates, precursors of the biologically relevant 1,1-bisphosphonates (e.g., treatment of bone diseases). Thus, the oxidative conversion of 1,1-bis-*H*-phosphinates to the corresponding bisphosphonates, as well as the synthesis of a series of bio-conjugates (steroids, carbohydrates, fluoroquinolones) was investigated.

In the last chapter, the palladium-catalyzed hydrophosphinylation of hypophosphorous acid derivatives to terminal alkynes is reported. In an effort to improve the regioselectivity of the reaction, various terminal alkynes were tested, as well as the solvent and catalyst system.