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

by

KARLA BRAVO-ALTAMIRANO

Bachelor of Science, 2002
Universidad de las Américas Puebla
Puebla, Mexico

Submitted to the Graduate Faculty of the
College of Science and Engineering
Texas Christian University
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy

May 2007

ACKNOWLEDGMENTS

I thank my advisor Prof. Jean-Luc Montchamp for his invaluable time, advice, teaching and encouragement during my graduate studies. I especially value his interest in transmitting his extensive knowledge of chemistry and critical thinking, as well as his ability to develop novel and creative ideas. All of them have helped me to become a better chemist.

I thank God for the strength and blessings in my life.

I am very grateful to my mother, whose unconditional love is the most precious thing I possess in my life.

To my lovely husband Carlos, whose analytical thinking, passion for learning and fearless spirit encourage me to pursue my goals.

I thank my aunt Susana for stimulating curiosity and unconventional reasoning in me, and for all her love.

I also express my gratitude to my friends and professors for their priceless help and guidance, and for sharing with me unforgettable experiences.

I acknowledge the Chemistry Department at Texas Christian University and National Science Foundation (CHE-0242898) for their financial support.

TABLE OF CONTENTS

LIST OF EQUATIONS

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

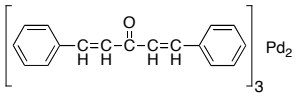
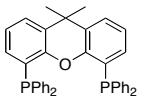
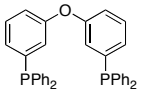
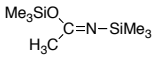
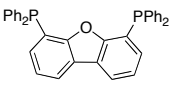
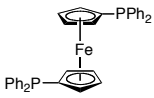
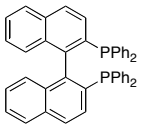
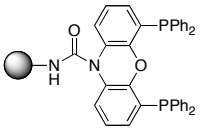
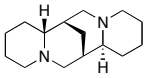
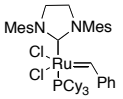
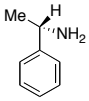
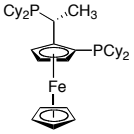
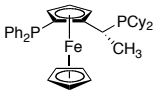
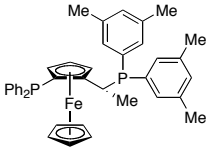
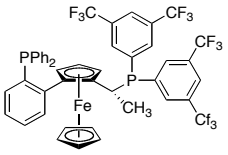
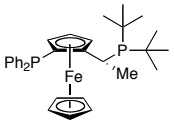
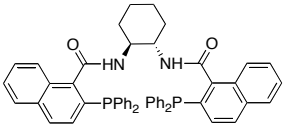
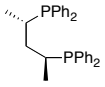
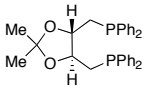
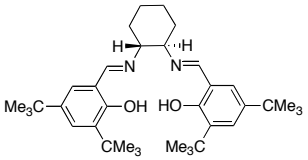
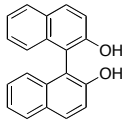
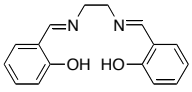
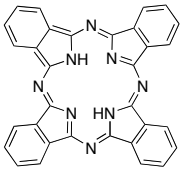
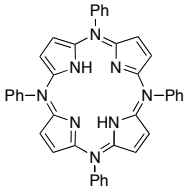
Ac	Acetyl
acac	Acetylacetonate
ACE	Angiotensin-Converting Enzyme
AHP	Anilinium hypophosphite
AIBN	2,2′-Azobis(2-methylpropionitrile)
Alk	Alkyl
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
BDPP	2,4-Bis(diphenylphosphino)pentane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BOC	*tert*-Butyl carbamate
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
BTSP	Bis(trimethylsiloxy)phosphine
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
Cin	Cinnamyl
Cbz	Benzyloxycarbonyl
cod	Cylooctadienyl

conc.	Concentrated
Cp	η^5-Cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DACH	1,2-Diaminocyclohexane
DAHP	3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate
dba	Dibenzylideneacetone
de	Diasteromeric excess
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DBFphos	4,6-Bis(diphenylphosphino)-dibenzofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIEA	*N*,*N*-Diisopropylethylamine
DIOP	4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxidel
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1’-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
EDC	1-Ethyl-3-(3’-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
eq	Equivalent

Et	Ethyl
EWG	Electron withdrawing group
GABA	γ-Aminobutyric acid
GC	Gas chromatography
Hex	Hexyl
HMDS	Hexamethyldisilazane
HPLC	High Performance Liquid Chromatography
i-Pr	Isopropyl
L	Ligand
LDA	Lithium diisopropylamide
m. p.	Melting point
Me	Methyl
Men	Menthyl
MMP	Matrix metalloproteinases
MOM	Methoxymethyl
MS	Mass spectroscopy
MW	Microwaves
NMP	*N*-Methylpyrrolidinone
nixantphos	4,6-Bis(diphenylphosphino) phenoxazine
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
Oct	Octyl
PAMP	1,2-Bis[(2-methoxyphenyl)(phenyl)phosphino]ethane
PCC	Pyridinium chlorochromate

PEG	Poly(ethylene glycol)
Pent	Pentyl
Ph	Phenyl
Pht	Phthalimide
Piv	Pivaloyl
PPAPM	Pyrrolidine-2-phosphonic acid phenyl monoester
Pr	Propyl
Pyr	Pyridine
RCM	Ring-closing metathesis
rt	Room temperature
SALEN	Ethylenebis(salicylimine)
SSPS	Solid-Phase Peptide Synthesis
TBDMS	tert-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosylate
xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

STRUCTURES OF COMMON CATALYSTS AND REAGENTS

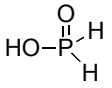
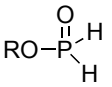
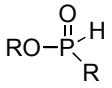
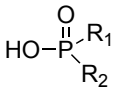
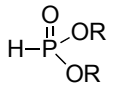
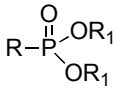
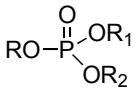
Pd_2dba_3		dppp n = 1 dppb n = 2	
xantphos		DABCO	
DPEphos		BSA	
DBFphos		dppf	
BINAP		polystyrene-supported nixantphos	
(-)-Sparteine		2nd generation Grubbs catalyst	
(*S*)-(-)-α-Methylbenzylamine		Josiphos SL-J003-1	
Josiphos SL-J001-1		Josiphos SL-J005-1	
Walphos SL-W001-1		Josiphos SL-J002-1	
(S,S)-DACH-Naphtyl Trost Ligand		*(S,S)*-BDPP	
(S,S)-DIOP		*(R,R)*-Jacobsen Ligand	
BINOL		SALEN	
Phthalocyanine		Meso-tetraphenyl-porphine	

<u>Chapter One:</u> Background, preparation and reactivity of *H*-phosphinic acid derivatives

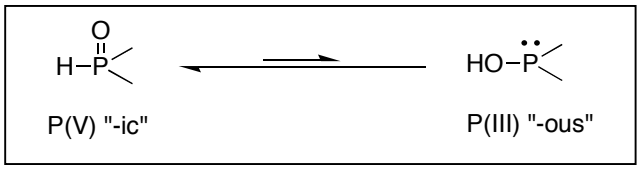
1.1 *H*-phosphinic acid derivatives, useful synthons of organophosphorus compounds

Interest in the preparation of organophosphorus compounds continues to expand in response to the developing applications of phosphorus compounds in synthesis, as well as an understanding of their role in biological systems. Organic phosphorus compounds are important in the preparation of agricultural chemicals, flame-retardants, corrosion inhibitors, nanostructures, metal extractants, medicinal molecules, olefination reagents, and ligands for catalysis.[1] A particular family of organophosphorus compounds (Scheme 1.1) is constituted by phosphorus-containing acids [P(O)(OH)]. Some members of this family, including *H*-phosphinic acids and their corresponding esters, 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 (Scheme 1.2).

Scheme 1.1 Acids and esters in organophosphorus chemistry

Hypophosphorous acid		
R = salt	Hypophosphite	
R =alkyl	Alkyl Phosphinate or alkyl hypophosphite	
R = H	H-phosphinic acid	
R = Alkyl	H-phosphinate	
Phosphinic acid or Disubstituted phosphinic acid		
R = H	Phosphorous acid	
R = Alkyl	H-Phosphonate or Dialkyl phosphite	
R_1 = H	Phosphonic acid	
R_1 = Alkyl	Phosphonate	
Phosphate		
R = R_1 = R_2 = H	Phosphoric acid	

Scheme 1.2 Phosphinylidene moiety (P(=O)H)



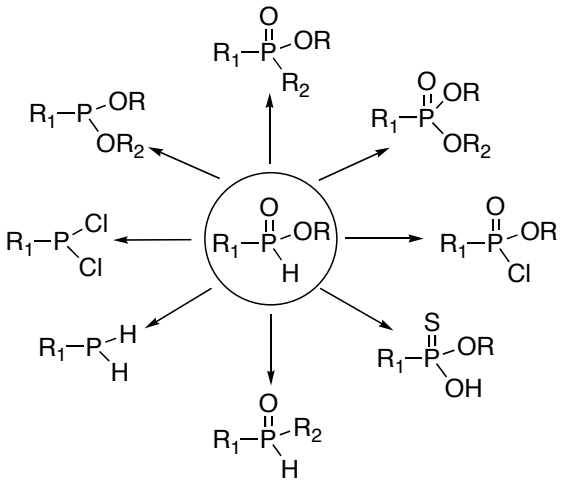
Bond energies (kcal/mol)

H—P = 76	O—H = 111
O—P = 95	C—P = 70

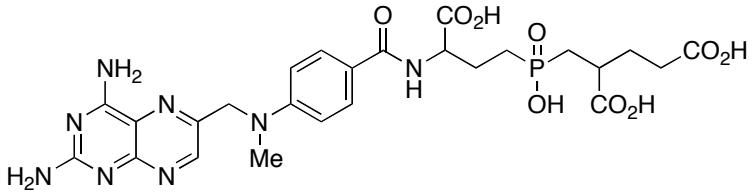
H_3PO_2	$K \sim 10^{-12}$
$(RO)_2P(O)(H)$	$K \sim 10^{-6}$

Over the last few years, the Montchamp group has focused on *H*-phosphinic (phosphonous) acids and derivatives $R_1P(O)(OR)(H)$, an underdeveloped class of compounds. *H*-phosphinic acid derivatives are valuable synthetic intermediates in preparing other more common phosphorus functionalities, including phosphonates, phosphinates, as well as primary phosphines and secondary phosphine oxides, to name a few examples (Scheme 1.3).[2] Particularly, they are useful intermediates in the synthesis of disubstituted phosphinic acids. These compounds can mimic tetrahedral transition states in enzyme-catalysed reactions and have been extensively studied to achieve pharmaceutical activity through the potent inhibition of these enzymes.[3] Representative examples of biologically active phosphinic acids are shown in Scheme 1.4. Additionally, phosphinic acids are used to replace labile phosphate groups with a non-hydrolysable equivalent,[4] and to probe deprotonation states in enzyme and receptors,[5] although this has only been exploited recently because of the lack of methodologies to prepare highly functionalized phosphinic acids. Replacement of carboxylate moieties in biological compounds can lead as well to an improved activity or selectivity for a particular receptor.[6] Phosphinic acid peptides where one peptide bond is substituted by a non-hydrolyzable phosphinate moiety represents a very convenient mimic of a substrate in the transition state for Zn-metalloproteinases and aspartic acid proteinases.[7] Finally, *H*-phosphinic acids can also function as pro-drugs of biologically-active phosphonates (i.e. bisphosphonates),[8] through *in vivo* oxidation,[3a] or as synthetic precursors via chemical oxidation.[9]

Scheme 1.3 Transformations of *H*-phosphinic acid derivatives

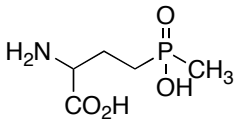


Scheme 1.4 Examples of biologically-active phosphinic acids



Pseudopeptide Prodrug

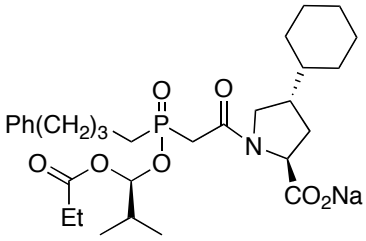
Potent Inhibitor of Folypoly-γ-glutamate Synthetase



Phosphinothricin

Glutamine Synthetase Inhibitor

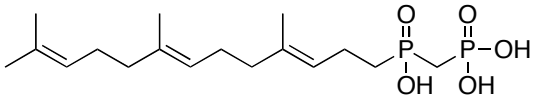
α-Aminobutyric Acid-Based Herbicide



Monopril

Inhibitor of angiotensin-converting enzyme

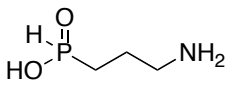
High blood pressure, heart failure



Analogs of Farnesyl Pyrophosphate

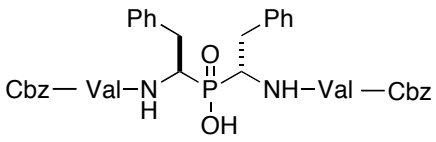
Farnesyltransferase and

Squalene Synthase Inhibitor



CNS Agent

Potent GABA-B Agonist

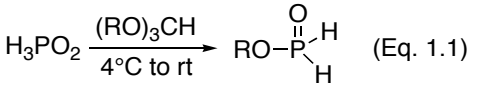


HIV-1 Protease Inhibitor

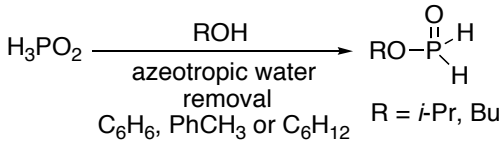
1.2 Preparation of H-phosphinic acid derivatives

1.2.1 Preparation of the precursors alkyl phosphinates

Hypophosphite esters (alkyl phosphinates, $ROP(O)H_2$) are important precursors of *H*-phosphinic acid derivatives and are the most reactive of the phosphorous esters. These compounds are sensitive to moisture, air, and heat (disproportionation). Several methods have been described for the preparation of alkyl phosphinates, but only a few are commonly employed.[10] Kabachnik reported the preparation of methyl and ethyl phosphinates by esterification of hypophosphorous acid (H_3PO_2) with diazoalkanes.[11] Fitch described their preparation by esterification of crystalline H_3PO_2 with orthoformates (Eq 1.1),[12] which requires the use of hazardous crystalline H_3PO_2 and side products are usually observed.[13] Nifant'ev discovered the direct esterification of H_3PO_2 with alcohols under azeotropic water removal (Eq 1.2),[14] where thermal decomposition competes with product formation, lowering the reaction yield. Alkyl phosphinates of certain alcohols have also been prepared by transesterification reactions with $MeOP(O)H_2$.[15]



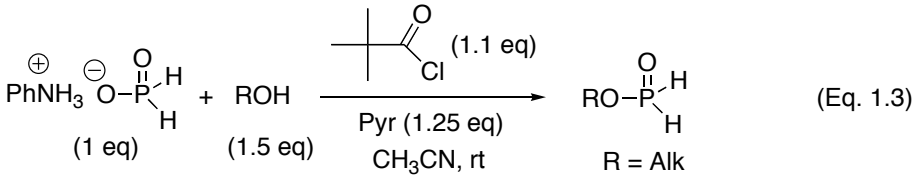
(Eq. 1.1)



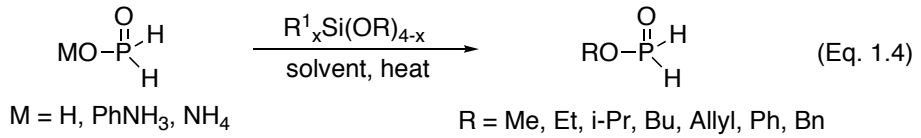
(Eq. 1.2)

Montchamp reported recently the three most general methods for the preparation of alkyl phosphinates. Hypophosphite amine salts react with alcohols in presence of pivaloyl chloride as activating agent (Eq 1.3) yielding alkyl phosphinates in good yields,[16,17] and H_3PO_2 and its anilinium or ammonium salts are esterified with alkoxysilanes (Eq 1.4).[18] Additionally, he demonstrated the effectiveness of $PhOP(O)H_2$, prepared by the alkoxysilane method, in transesterification reactions with alcohols (Eq 1.5). This reaction proceeds in excellent yields, in several solvents, and unlike in other preparative methods, the resulting alkyl phosphinates are

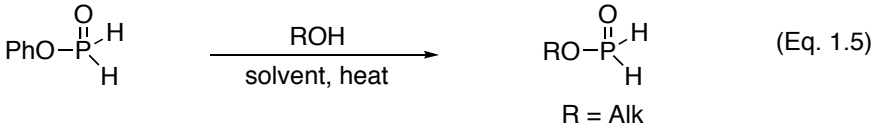
thermally stable. When methyl phosphinate was prepared by esterification with alkoxysilanes, it only decomposed slightly after heating it for 20 h at 80°C; whereas the same compound, prepared by the Fitch method (using orthoformates) decomposed totally after 1 h at the same temperature. In addition, stock solutions of alkylphosphinates can be stored at room temperature under N_2 for over a month, with less than 10% decomposition.



(Eq. 1.3)



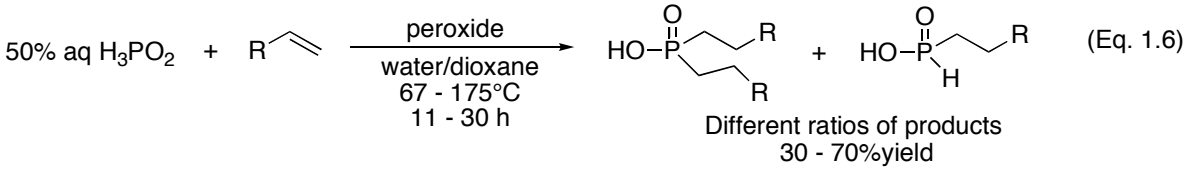
(Eq. 1.4)



(Eq. 1.5)

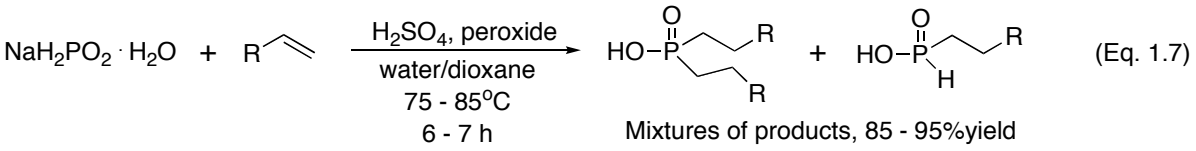
1.2.2 Free-radical hydrophosphinylation reactions of alkenes and alkynes

The addition of phosphorus-centered radicals to olefins is well documented.[19] In 1955, Williams and Hamilton reported for the first time the addition of aqueous H_3PO_2 to olefins initiated by organic peroxides, at high temperatures (Eq. 1.6),[20] where the reaction yields could be increased by using hazardous crystalline H_3PO_2.[21] In parallel work, hydrophosphinylation of olefins with salts of H_3PO_2 ($MOP(O)H_2$) in an autoclave at 120-150°C was also reported.[22] As a result, mixtures of *H*-phosphinic acids and disubstituted phosphinic acids were obtained.

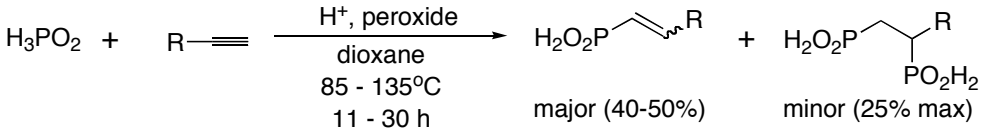


(Eq. 1.6)

Nifant'ev and coworkers improved this reaction, which has become a preparative method for *H*-phosphinic acids.[23] In these reactions, H_3PO_2 or sodium or potassium hypophosphite salts were added to alkenes (Eq. 1.7) and alkynes (Eq. 1.8) in presence of peroxides and mineral or organic acids. The use of acid catalysts enables lowering the temperature of the reaction by helping the breakdown of the peroxide initiators.



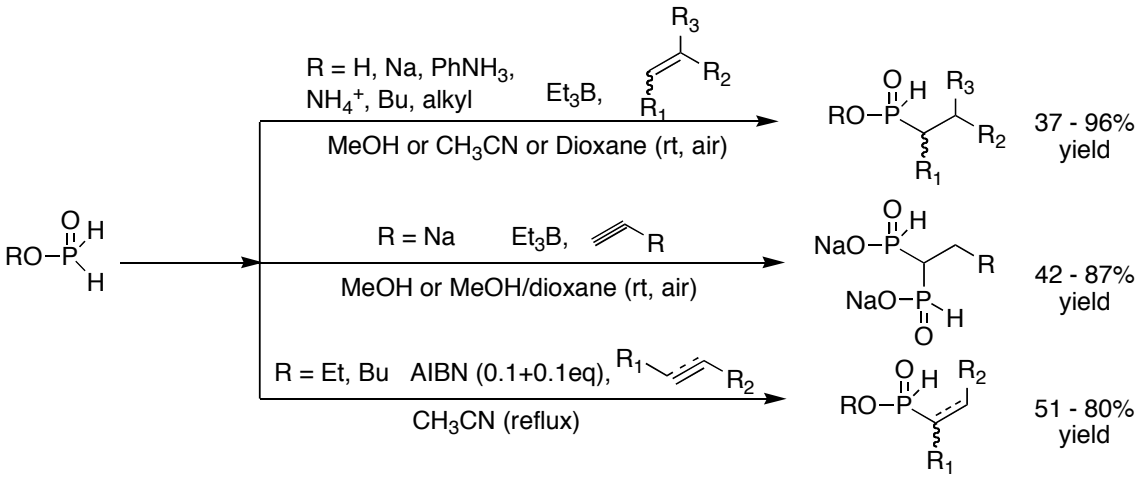
(Eq. 1.7)



(Eq. 1.8)

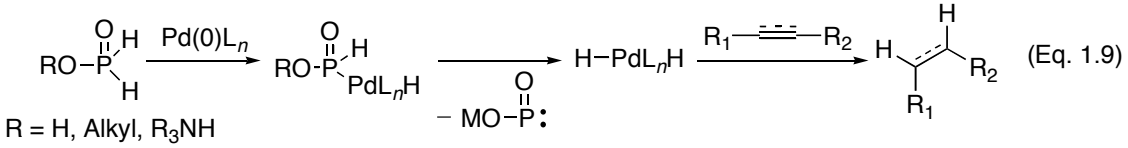
Karanewsky discovered that even AIBN could be used in refluxing EtOH,[24] providing a major practical breakthrough, but the conditions remained strongly acidic and therefore incompatible with functionalized molecules. Montchamp has recently reported more efficient approaches for the free-radical addition of hypophosphorous compounds to unsaturated substrates (Scheme 1.5). Using Et_3B/O_2 as initiators, addition of H_3PO_2, its salts (AHP and $NaOP(O)H_2$), or even alkyl phosphinates to alkenes occurs at room temperature, in an open flask.[25] AIBN-initiated radical hydrophosphinylations of alkenes and alkynes with alkyl phosphinates proceeds effectively at 80°C.[26] 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,[9,27] which are novel precursors of the biologically important 1,1-bisphosphonates.[8] This new radical-based methodology has already been used by various research groups. For example, in the preparation of α,α-difluoro-*H*-phosphinic acids,[28] as well as in the synthesis of an intermediate of an inhibitor of Folypoly-γ-Glutamate Synthetase. This last compound was obtained by addition of $NaOP(O)H_2$ to vinylglycine, reaction that failed with other approaches.[3e]

Scheme 1.5 Free radical reactions of hypophosphorous compounds



1.2.3 Metal-catalyzed hydrophosphinylation

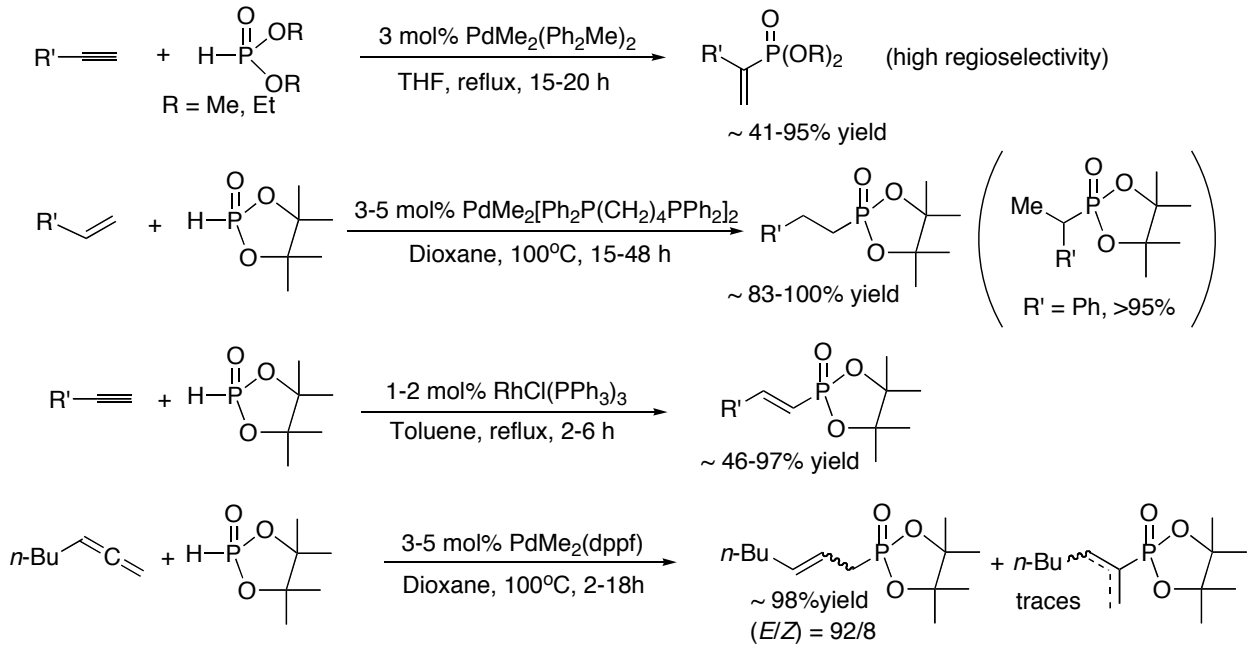
In the last decade, several examples of the addition of phosphorus-hydrogen bonds across unsaturated substrates, which are catalyzed by transition metal-complexes have been reported.[29] Among organophosphorus compounds, hypophosphorous derivatives are particularly strong reducing agents. In fact, the preparative useful transfer hydrogenation of alkenes, alkynes, aldehydes, ketones, and aryl halides, is well known to take place with H_3PO_2 or its sodium and amine salts, under the influence of virtually all transition-metals.[30] This process is believed to occur via insertion of the metal into a P-H bond with subsequent formation of a metal hydride, which is the catalytically active reducing agent (Eq. 1.9).



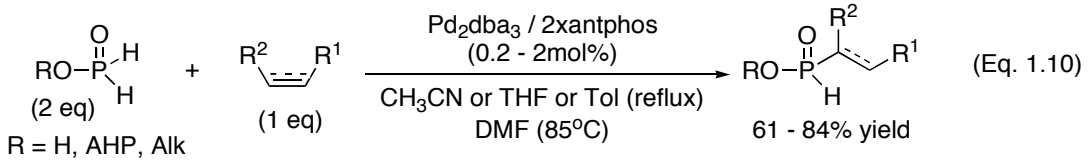
In particular, Tanaka reported a catalytic hydrophosphorylation of alkenes, alkynes and allenes with *H*-phosphonates, using palladium- and rhodium-based catalysts (Scheme 1.6).[31] The mechanism of the reaction is based on the insertion of Pd and Rh into the P-H bond of *H*-phosphonates, which is not a surprising transformation considering the body of literature

regarding transfer hydrogenation on hypophosphorous acid derivatives. Alkynes reacted well with various *H*-phosphonates, but alkenes and allenes only reacted satisfactorily with pinacol *H*-phosphonate, which is a significant limitation because of the harsh conditions needed for the cleavage of pinacol phosphonate esters.[32]

Scheme 1.6 Hydrophosphonylation of alkenes, alkynes and allenes



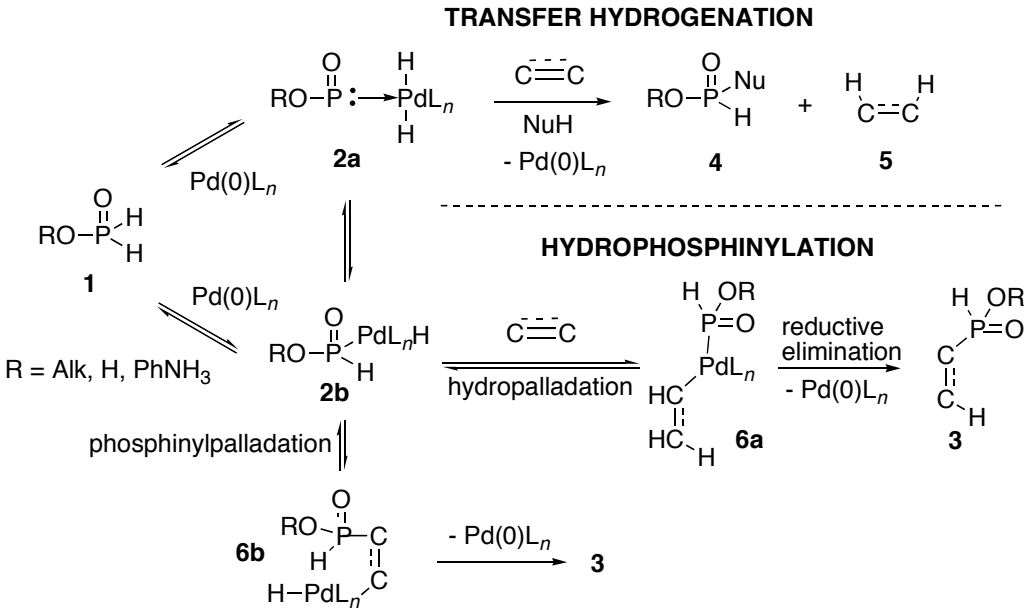
However, Montchamp and coworkers published the only examples of metal-catalyzed hydrophosphinylation of hypophosphorous derivatives with unsaturated substrates.[17] Initially, they developed a remarkably general Pd-catalyzed addition of H_3PO_2, AHP and alkyl phosphinates to alkenes and alkynes under homogeneous catalytic conditions. This reaction yields *H*-phosphinic acid derivatives in high yields and does not require strict anhydrous conditions (Eq. 1.10).[33]



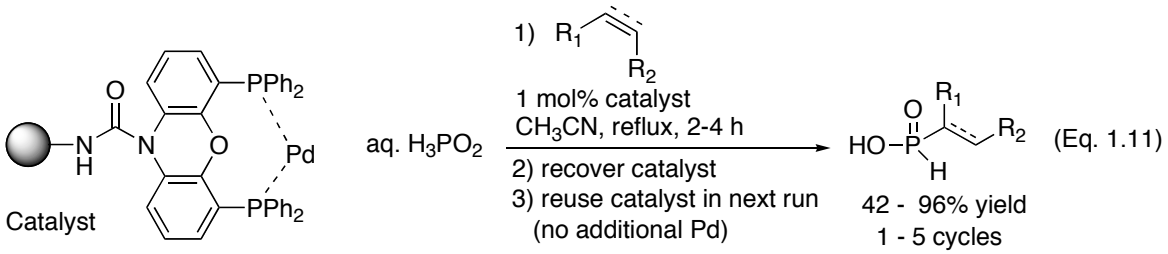
(Eq. 1.10)

The mechanism for this reaction indicates that the appropriate selection of ligands around the Pd harnesses the reactivity of the postulated phosphinyl palladium intermediate before its decomposition to palladium dihydride species, steering in this way the reaction towards addition instead of transfer hydrogenation (Scheme 1.7). Pd_2dba_3/xantphos emerged as the most useful catalytic system, where loadings as low as 0.02 mol% Pd provide good conversions.[33]

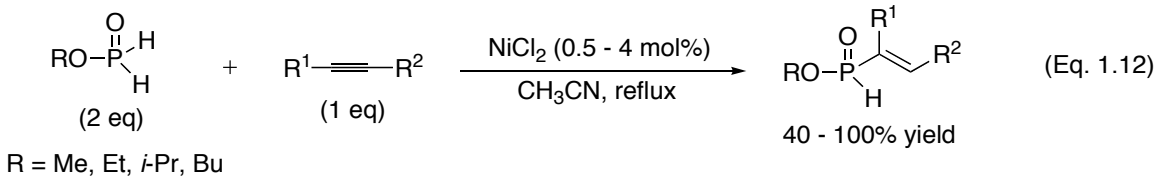
Scheme 1.7 Postulated mechanistic pathways in the Pd-catalyzed hydrophosphinylation reaction



An environmentally benign variant of this process was later developed using a water-tolerant, recyclable polymer-supported catalyst (Eq. 1.11).[34] The ligand can even be employed with Pd/C to furnish a doubly-heterogeneous reusable catalyst.



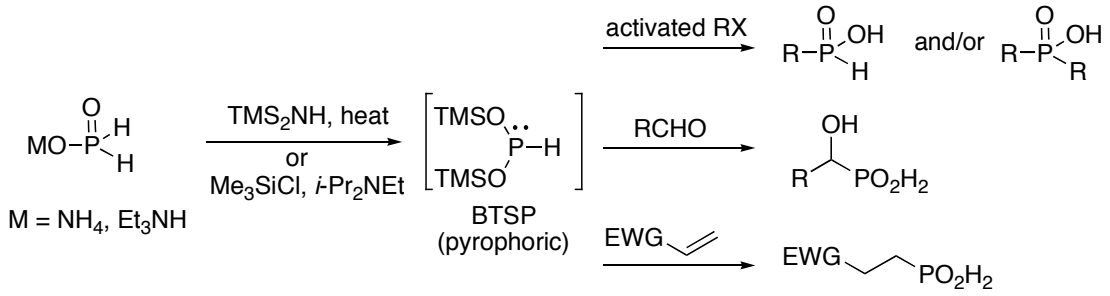
More recently, the Montchamp group discovered a nickel-catalyzed hydrophosphinylation of internal and terminal alkynes with alkyl phosphinates (Eq. 1.12), which corresponds to part of the work that will be disclosed in this dissertation (Chapter Two, Section 2.2).[35]



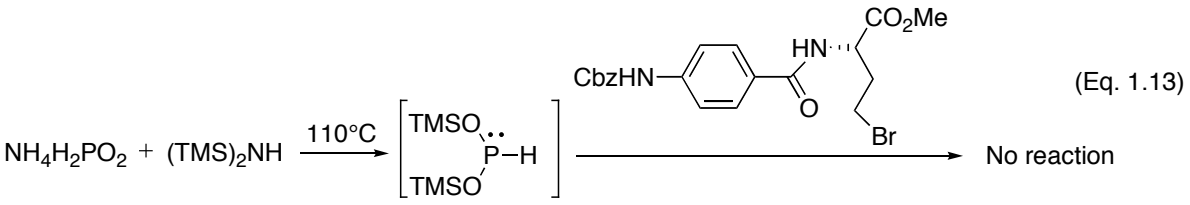
1.2.4 Nucleophilic addition and substitution reactions of silyl phosphonites

Boyd and Regan reported for the first time the use of $(TMSO)_2PH$ (BTSP) as a synthon for the preparation of *H*-phosphinic acids,[36] where BTSP was prepared *in situ* from phosphinate salts of amines and an excess of $TMSCl/Et_3N$ (0ºC to rt) or HMDS (110ºC). Isolation and use of BTSP was avoided due to its extreme pyrophoric nature.[37] H-phosphinic acids were prepared by the addition of α,β-unsaturated esters or highly reactive alkyl halides (Scheme 1.8).

Scheme 1.8 Synthesis of *H*-phosphinic acids from silyl phosphonites



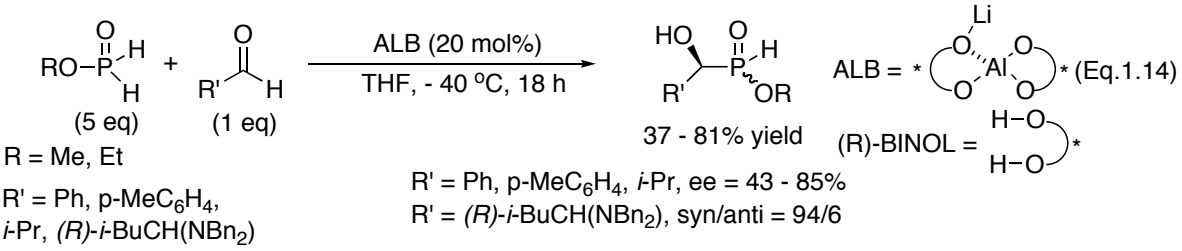
Practical applications of this methodology have been reported,[38] which show often several problems in terms of reactivity (Eq. 1.13)[3e] and selectivity towards formation of monosubstituted phosphinic acids. Elevated temperatures (>110ºC) and large excesses of BTSP are required in order to avoid the formation of symmetrically disubstituted phosphinates.



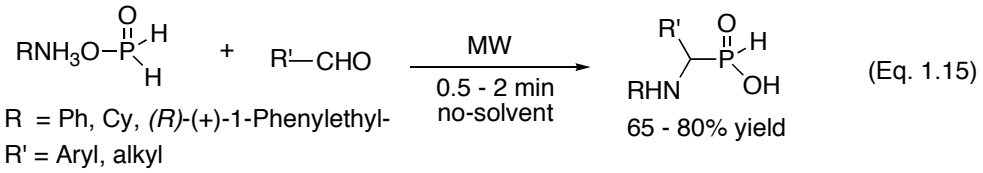
(Eq. 1.13)

1.2.5 Nucleophilic addition reactions of hypophosphorous derivatives

Hypophosphorous compounds add to carbonyl compounds and Michael acceptors.[18] The first reports for this transformation consisted of the thermal hydrophosphinylation of aldehydes with the highly unstable methyl phosphinate, generated *in situ* from anhydrous H_3PO_2 and methyl orthoformate.[12,15a] Shibuya reported recently an elegant asymmetric version of this transformation, catalyzed by Al-Li-BINOL complexes (Eq. 1.14).[39] No desymmetrization of the phosphinate esters was observed, but induction at the carbinol carbon was achieved in moderate enantiomeric excesses.

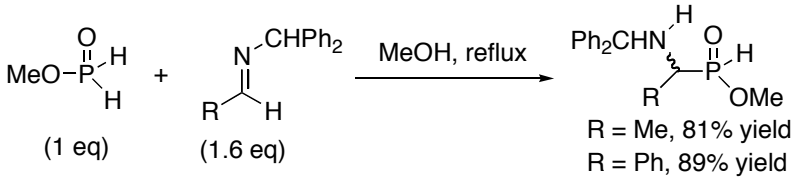


Preparation of α-amino-*H*-phosphinic acids consists usually of heating anhydrous hypophosphorous acid with a Schiff's base and Mannich-type reactions of amines with aldehydes and anhydrous hypophosphorous acid.[40] Harsh reaction conditions, long reaction times and side reactions are usually involved.[15a] A more efficient method consist in the reaction of hypophosphorous salts, introduced by Montchamp,[41] with aldehydes under microwave irradiation, which avoids the problems associated with handling anhydrous H_3PO_2 (Eq. 1.15).[42]



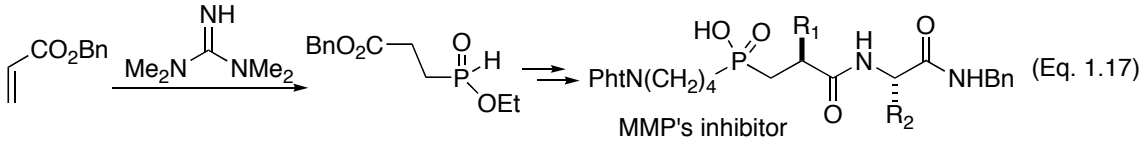
(Eq. 1.15)

Cristau and coworkers have used a slightly modified version of this methodology in the synthesis of phosphinodipeptide analogs (Eq. 1.16).[43] Other examples of addition of alkyl phosphinates to imines and triazines have been reported.[44]



(Eq. 1.16)

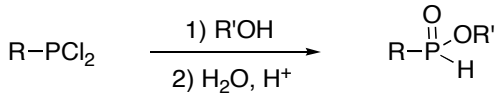
Maier discovered that alkyl phosphinates react with acrylate derivatives under basic conditions (amines or alkoxides).[45] This reaction has been applied in the synthesis of *P*-heterocycles,[46] and in the synthesis of matrix metalloproteinases (MMP) inhibitors (Eq. 1.17).[47]



(Eq. 1.17)

1.2.6 Hydrolysis or alcoholysis of dichlorophosphines

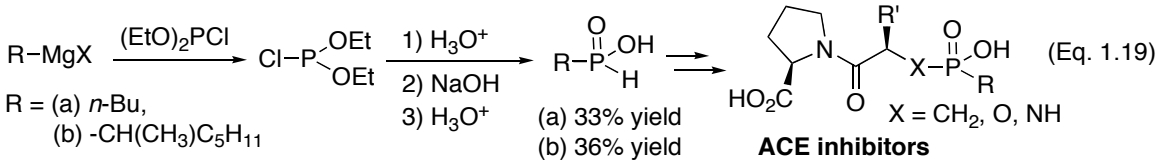
The only widely available and inexpensive *H*-phosphinic acid is phenyl-*H*-phosphinic acid PhP(O)(OH)H, which is prepared by the hydrolysis of $PhPCl_2$,[48] a compound itself obtained by the Friedel-Crafts reaction of benzene and PCl_3. The addition of $PhPCl_2$ to some alcohols has also been described to prepare *H*-phosphinate esters, but inseparable mixture of products are usually obtained.[49] Other $RPCl_2$ compounds are available but they are expensive, very reactive and hazardous, making this process certainly not convenient and not atom-economical (Eq. 1.18).



(Eq. 1.18)

1.2.7 Reaction of organometallic reagents with dialkoxychlorophosphines

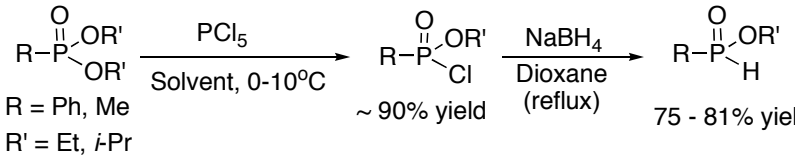
In 1960's, Kabachnik demonstrated the selective replacement of the chlorine atom in dialkoxychlorophosphines $(RO)_2PCl$ by Grignard and organolithium reagents to generate the phosphonites $(RO)_2PR$.[50] However, this process can only be used when the precursor is stable toward Grignard formation. Karanewsky applied this methodology in the preparation of ACE inhibitors (Eq. 1.19).[24] He demonstrated that *H*-phosphinic acids can be obtained in low yields by acidic hydrolysis of $(RO)_2PR$ at room temperature, followed by purification of their corresponding sodium salts (Eq.1.19). Xu *et al.* used this approach in the preparation of bis-phosphinates and bis-phosphine oxides.[51]



(Eq. 1.19)

1.2.8 Reduction of chlorophosphonates

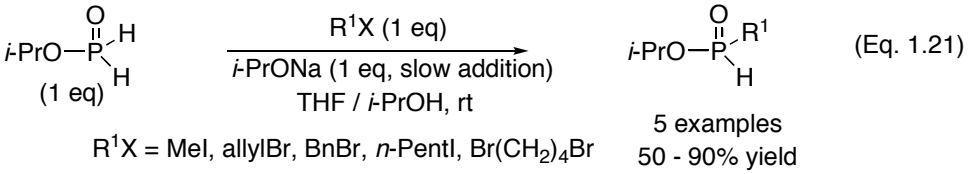
Another conceivable approach to *H*-phosphinates would be the direct selective reduction of phosphonate diesters $RP(O)(OR')_2$.[52] However, this transformation has not been achieved. Instead, phosphonates must first be converted into chlorophosphonate RP(O)(OR)Cl by known procedures,[53] following by reduction with sodium borohydride.[54] This overall transformation is very limited in terms of functional group tolerance and is obviously cumbersome (Eq. 1.20).



(Eq. 1.20)

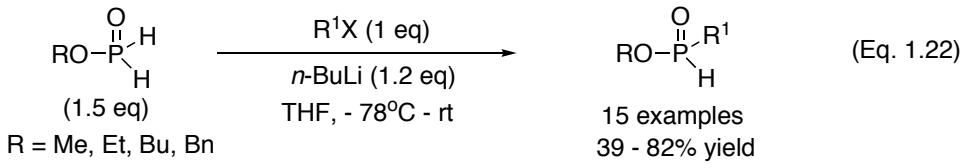
1.2.9 Direct alkylation of alkyl phosphinates

Gallagher reported the alkylation of isopropyl phosphinate using alkyl halides and sodium isopropoxide as base (Eq. 1.21).[55] Less hindered alkyl phosphinates cannot be alkylated under these conditions because of rapid base-promoted decomposition of the anion formed upon deprotonation of unhindered alkyl phosphinates.[56] This method has not found widespread use.



(Eq. 1.21)

Montchamp recently established a butyl lithium-promoted alkylation of primary alkyl phosphinates with reactive electrophiles, such as as alkyl iodides, and allylic/benzylic bromides (Eq. 1.22).[57] DBU in refluxing acetonitrile also promoted this direct alkylation reaction.



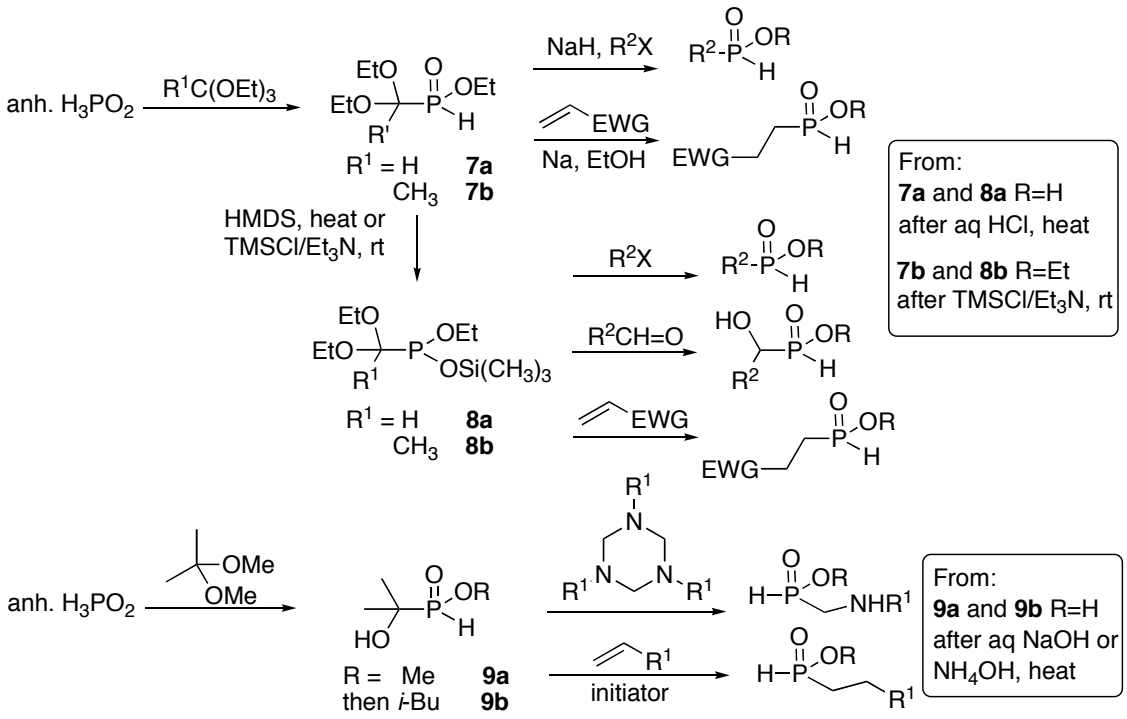
(Eq. 1.22)

1.2.10 Ciba-Geigy methodology

Ciba-Geigy (currently Novartis/Syngenta) introduced the use of masked hypophosphorous acid synthons (**7**, **8**, **9**, in Scheme 1.9) for the preparation of α-,β-, and γ-amino-*H*-phosphinic acids.[58,3a-b] These reagents possess a protected form of hydrogen connected to phosphorus, which solves certain limitations; however their use relies on a protection-deprotection strategy, which reduces the compatibility with functionalized compounds since an acidic cleavage of the acetal is required. Some reactions of these synthons are shown in Scheme 1.9. The first generation uses 1,1-diethoxymethyl as protecting group (**7a**, **8a**), which demands vigorous acidic conditions for its removal (aq. HCl, 100°C).[58a-c] The second generation of reagents uses a slightly modified ketal protecting group (1,1-diethoxyethyl) (**7b**, **8b**), which can

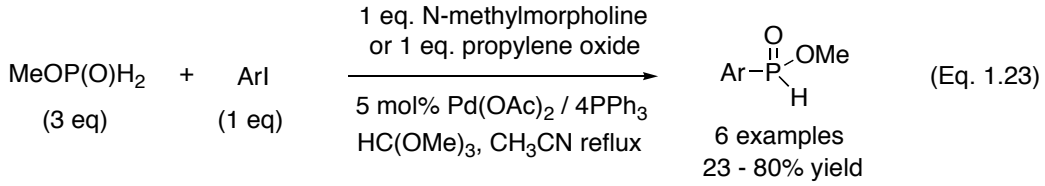
be cleaved under milder conditions (excess TMSCl in $CHCl_3$, rt),[58d] while reagents **9** hold a 1-hydroxyalkyl protecting group that is stable to acid, but can be removed under basic conditions (aq. NH_4OH or NaOH, 50-80°C).[58e]

Scheme 1.9 Preparation of *H*-phosphinic acids from Ciba-Geigy synthons

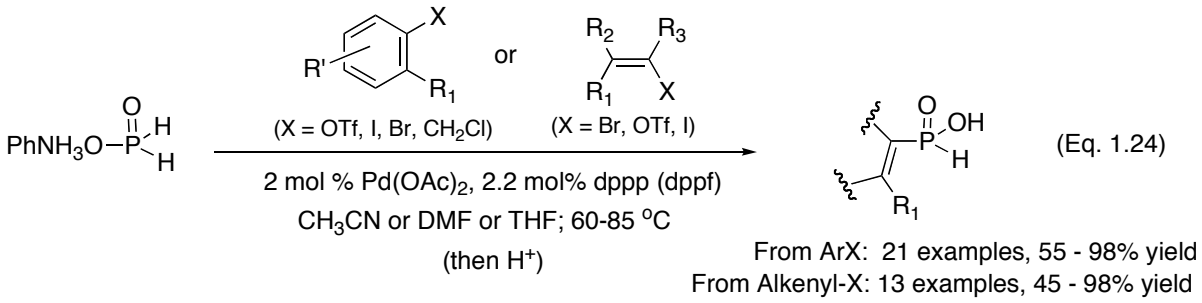


1.2.11 Cross-coupling reactions of aryl, alkenyl, benzylic, and allylic electrophiles

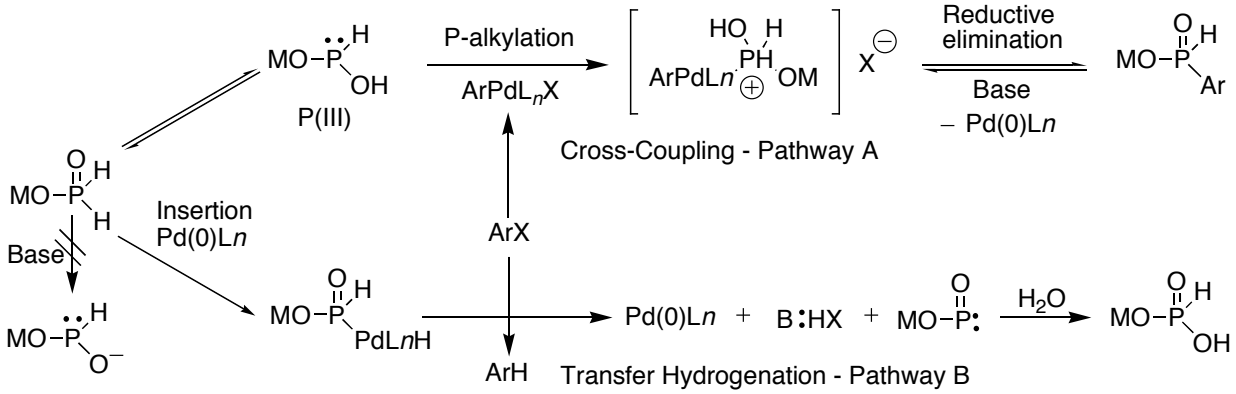
Literature reveals few publications regarding the cross-coupling of hypophosphorous compounds. Holt reported a single example of the cross-coupling between triethylammonium hypophosphite with a steroid-derived dienyl triflate, but the generality of the reaction was not established.[59] Few years later, Schwabacher developed a palladium-catalyzed cross-coupling of aryl iodides with methyl- or *tert*-butyl-phosphinates prepared *in situ*, using Fitch's orthoformate method (Eq. 1.23).[15a,60] However, this reaction requires strict anaerobic and anhydrous conditions, and is limited to be used with very reactive aryl iodides due to the competing transfer hydrogenation (Pathway B, Scheme 1.10), as well as to the rapid thermal decomposition of the alkylphosphinates prepared by this method (see Section 1.2.1 from this Chapter).[12,60]



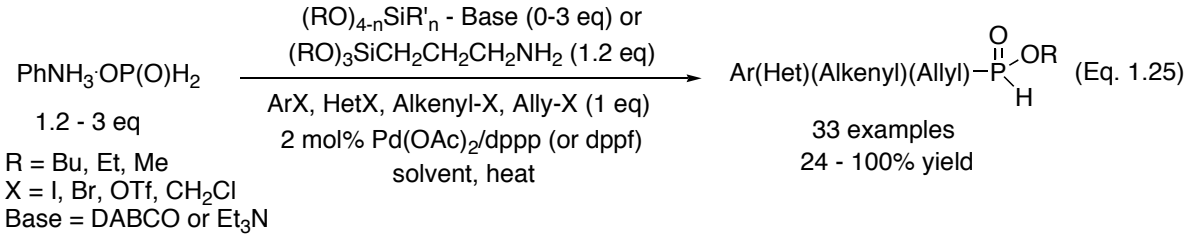
Montchamp contributed in this area with the development of Pd-catalyzed cross-coupling reactions of hypophosphite salts with aryl halides, and alkenyl bromides and triflates (Eq. 1.24).[41,61] Careful inspection of the possible mechanistic pathways indicated that oxidative addition of the metal into the C-X and P-H bonds are two competitive processes, and that the ligand around the metal controls the partition between them (Scheme 1.10). With $Pd(OAc)_2$/dppp (2 mol% or less) as the catalyst, the competing reduction was highly decreased and even the coupling of one activated aryl chloride was reported for the first time.[41] In the case of alkenyl electrophiles, steric hindrance due to *Z*-substitution required a ligand switch from dppp to dppf.[61]



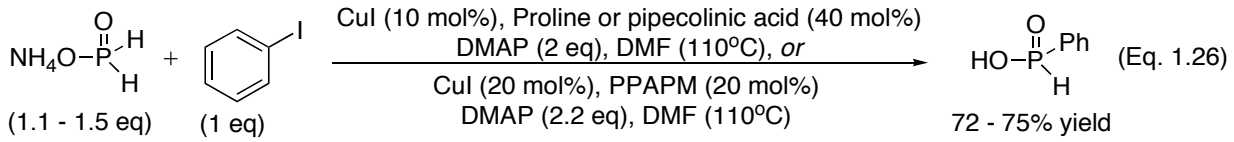
Scheme 1.10 Cross-coupling vs. transfer hydrogenation competing pathways



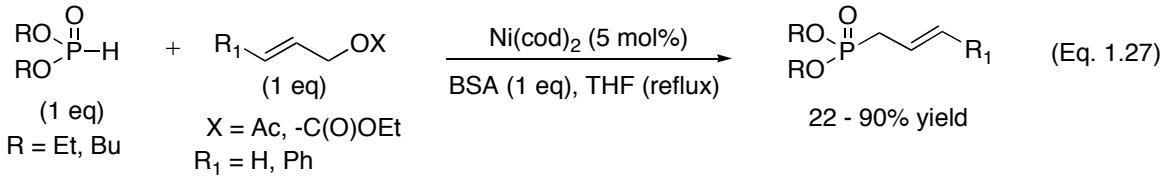
More recently, Montchamp and coworkers developed a direct cross-coupling of alkyl phosphinates with a wide variety of aryl, heteroaryl, and alkenyl, and even some allylic electrophiles through the use of their alkoxysilane method (Eq. 1.25).[62,63] This work will be disclosed in Chapter Three of this dissertation.



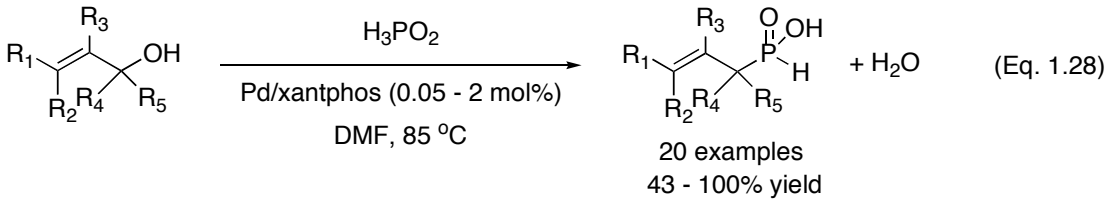
One more example on cross-coupling of hypophosphorous compounds is the Cu-catalyzed reaction of ammonium hypophosphite with iodobenzene, using CuI and PPAPM (pyrrolidine-2-phosphonic acid phenyl monoester) or CuI and proline or pipecolinic acid. (Eq.1.26).[64]



In terms of cross-coupling reactions with allylic electrophiles, some related work by Lu *et al.* showed that O,O-dialkyl phosphonates $(RO)_2P(O)(H)$ react with allylic acetates or carbonates in the presence of bis(trimethylsilyl)acetamide (BSA) and nickel(0), $Ni(cod)_2$ as a catalyst (Eq. 1.27).[65] This approach is not practical due to the formation of sensitive P(III) compounds, as well as to the fact that the nickel catalyst is hard to manipulate.



The only reports on cross-coupling of hypophosphorous acid derivatives with allylic electrophiles have been published by the Montchamp group.[63,66] Of particular relevance is an elegant and environmentally friendly cross-coupling reaction between H_3PO_2 and allylic alcohols (Eq. 1.28),[66] which corresponds to the work to be discussed in Chapter V from this dissertation.

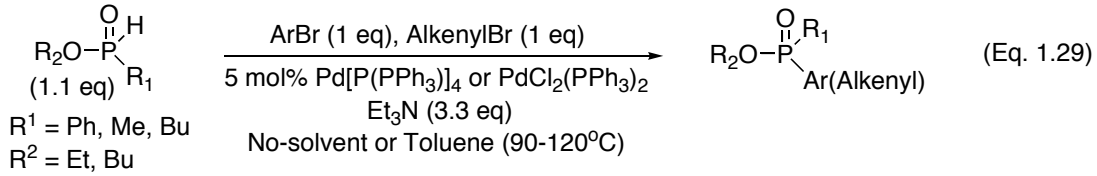


1.3 Reactivity of *H*-phosphinic acid derivatives

A wide range of methodologies has been published concerning the utility of *H*-phosphinates as starting materials, unlike the case where these compounds are the products.

1.3.1 Cross-coupling reactions[67]

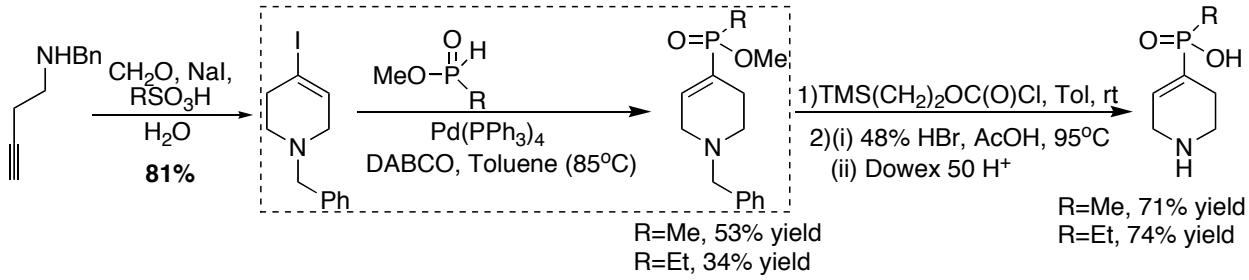
Some of the first reports on cross coupling reactions of *H*-phosphinate esters with aryl halides correspond to Xu *et al.*, who discovered that aryl and alkenyl bromides cross-couple with phenyl-*H*-phosphinate,[68a,c] and alkyl-*H*-phosphinates esters,[68b,c] in the presence of Pd-catalysts and a base (Eq. 1.29). Subsequently, these authors showed that enantiomerically pure (*S*)- and (*R*)-isopropyl methyl-*H*-phosphinates undergo these reactions with complete retention of configuration.[69] More recently, a Cu-catalyzed version of this cross-coupling was discovered.[64] Schwabacher demonstrated that disubstituted methyl phosphinates could be prepared from the mono substituted product, isolated in crude form and exposed to a different aryl iodide, base and $Pd(PPh_3)_4$.[60] Montchamp has also applied this Pd-catalyzed cross-coupling in tandem hydrophosphinylation–cross-coupling reactions of alkyl phosphinates that lead directly to disubstituted aryl-alkenyl phosphinate esters in good yields.[35]



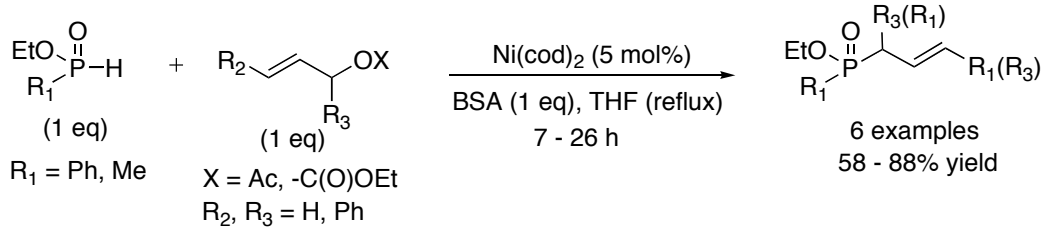
(Eq. 1.29)

The usefulness of these methodologies has been demonstrated in several synthetic applications, as in the preparation of GABA analogs (Scheme 1.11),[70] design of haptens aimed at producing catalytic antibodies to hydrolyze heterocyclic amides,[71] and in the synthesis of phosphinate linked bis-amino acids for incorporation into peptides.[72]

Scheme 1.11 Overman's route to unsaturated GABA analogs



A catalytic allylation reaction of ethyl phenyl- or ethyl methyl-*H*-phosphinates via cross-coupling with allylic acetates or carbonates was also reported by Lu, using BSA/Ni(cod)$_2$ (Eq. 1.30).[65a]



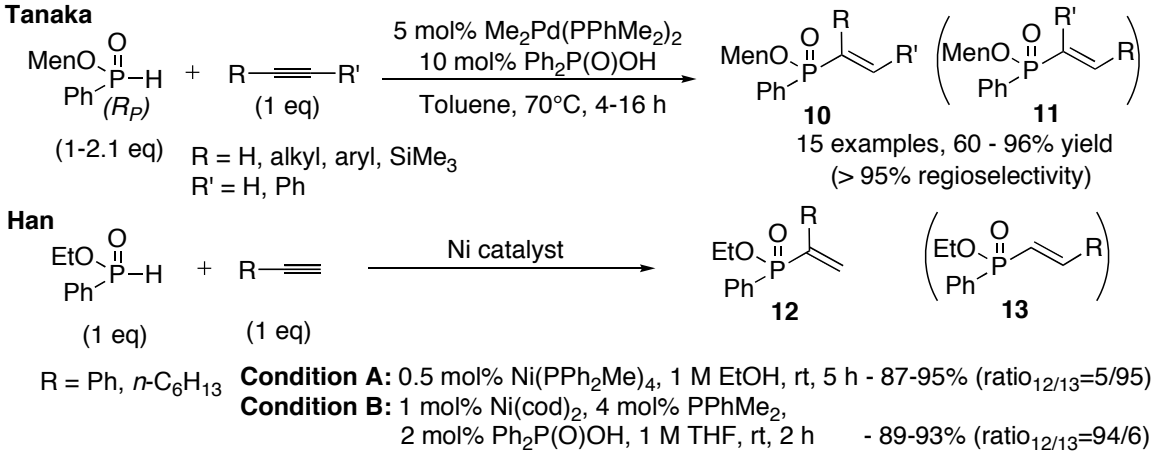
(Eq. 1.30)

1.3.2 Metal-catalyzed hydrophosphinylation reactions

Since the metal-catalyzed hydrophosphinylation of unsaturated compounds is triggered by the oxidative addition of the metal into the P-H bond (Scheme 1.7), this process can be considered a P-H bond activation. There are only two reports in the literature where metals have inserted into the P-H bond of *H*-phosphinates (Scheme 1.12).[73,74] Tanaka showed that the

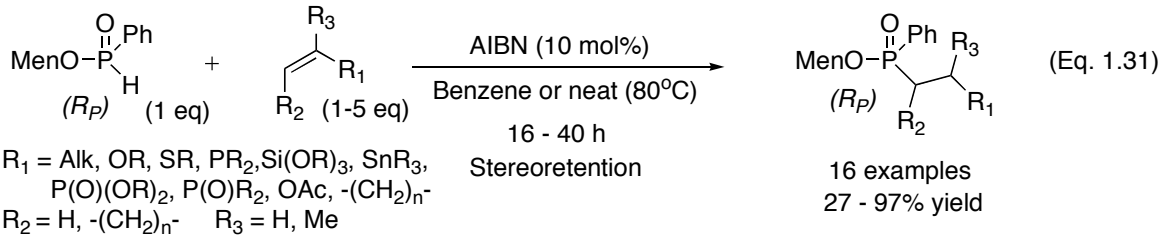
oxidative addition of the P-H bond to Pt (0) proceeds stereospecifically, and developed a highly regioselective Pd-catalyzed stereospecific hydrophosphinylation of (R_P)-menthyl phenyl-*H*-phosphinate with alkynes.[73] A similar procedure was developed by Han, where ethyl phenyl-*H*-phosphinate adds to terminal alkynes in a regioselective manner, via Ni-catalysis.[74]

Scheme 1.12 Metal-catalyzed hydrophosphinylation reactions of *H*-phosphinates



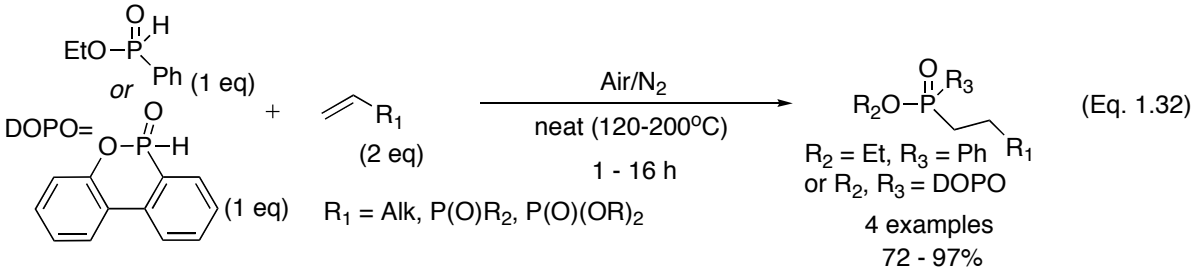
1.3.3 Free-radical and microwave-assisted hydrophosphinylation reactions

Radical initiators such as benzoyl peroxide or AIBN are known for promoting the addition of *H*-phosphinates to unsaturated substrates.[19] There are a few reports in the literature of this reaction but in general they are inefficient, and often require specialized radical initiators, very harsh conditions, and a large excess of one of the reagents.[75] There is an exception that corresponds to aryl-*H*-phosphinate alkyl esters, which do not only undergo addition to olefins in presence of Et_3B/air at room temperature, as described by Montchamp,[25] but also experience AIBN-mediated stereospecific addition to alkenes in refluxing benzene (Eq. 1.31).[76]

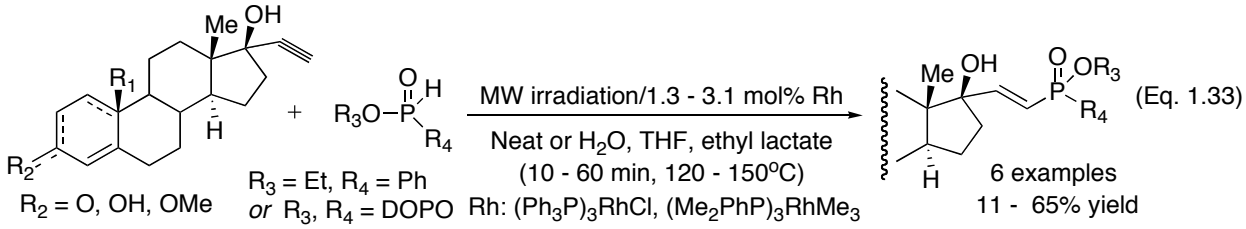


(Eq. 1.31)

More recently, Han described the air-induced anti-Markovnikov addition of reactive aryl-*H*-phosphinates to alkenes, which requires elevated temperatures (Eq. 1.32).[77]

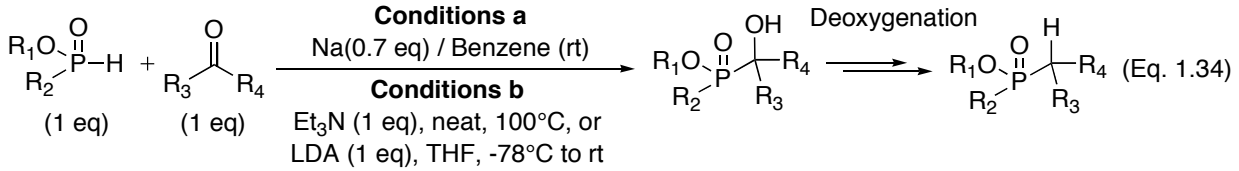


Stockland reported the addition of aryl-*H*-phosphinates to activated alkenes using microwave irradiation in the absence of solvent;[78] which was later extended to a microwave-Rh-assisted addition to ethynyl steroids (Eq. 1.33).[79]

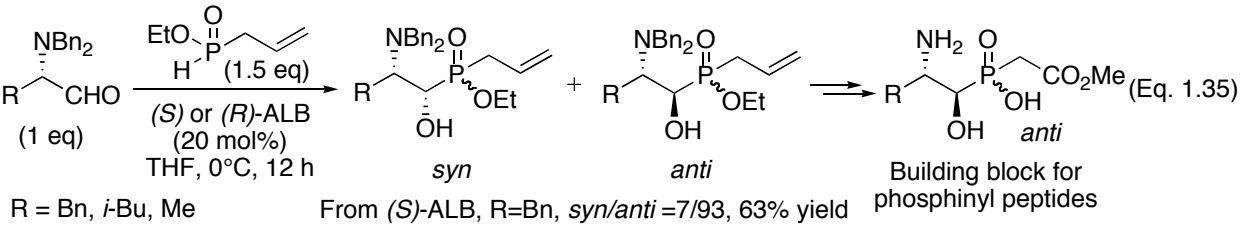


1.3.4 Nucleophilic addition reactions

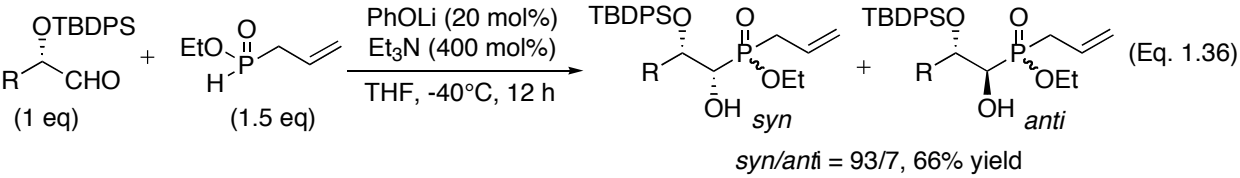
Pudovik reported for the first time the addition of *H*-phosphonates to aldehydes or ketones, i.e. heating under base-catalyzed conditions, typically with alkoxides or tertiary amines.[80] Yamashita,[81a] and Hansen[81b] used this approach to prepare, by addition-deoxygenation processes, alkyl(*sec*-alkyl)phosphinates, which are otherwise difficult to obtain by Arbuzov-or Michaelis-Becker reactions of secondary alkyl halides (Eq. 1.34).[82,36a,55] However, Hansen *et al.* found that under amine-catalysis, *H*-phosphinates exclusively undergo addition to aldehydes and reactive ketones, while acyclic ketones are unreactive, even under forcing conditions.[81b]



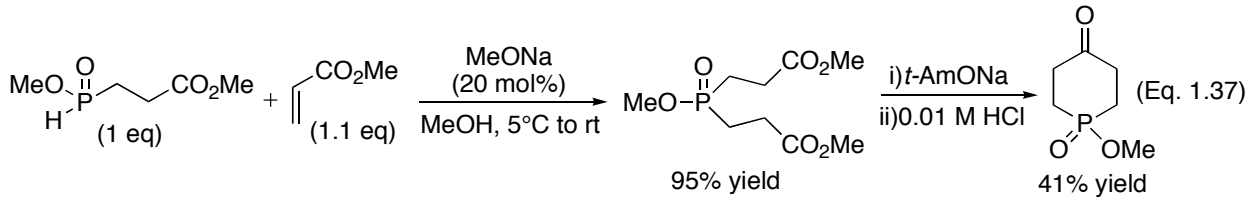
Yokomatsu, Shibuya, and coworkers used Al-Li-BINOL (ALB, see Eq.1.14) complexes to prepare α,α'-dihydroxyphosphinates with low diastereoselectivities.[39a] Later on, they successfully applied this methodology in the highly diastereoselective synthesis of β-amino-α-hydroxyphosphinates, which are useful intermediates in the synthesis of phosphinyl peptides (Eq. 1.35).[83]



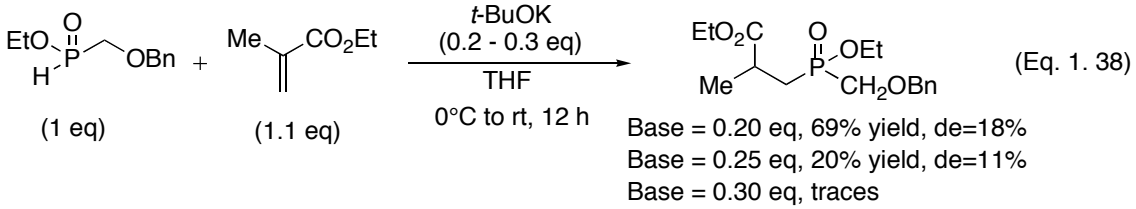
More recently, the same authors reported the utility of lithium phenoxide (PhOLi) as catalyst for the hydrophosphinylation of α-heteroatom-subsituted aldehydes. The addition of Et_3N to the PhOLi-catalyzed hydrophosphinylation of α-oxy aldehydes affords monoprotected *syn*-α,β-dihydroxyphosphinates in high diastereoselectivity (Eq. 1.36).[84]



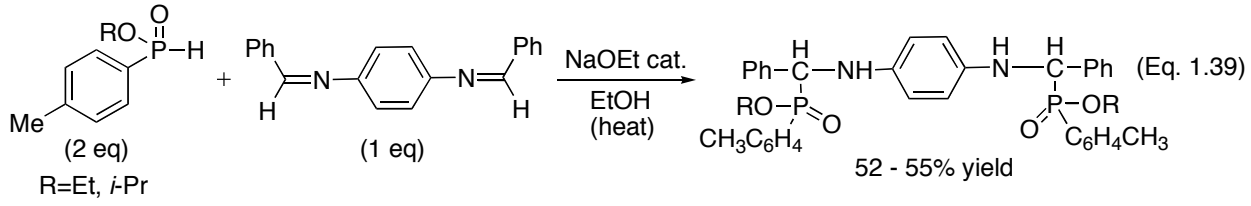
Conjugate addition reactions of *H*-phosphinate alkyl esters to acrylate esters and acrylonitrile, using catalytic amounts of sodium alkoxides was initially reported by Pudovik.[85] Verkade used this reaction in the synthesis of 1-methoxy-1-oxophosphorinan-4-one (Eq. 1.37).[46]



Cristau and coworkers applied this reaction in the synthesis of phosphinodipeptide analogs.[43c] They also developed a modified version of this process using a catalytic *tert*-butoxide activation, and analyzed the influence of the amounts of alkoxide in the diastereoselectivity of the reaction with ethyl methacrylate as substrate (Eq. 1.38).[86] A series of potent inhibitors of NAALADase (N-acetylated-α-linked acidic dipeptidase, EC 3.4.17.21) has also been prepared by NaH-catalyzed addition of *H*-phosphinates to acrylates,[87] providing a new approach for the treatment of neurodegenerative disorders and peripheral neuropathies.

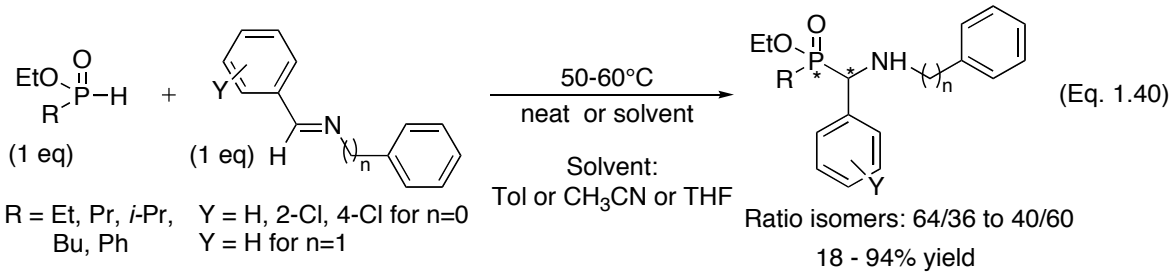


The addition of *H*-phosphinates to imines (Kabachnik-Field type reaction) in the presence of sodium ethoxide was also described by Pudovik during the sixties (Eq. 1.39).[85]

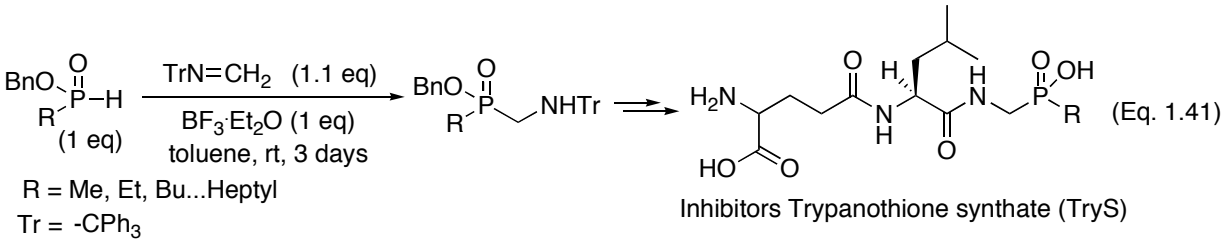


Phosphoryl analogs of glycine that exhibit herbicidal and antitumor activity have been prepared by thermal addition of *H*-phosphinic acid derivatives to triazines.[44a] Szabó studied the thermal reaction of ethyl alkyl- and ethyl phenyl-*H*-phosphinates with imines, and observed a small effect of the size of the substituents on the C=N on the diastereoselectivity of the reaction

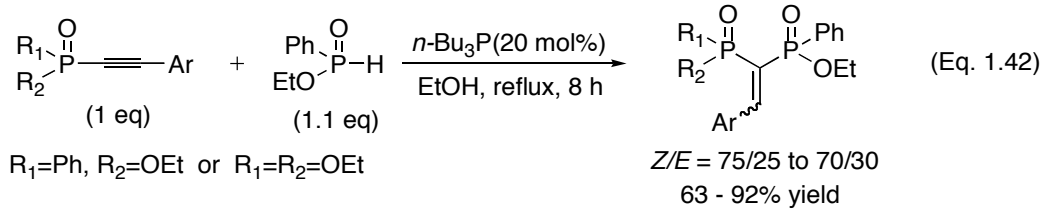
(Eq. 1.40).[88] Cristau has also synthesized α-amino-alkyl hydroxymethylphosphinic acids by thermal addition of *H*-phosphinates to imines.[86]



Coward used catalytic amounts of a Lewis acid ($BF_3{\cdot}Et_2O$) to synthesize functionalized trityl-protected α-aminophosphinates, including the core of complex phosphinopeptide analogues of glutathionylspermidine.[89] This methodology has been recently applied in the synthesis of phosphinopeptides against *Trypanosoma cruzi* (Eq. 1.41).[90]



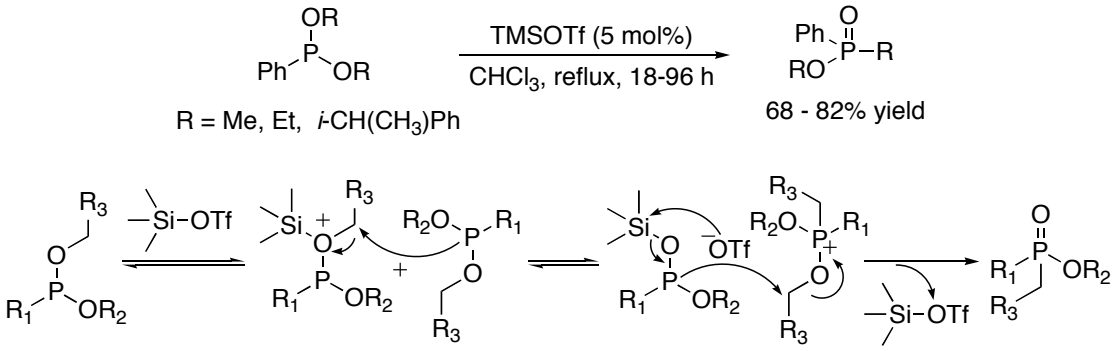
Taran and coworkers recently discovered that PBu_3 efficiently catalyzes the α-P addition of *H*-phosphinates to alkynes bearing phosphane oxide activating moieties. The reaction leads to 2-aryl-1-vinyl-1,1-diphosphane dioxide derivatives in good yields (Eq. 1.42).[91]



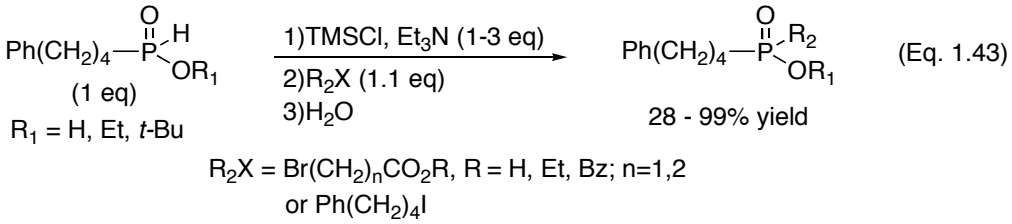
1.3.5 Arbuzov-kind reactions of *H*-phosphinic acid derivatives

A classical approach for the synthesis of disubstituted phosphinates is the Michaelis-Arbuzov rearrangement, which involves the thermal reaction of a phosphonite, $R^1P(OR^2)(OR^3)$ with an alkyl halide (Scheme 1.13).[92] Recently, Lewis acids (5 mol% of TMSOTf or $BF_3{\cdot}OEt_2$) have shown to catalyze this rearrangement under milder conditions, where the migrating groups are limited to primary or activated secondary alkyl groups.[93]

Scheme 1.13 Lewis acid catalyzed Michaelis-Arbuzov rearrangement of phosphonites



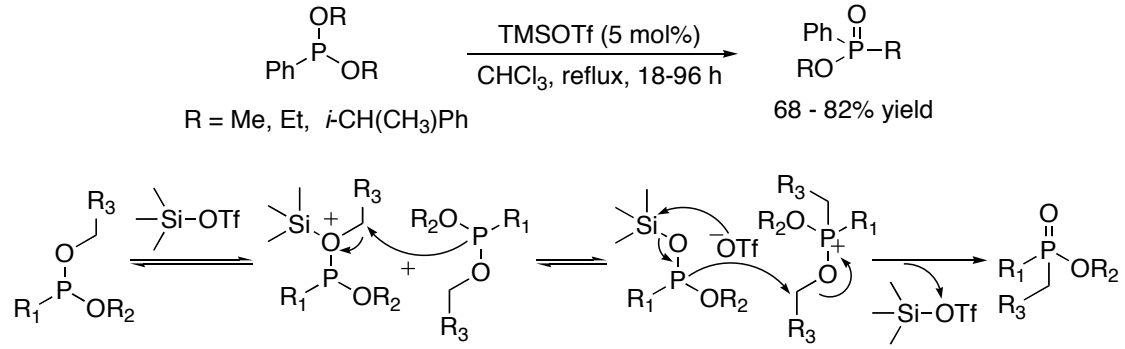
Stepwise silylation and alkylation of *H*-phosphinates (silyl-Arbuzov reaction) was initially demonstrated by Thottathil, using reactive bromoacetates as electrophiles (Eq. 1.43).[94]



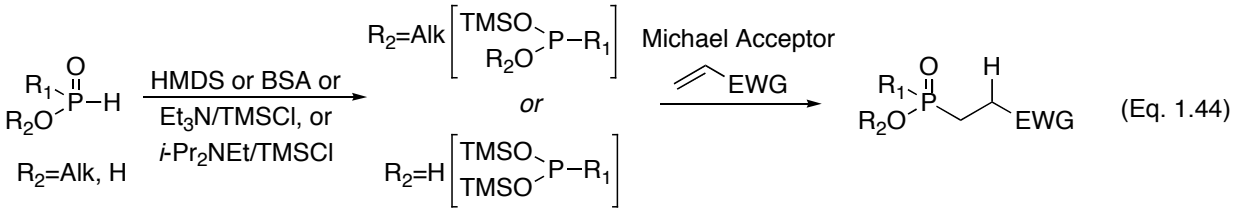
Majewsky reported the formation of symmetrical disubstituted phosphinates by reaction of BTSP with highly reactive halides (benzyl, allyl and α-carbonyl).[95] Subsequently, Boyd and Regan prepared both symmetrical and unsymmetrical disubstituted phosphinic acids using reactive halides.[36a] This methodology has been widely applied in synthesis, such as in the preparation of γ-aminopropyl-*H*-phosphinic acids (GABA analogs),[3a-b] synthesis of

phosphasugars[96] and mono-, bi-, or spyrocyclic phosphinic acid analogues of phosphodiesters,[38e] in the preparation of the commercial heart drug Monopril (fosinopril Sodium) (Scheme 1.14),[2h] and of pseudopeptides that inhibit the human cyclophilin hCyp-19,[97] as well as in the synthesis of MMP's inhibitors,[47a] to name a few.

Scheme 1.14 Preparation of fosinopril sodium



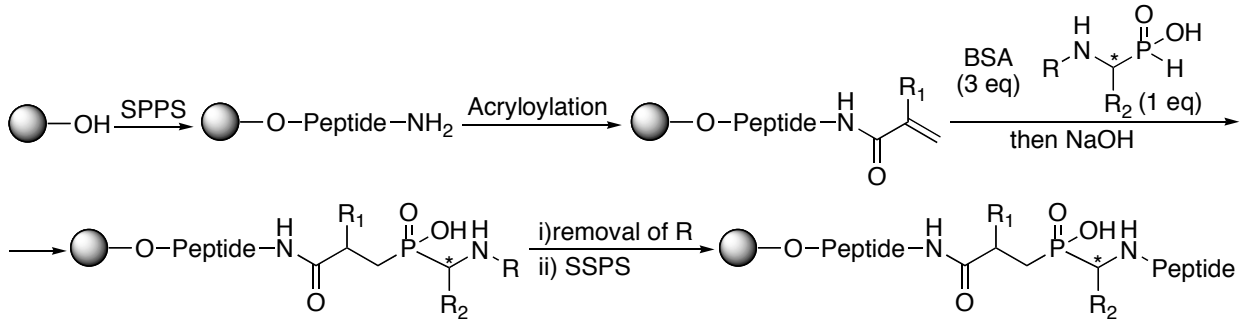
Another convenient procedure to access disubstituted phosphinic acid derivatives consists in the Michael addition of *H*-phosphinates to 1,4-conjugated systems involving silyl alkyl phosphonite intermediates (Eq. 1.44).[98,36c] This transformation constitutes a key step in the preparation of phosphinic pseudopeptides,[99] or phosphinic synthons, suitable for the solid-phase preparation of inhibitors of various metalloproteases.[100]



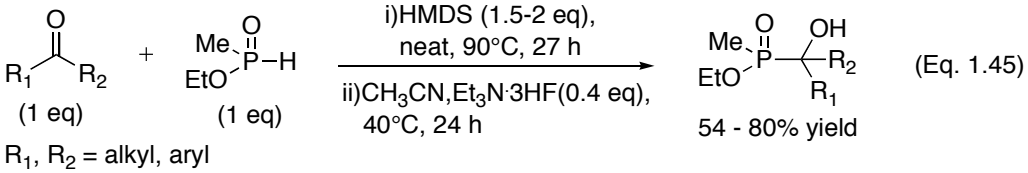
(Eq. 1.44)

Meldal *et al.* developed a solid-phase synthesis of phosphinic peptides in which the carbon-phosphorus bond is formed on a polymer support during peptide synthesis (Scheme 1.15).[101] Numerous preparations of enzymatic inhibitors have used this transformation, i.e. the syntheses of inhibitors of zinc metallopeptidases (analgesics)[102] and inhibitors of folypoly-γ-glutamate synthetase (antifolates).[3f]

Scheme 1.15 Solid-phase peptide synthesis (SPPS) in the preparation of a phosphinic peptide

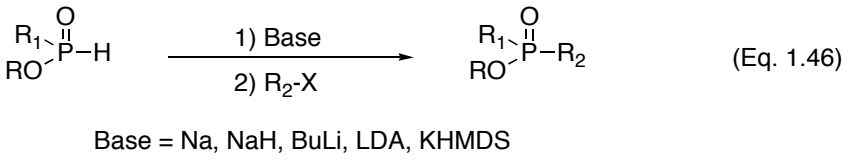


The reaction of trimethylsilyloxy derivatives of *H*-phosphinates with aldehydes and ketones has also been reported (Eq. 1.45).[81b]



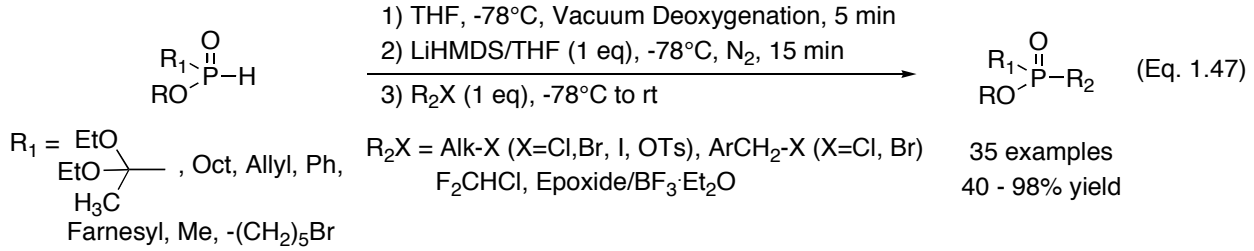
1.3.6 Base-promoted alkylation reactions

Many examples of base-promoted *H*-phosphinate alkylation (Michaelis-Becker type reactions) have appeared in the literature, using a variety of bases (Na, RONa, NaH, BuLi, LDA, KHMDS) (Eq. 1.46).[103,58d,3a-b]



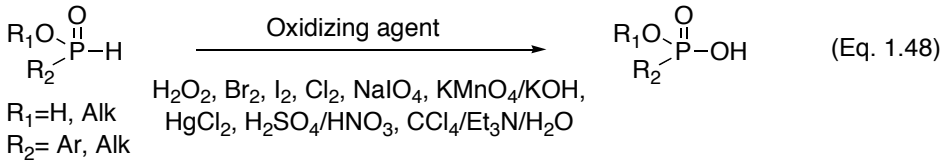
In the seventies, Mislow demonstrated that the NaH-promoted alkylation of enantiomerically pure menthyl phenyl-*H*-phosphinate with methyl and isopropyl iodides (50°C) proceeds with predominant retention of configuration, but yields were not reported.[103a] Remarkable applications of this direct alkylation reaction are found in the synthesis of phosphinic acids analogs of GABA, using NaH or *n*-BuLi as the base;[3a-b] and in the preparation

of 1,1-bisphosphonate squalene synthase inhibitors.[103c] However there did not appear to be a standard set of conditions, nor a general study of this reaction, until recently, when Montchamp and coworkers developed a general protocol for this transformation, using LiHMDS as the base (Eq. 1.47).[104] This reaction works successfully with secondary alkyl iodides, and even with primary alkyl chlorides. Its effectiveness was demonstrated in the synthesis of several GABA analogs or their precursors.[104]

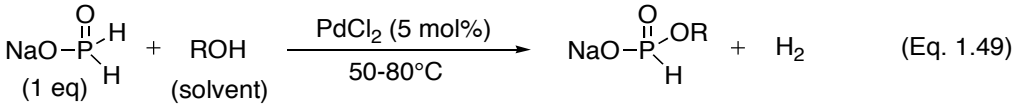


1.3.7 Oxidation and oxidative esterification reactions

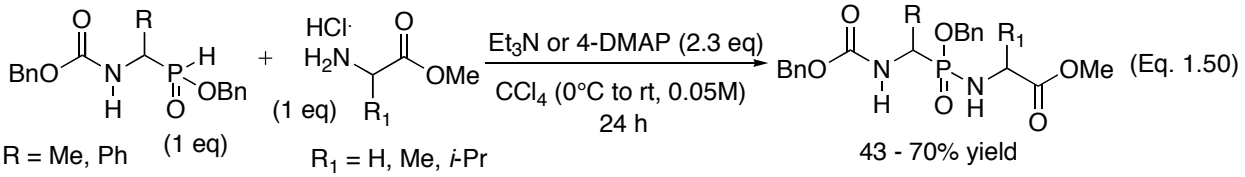
The preparation of phosphonic acids through oxidation of *H*-phosphinic acids is a well-known methodology (Eq. 1.48), which generally requires harsh conditions and strong oxidative agents such as H_2O_2 (30%, 80-90°C);[105] Br_2, I_2 or Cl_2 in H_2O/DMSO or in conc. HI/HCl (20-75°C);[40b,106] $HgCl_2$ or HgO in H_2O (90-95°C);[40b,107] $KMnO_4$/KOH in H_2O (50-250°C);[108] H_2SO_4/HNO_3 (100-110°C);[108] $CCl_4/Et_3N/H_2O$ (35°C);[105c,109] pyridinium chlorochromate/TsOH in DMSO;[110] or $NaIO_4$ (50°C).[103e,111] This transformation is a subject of study in this dissertation (Chapter VI).



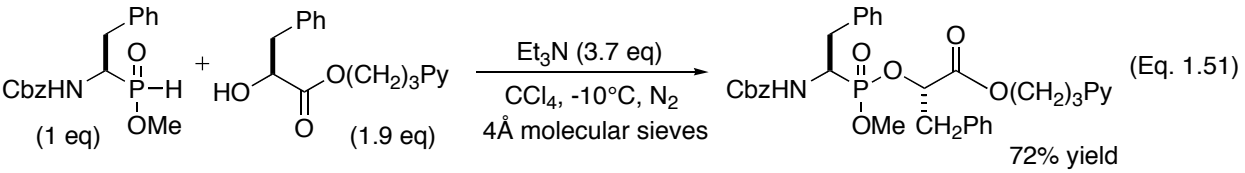
The direct oxidation of sodium hypophosphite ($NaOP(O)H_2$) with MeOH or BuOH in the presence of palladium at 50-80°C was described to produce sodium monoalkylphosphite (NaO)(RO)P(O)H, at stationary hydrogen potential, but yields were not reported (Eq. 1.49).[112]



H-phosphinate esters readily react with carbon tetrachloride and secondary amines, as shown by Atherton *et al.*[113] This transformation has been used in the synthesis of phosphonopeptides (Eq. 1.50).[114]



Phosphonates $(R^1O)(R^2O)P(O)R^3$ can also be prepared by oxidation of *H*-phosphinates with CCl_4 in the presence of an alcohol and triethylamine,[115a] as demonstrated in the synthesis of phosphonate peptide inhibitors of pepsin (Eq. 1.51);[115b] or in tandem hydrophosphinylation-oxidative esterification processes, as shown in Ref. 35, which corresponds to part of the work from this dissertation (Chapter Two).

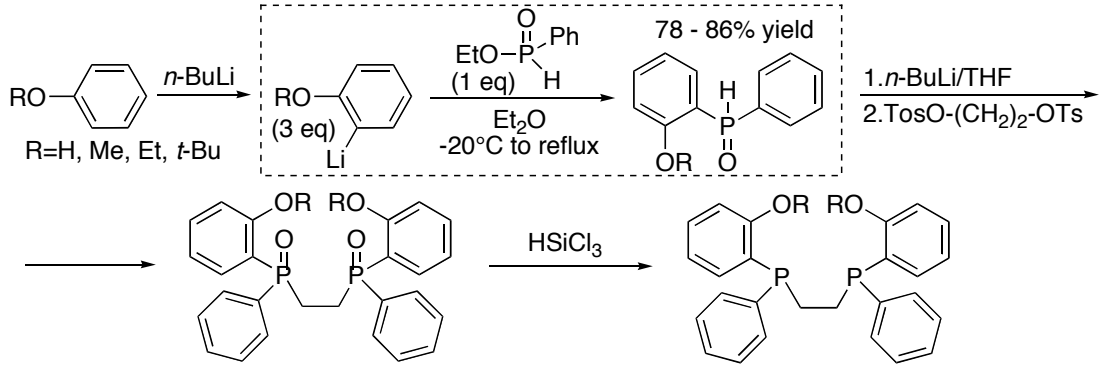


1.3.8 Displacement reactions with organometallic reagents

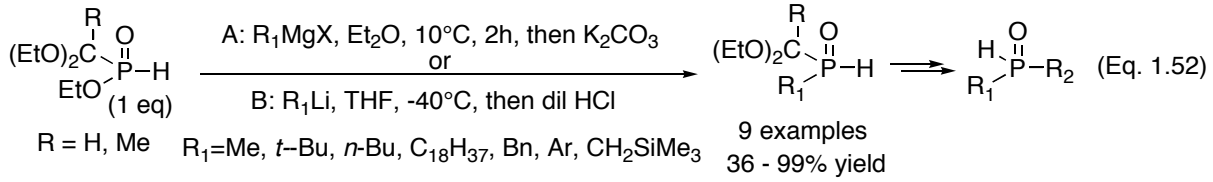
H-phosphinate esters undergo displacement reactions with Grignard reagents to afford secondary phosphine oxides.[116] Van Leeuwen used a variant of this process in the preparation of phosphine ligands, where an alkyllithium reagent displaces the RO- group in *H*-phosphinates,

followed by deprotonation with *n*-BuLi, trapping of the anion with a tosylate and reduction with a silane reagent (Scheme 1.16).[117]

Scheme 1.16 Synthesis of Phosphines by Displacement Reactions with Organolithium Reagents

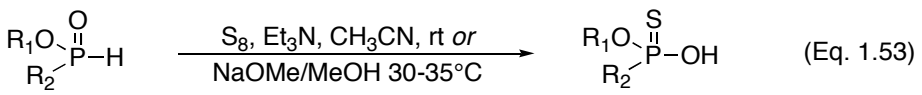


Hall *et al.* prepared protected primary phosphine oxides (otherwise unstable) by the reaction of Ciba-Geigy synthons (**7a** and **7b** in Scheme 1.9) with Grignard or organolithium reagents, and functionalized them into secondary or tertiary phosphine oxides (Eq. 1.52).[118]



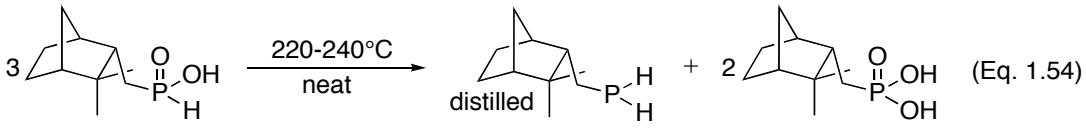
1.3.9 Preparation of phosphonothioic acids

Phosphonothioic acids ($R^1R^2P(S)OH$) have been prepared by the reaction of sulfur (S_8) with *H*-phosphinate esters, in the presence of an amine (Eq. 1.53).[119,35] The reaction occurs with retention of configuration at the *P*-chiral center.[119a] Additionally, the corresponding phosphonothioic acids have been resolved as their salts, using chiral amines, i.e. quinine, brucine or α-phenylethylamine.[119b,120]



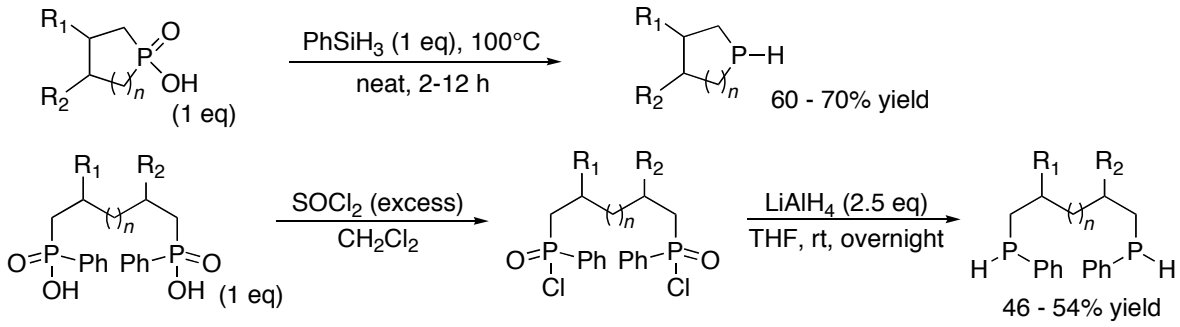
1.3.10 Reduction to primary and secondary phosphines

The disproportionation of *H*-phosphinic acids at elevated temperatures is an useful route for the synthesis of primary phosphines although the reactions proceed in low yields with the corresponding phosphonic acids, as byproducts.[121] One recent example of this process is the disproportionation of endo-8-camphanyl-*H*-phosphinic acid ($camPO_2H_2$) under heating at 240°C, where the corresponding phosphine ($camPH_2$) was collected by distillation (Eq. 1.54).[122]



There are a few reports on reduction of disubstituted phosphinic acids and their corresponding esters to secondary phosphines using silane reagents (i.e. Ph_2SiH_2, $PhSiH_3$ or $SiHCl_3$).[123] Clément showed that heterocyclic disubstituted phosphinic acids can be efficiently reduced to secondary phosphines with $PhSiH_3$, after 2 h at 80-100°C; while the highly polar bis(phosphinic acids) must be converted first into their corresponding chlorides with thionyl or oxalyl chloride, and then reduced with $LiAlH_4$ (Scheme 1.17).[123b]

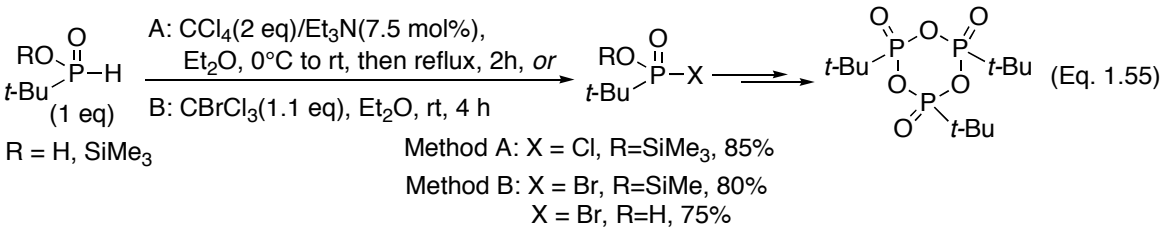
Scheme 1.17 Preparation of phosphines through reduction of disubstituted phosphinic acids



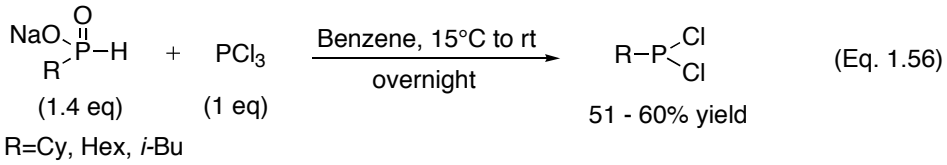
1.3.11 Halogenation and reductive halogenation reactions

Halogenophosphonic acids (RP(O)(OH)X) are very unstable, and are generally prepared and reacted *in situ* by displacement of the halogen atom with nucleophiles (Atherton-Todd reactions).[35,113-115] A few examples of fluorophosphonic acids have been successfully isolated

and characterized.[124] A detailed study of the synthesis, properties and reactivity of halogenophosphonic acid derivatives was published by Kolodiazhnyi and coworkers.[125] They prepared chloro- and bromo-*tert*-butylphosphonic acids, as well as their amine salts and trimethylsilyl esters, through oxidation of *tert*-butylphosphinic acid derivatives with CCl_4 and $CBrCl_3$ (Eq. 1.55).[125] These compounds are precursors, through thermolysis, of the highly unstable dioxophosphorane species, which readily transform into trimers at room temperature.[125]



The reductive halogenation of sodium *H*-phosphinate salts with PCl_3 or $SOCl_2$, instead of their corresponding acids, yields dichlorophosphines in good yields and facilitates their isolation, as described by Nifant'ev (Eq. 1.56).[126] *H*-phosphinate esters have also been converted into dichlorophosphines by treatment with PCl_3.[127]



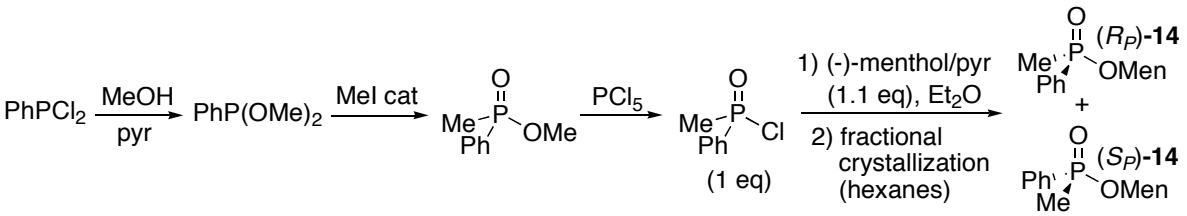
1.4 Preparation of *P*-chiral phosphinates and *H*-phosphinates

1.4.1 Resolution of racemic mixtures using chiral auxiliaries in stoichiometric amounts

In spite of the advances regarding the preparation of phosphinic acids derivatives,[1-3,17] $R^1R^2P(O)(OR)$ and considering the well established methodologies for their transformation to phosphines,[128] achieving their preparation in an enantiopure form continues to be attractive.[129] Use of a chiral auxiliary in stoichiometric amounts is the most common method to prepare *P*-chiral phosphinates.[128,130] Nudelman and Cram,[128c] Mislow and coworkers,[128b,130a] and later

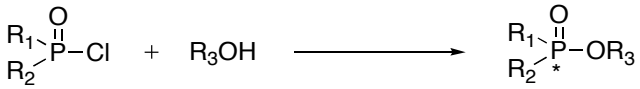
Knowles demonstrated that unsymmetrically substituted menthyl phosphinates **14** can be separated readily into their diasteroisomers by fractional crystallization (Scheme 1.18).[130b]

Scheme 1.18 Preparation of *P*-chiral phosphinates via chemical resolution with a chiral alcohol



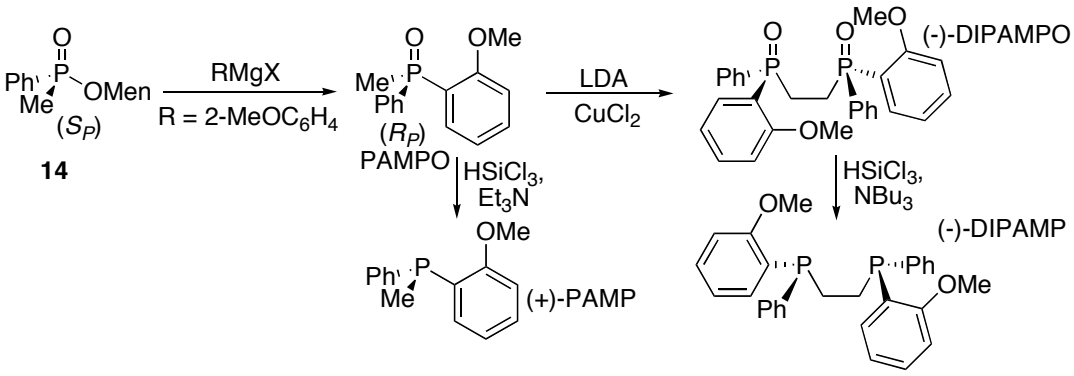
The reaction of phosphinic acid chlorides with chiral alcohols has been established as an important route to prepare *P*-chiral phosphinate esters (Table 1.1)[131,130e-f] which can then undergo stereospecific displacement reactions with Grignard reagents and/or reduction to produce chiral organophosphorus ligands.[128] For example, the reaction of *o*-anisylmagnesium bromide with the phosphinate **14** gives optically active (+)-(*R*)-*o*-anisylphenylmethylphosphine oxide (*R*-PAMPO), which is used in the synthesis of (+)-PAMP, (-)-DIPAMPO and (-)-DIPAMP (Scheme 1.19).[128d,132]

Table 1.1 Reaction of phosphinic acid chlorides with chiral alcohols



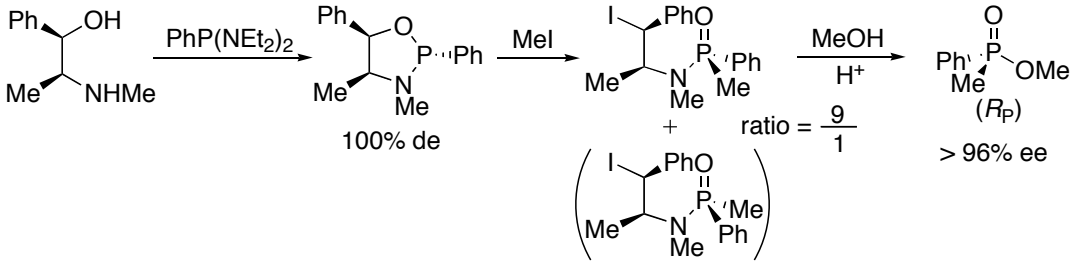
R_1	R_2	R_3OH	Base	Ratio Products	Ref.
Ph	Me	*D*-glucofuranose	Et_3N	90:10	131c
Ph	Et	*D*-glucofuranose	Et_3N	96:4	131c
Ph	Me	Diacetone-*D*-glucose	Et_3N	97:3	130e
Ph	Bn	*D*-glucofuranose	Et_3N	100:0	131a
Ph	Me	*(1S)*-Borneol	DMAP	4:1	130f
Ph	Me	(-)-Menthol	DMAP	2:1	131d
Ph	Me	(-)-Isopinocampheol	DMAP	1:1	130f
Ph	Me	(+)-Isoborneol	DMAP	74:26	130f
4-$MeOC_6H_4$	Ph	(-)-Menthol	Et_3N	4:1	130b,131b

Scheme 1. 19 Preparation of *P*-chiral organophosphorus ligands



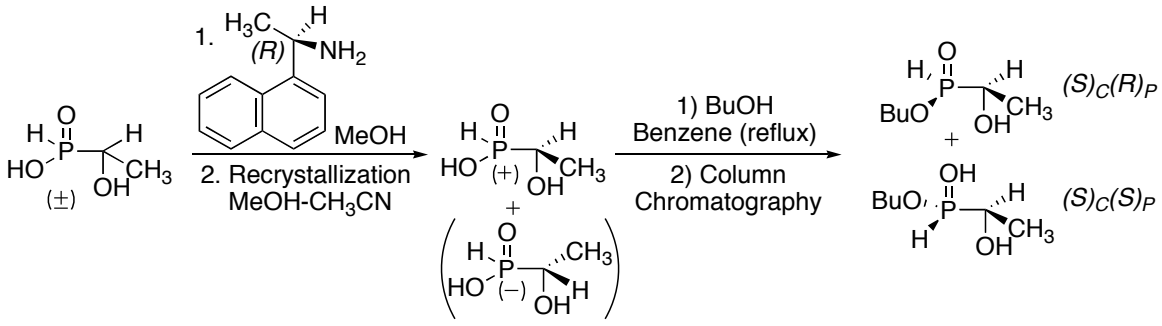
The asymmetric Arbuzov-reaction has also been investigated as an approach to *P*-chiral phosphinates. Juge *et al.* reported the most successful development in this area, based on the formation of an oxazaphospholidine from ephedrine (chiral auxiliary), which undergoes an Arbuzov reaction with alkyl halides to form a mixture of phosphinamide diastereoisomers in a ratio of 9:1. Subsequent separation by crystallization, followed by acid-catalyzed methanolysis produces *P*-chiral disubstituted phosphinate esters (Scheme 1.20).[128d,130g]

Scheme 1.20 Synthesis of *P*-chiral phosphinates via asymmetric Michaelis-Arbuzov reaction



P-Chiral *H*-phosphinate esters have been less studied and only a few successful asymmetric syntheses (where the chirality resides at the *P*-atom) of these compounds exist in the literature. One representative example is the resolution (at the α-carbon) of 1-hydroxyethyl-*H*-phosphinic acid with a chiral amine, which results in a pair of enantiomers that can be separated by recrystallization. Subsequently esterification affords a 50:50 mixture of diastereoisomers possessing two chiral centers (*P*-atom and α-carbon) (Scheme 1.21).[133]

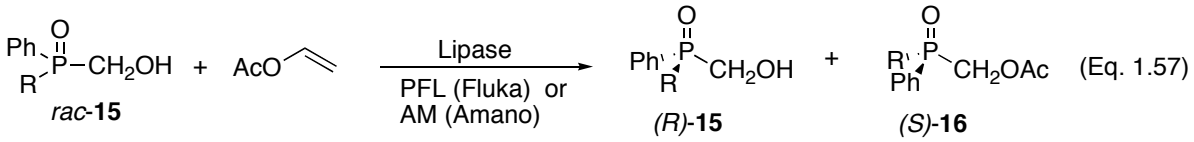
Scheme 1.21 Resolution of 1-hydroxyethyl-*H*-phosphinic acid and its esters



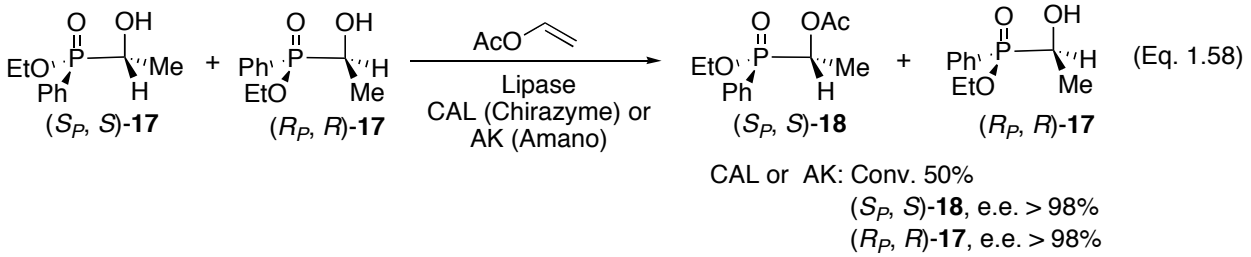
A more convenient approach would be the desymmetrization of tetrahedral prochiral phosphinates [(RO)P(O)H_2] through conversion into *H*-phosphinate esters RP(O)(OR)(H) via different P-C bond forming reactions, which is a subject of study in this dissertation (Chapter Seven). Moreover, the direct measurement of enantiomeric purity of *H*-phosphinates using a column with a chiral stationary phase has thus far not been reported with any success.[134] Some attempts to resolve them by HPLC will be discussed in Chapter Seven. Alternative methods to determine optical purity are the use of NMR chiral shift reagents,[69b,135] or derivatization to diastereoisomeric products via stereospecific alkylation or cross-coupling.[69,103a]

1.4.2 Enzymatic kinetic resolutions

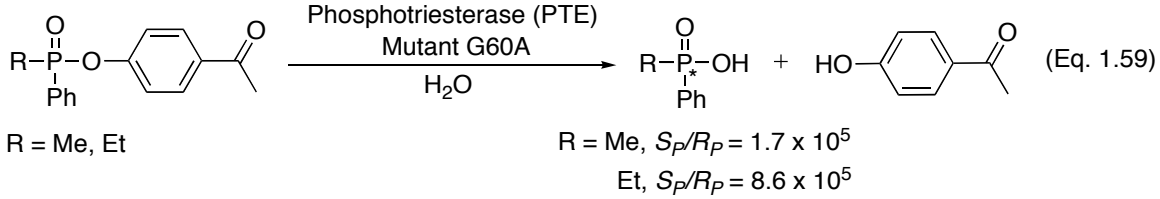
Only a few examples of enzymatic kinetic resolutions of hydroxyphosphinates have appeared in the literature. Initially, Kielbasinski demonstrated that a lipase-catalyzed acetylation of racemic *P*-chiral hydroxymethylphosphinates *rac*-**15** under kinetic resolution conditions proceeded stereoselectively to give enantiomerically enriched unreacted substrate **15** and product **16**, with enantiomeric excesses over 90% (Eq. 1.57).[136] The reaction was performed in organic solvents, ionic liquids, and supercritical carbon dioxide.



Shioji extended this enzymatic kinetic resolution to *H*-phosphinates **17** containing two stereogenic centers, the phosphorus and the α-carbon (Eq. 1.58);[137] while Yamagishi accomplished the lipase-catalyzed hydrolysis of the acetate precursors of racemic α-hydroxy-*H*-phosphinates.[138]



Recently, Raishel published an interesting enzymatic kinetic resolution of *P*-chiral phosphinates using an enantioselective enzyme library constituted by the bacterial phosphotriesterase and 15 mutant enzymes. These enzymes catalyze the stereoselective hydrolysis of racemic mixtures of phosphinate esters. With a single active-site mutant G60A, one enantiomer can be preferred for up to 6 orders of magnitude (Eq. 1.59).[139]

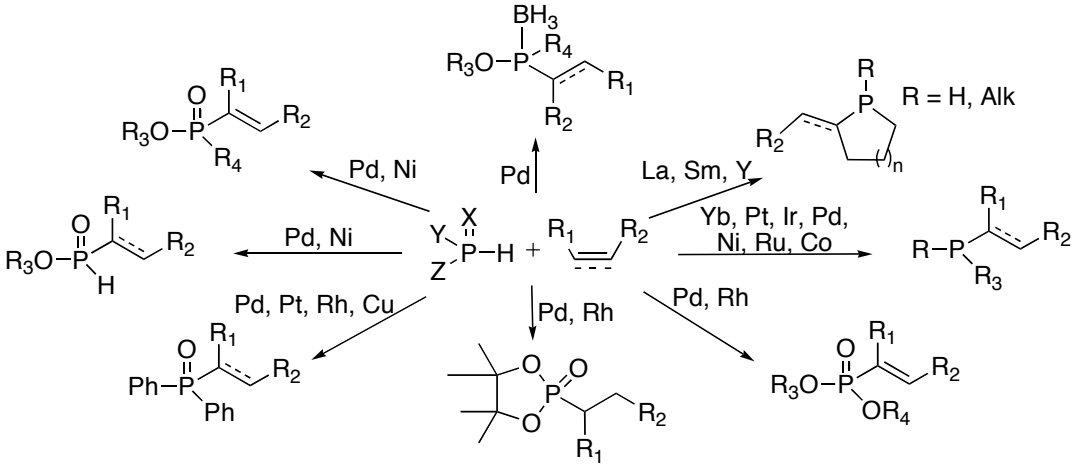


Chapter Two: Transition metal-catalyzed hydrophosphinylation reactions

2.1 Introduction

Recently, metal-catalyzed transformations that involve addition of phosphorus compounds along carbon-carbon unsaturated linkages have emerged as the subject of intensive research due, not only to the wide availability of the starting materials, but also to the fact that they are highly atom economical (since no atom loss is observed) and efficient approaches for the synthesis of organophosphorus compounds.[29] Although some of these reactions can be carried out under radical and base-catalyzed conditions, and to a lesser extent using acid-catalysis and thermal activation with activated alkenes,[140,78,79] significant improvements on the selectivity and rate have been achieved through metal catalysis.[29] In this area, the formation of carbon-phosphorus bonds by addition of P(III) reagents (hydrophosphination) and P(V) reagents (hydrophosphinylation and hydrophosphorylation) to various unsaturated substrates has been studied as a viable route to phosphines,[140-142] tertiary phosphine boranes,[143] phosphonates,[31,32,144] tertiary phosphine oxides,[145] phosphinates,[73,74] and *H*-phosphinates[33-35] (Scheme 2.1).

Scheme 2.1 Metal-catalyzed additions of phosphorus compounds to unsaturated substrates

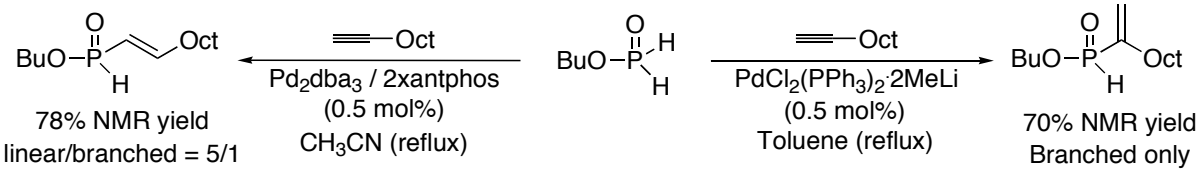


For example, various groups have reported the transition metal-catalyzed addition of PH_3 to activated alkenes,[141] Marks and Tataki described hydrophosphination processes with primary

and secondary phosphines using organolanthanide complexes,[142a-i] while Beletskaya reported the Pd- and Ni-catalytic addition of diphenylphosphine to vinylarenes and several internal and external alkynes.[142j-o] Recently, Dixneuf (ruthenium) and Oshima (cobalt) described also the addition of diphenylphosphine to alkynes[142p] and propargyl alcohols,[142q] respectively. The Pd-catalyzed addition of secondary phosphine-borane complexes to alkynes has also been developed and its asymmetric version provided low enantiomeric excesses of tertiary phosphines (up to 42%).[143] More related to our research is the formation of carbon-phosphorus bonds by addition of P(V) compounds across carbon-carbon multiple bonds. As described in Chapter I (Section 1.2.3, Scheme 1.6), Tanaka pioneered the development of metal-catalyzed hydrophosphorylation reactions through addition of *H*-phosphonates to terminal alkynes,[31,32] and other authors have extended the work with these substrates.[144] However, with alkenes and dienes the scope is highly limited because pinacol-*H*-phosphonate is the only reactive substrate.[32] With respect to hydrophosphinylation processes, efforts have been mainly focused on the addition of secondary diphenyl phosphine oxide,[145,74] where the P-H bond appears to be very reactive and the reaction proceeds even at room temperature. Only two reports on hydrophosphinylation with a special kind of activated aryl-*H*-phosphinates to alkynes have appeared in the literature (Scheme 1.12).[73,74] In fact, the P-H bond activation in *H*-phosphinates is a subject of study in this dissertation (Chapter VI). Another interesting transformation is the hydrophosphinylation with hypophosphorous compounds, which possess two phosphorous-hydrogen bonds, and are highly prompted to undergo transfer hydrogenation reactions. Notably, Montchamp and coworkers effectively overcame the reductive pathway (Scheme 1.6) and prepared a broad range of synthetically versatile monosubstituted *H*-phosphinates using both homogeneous (Eq. 1.10)[33,35]

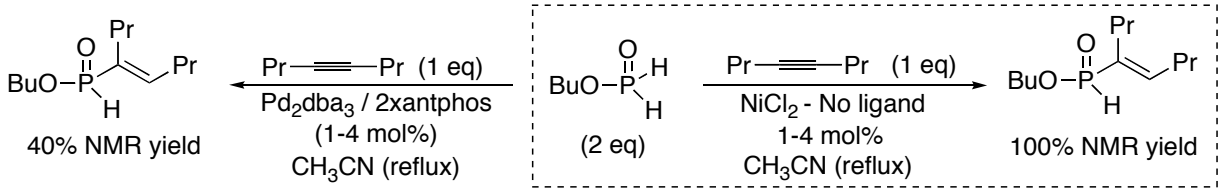
and heterogeneous catalytic conditions (Eq. 1.11).[34] As for the unsaturated partners, terminal and some internal alkenes, as well as internal and terminal alkynes participate successfully in the reaction with H_3PO_2, AHP and alkyl phosphinates in the presence of low catalyst loading of Pd_2dba_3/xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) (1 mol% or less).[33] For terminal alkynes, a good regioselectivity for the linear *vs* the branched isomers of alkenyl-*H*-phosphinates was reported (Scheme 2.2).[33] Nonetheless, it was still highly desirable to extend the scope of this transformation to other unsaturated partners, to improve the regiocontrol, and to explore the mechanism. We addressed these issues in the present study and the results will be disclosed in the following section (Section 2.2).

Scheme 2.2 Regioselectivity on addition to terminal alkynes from Ref. 33



Additionally, due to the fact that alkyl phosphinates proved to react sluggishly with internal alkynes using Pd-catalysts, we turned our attention to Ni-catalysis and we discovered that $NiCl_2$ effectively catalyses this hydrophosphinylation reaction in the absence of added ligand (Scheme 2.3). The results of this project were published in 2005, as a full paper,[35] and will be discussed in Section 2.3.

Scheme 2.3 Ni *vs* Pd catalysis in hydrophosphinylation of 4-octyne with alkyl phosphinates



2.2 Pd-catalyzed hydrophosphinylation of alkenes, alkynes, allenes and dienes

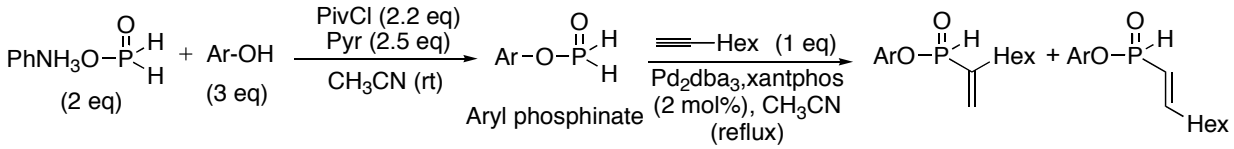
2.2.1 Scope of the reaction

As discussed in the preceding section, hypophosphorous compounds undergo addition to alkenes and alkynes in the presence of palladium catalysts.[33] To further investigate the scope of the reaction and to improve the regiocontrol in the addition to terminal alkynes, a series of experiments were designed through screening of several reaction parameters. The results are summarized in the following sections.

2.2.1.1 Regioselectivity on alkynes

The regioselectivity for the addition to terminal alkynes was initially investigated by means of controlling the size of the ester group in aryl phosphinates, however the results were not promising. This is probably related to the fast hydrolysis and oxidation of the corresponding aryl phosphinates under the reaction conditions (Table 2.1). As of today, there are no successful reports on the synthesis of these compounds. Since, we shifted our focus towards the screening of catalytic systems in order to achieve this regiocontrol. We screened various ligands and catalysts combinations, 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 2.2.

Table 2.1 Pd-catalyzed hydrophosphinylation of terminal alkynes with aryl phosphinates



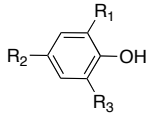
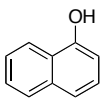
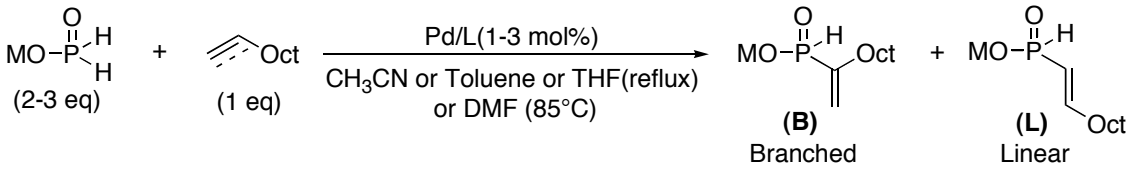
ArOH		^{31}P NMR δ (NMR yield, %) $ROP(O)H_2$	Hydrophosphinylation ^{31}P NMR yield, % (Outcome of the reaction)
	R_1, R_2, R_3= Me	14.7-t (60)	No P-C bond formation
	R_1=R_3= *t*-Bu; R_2= OMe	0	-
	R_1=R_3= *t*-Bu; R_2= H	14.4-t (100)	No P-C bond formation
		0	-

Table 2.2 Regioselectivity study in the Pd-catalyzed hydrophosphinylation of 1-alkynes



Entry	M	Method[a]	Solvent	Catalyst	RatioB/L	NMR Yield, % (Isolated Yield,%) Outcome
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	$PdCl_2dppf{\cdot}CH_2Cl_2$	12/1	100[b]
6	Bu	B	Tol	$PdCl_2dppf{\cdot}CH_2Cl_2$	8/1	100[b]
7	Bu	B	Tol	$PdCl_2(PPh_3)_2{\cdot}2MeLi$	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	$PdCl_2(PPh_3)_2{\cdot}2MeLi$	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	$PdCl_2(PPh_3)_2{\cdot}2MeLi$	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	100 (Messy)
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	-	Messy
32	$PhNH_3$	C	DMF	$PdCl_2$, xantphos	-	Messy
33	H	C	DMF	Pd_2dba_3, dppf	-	0

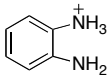
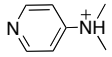
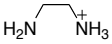
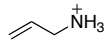
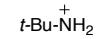
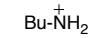
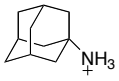
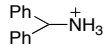
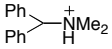
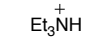
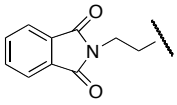
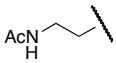
[a] Method A: 3 eq AHP, 3 eq $(RO)_3Si(CH_2)_3NH_2$, 3 eq TFA, 1 eq alkyne, 1 mol% Pd/L. Method B: 3 eq Stock solution $ROP(O)H_2$ (0.5 M), 1 eq alkyne, 1-3 mol% Pd-L; Method C: 2 eq H_3PO_2 or AHP, 1 eq alkyne, 1 mol% Pd/L; [b] Purification did not yield pure product (contamination with byproduct $(RO)_2P(O)H$); [c] Heterogeneous mixture.

As we can observe in Table 2.2, when using alkylphosphinates, we could achieve a good regiocontrol for the formation of the branched isomer over the linear (entries 1-6). The best result was obtained using a TFA salt of an aminosilicate as esterifying agent[18] and Pd_2dba_3/dppf as catalyst in toluene (entry 1, branched/linear = 16/1), however we could not repeat the previous result where the branched isomer was obtained exclusively using $PdCl_2(PPh_3)_2$/MeLi (Scheme 2.2),[33] instead we obtained a ratio of 4/1, favoring the branched alkenyl-*H*-phosphinate (entry 7). Good control was also accomplished using Pd_2dba_3/xantphos in CH_3CN (entry 16), where the linear isomer was obtained in a ratio of 10/1 over the branched product. In this case, the regioselectivity was improved compared to the previous results (linear/branched = 5/1, Scheme 2.2).[33] The results indicate that the main parameter appears to be the solvent, and to a lesser extent the ligand. Additionally, the use of aminosilicates (Method A) was crucial in the isolation of pure products as the silicate byproducts were eliminated by a simple acidic workup, and the other byproduct diethylphosphite $(EtO)_2P(O)H$ was removed in vacuo. Attempts to purify the products obtained from Method B by chromatography on silica gel were not successful due to the inability to separate the byproducts dialkylphosphites from the alkenyl-*H*-phosphinates. In sharp contrast, the use of AHP or H_3PO_2 did not furnish good results (entries 22-33). In general, the yields were low and/or the reactions were not selective (various unidentified products were obtained). In toluene, the reactions were not homogeneous and high "false" NMR yields were measured (entries 27-28), however the isolated yields were very low. In this case, the best result was obtained in DMF with H_3PO_2 (branched/linear = 2.5/1, entry 24), but unfortunately the regioselectivity was still not good and further optimization appears to be required.

2.1.1.2 Extension of the scope and investigation of the reaction insights

To further extend the scope of the reaction, we investigated the influence of the electronic, steric, and acidic character of various hypophosphorous compounds in the Pd-catalyzed hydrophosphinylation reaction with alkenes (Table 2.3).

Table 2.3 Reactivity of hypophosphorous compounds in the hydrophosphinylation with 1-octene

Entry	$MOP(O)H_2$ M =	Method for $MOP(O)H_2$[a]	Solvent	$MOP(O)H_2$ ^{31}P-NMR δ, (% yield)	Pd_2dba_3, xantphos (mol%)	^{31}P NMR Yield, %	Isolated Yield, %[b]
1		A	DMF	4.2 (100)	1	0	-
2		A	DMF	-0.6 (100)	1	20[c]	-
3		A	DMF	-2.2 (100)	1	12	-
4		A	DMF	-1.1 (100)	1	100[c]	19
5		A	DMF	-2.8 (100)	1	88[c]	40
6		A	DMF	-1.4 (100)	1	0	-
7		A	DMF	4.3 (82)	1	77[c]	28
8		A	DMF	-1.8 (100)	1	13[c]	-
9		A	DMF	5.7 (100)	1	137	98[g]
10		B	DMF	0.7	1	29	-
11		B	DMF	-0.6	1	4	-
12		B	DMF	-1.4	1	6	-
13		B	DMF	5.3	1	54	71[h]
14		A	DMF	3.3	1	0[c,d]	-
		B	DMF	5.0	1	60[c,e]	33
15		B	DMF	3.3	1	29[c]	-
16		C	CH_3CN	19.8 (19)	1	27	-
		D		20.6 (98)	2	100	-
17		C	CH_3CN	20.1 (39)	1	6[f]	-
		D		20.8 (67)	1	60[f]	-
18	Bu	E	CH_3CN	-	1	100	100[i]
		E	DMF	-	1	6	-

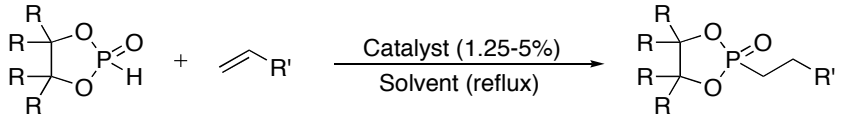
[a] Method A: 2 eq H_3PO_2, 2 eq amine, rt, 2 h, then 1 eq 1-octene and 1 mol% Pd/L, DMF (85°C), 12 h; Method B: 2 eq pre-prepared $ROP(O)H_2$, then alkene and Pd, as in Method A; Method C: 1 eq AHP, 1.5 eq MOH, 1.1 eq PivCl, 1.25 eq Pyr, rt, 2 h, then 2 eq alkene and 1 mol% Pd/L, reflux, 12 h; Method D: 1 eq H_3PO_2, 1 eq $(PhO)_4Si$, 2 eq MOH, reflux, 2 h, then 2 eq alkene and 1-2 mol% Pd/L, reflux, 12 h; Method E: One pot, 3 eq. H_3PO_2 or AHP, 2.1 eq $(BuO)_4Si$, 1 eq alkene and 1 mol% Pd/L, reflux, 12 h. [b] Isolated pure by acidic workup, unless otherwise noted. [c] Not homogeneous. [d] 2 eq TFA were added. [e] 1 eq $(cinchonidine)_2{\cdot}H_2SO_4{\cdot}3H_2O$ was used. [f] The low yield is due to hydrolysis to the acid. [g] 21% of oxidized product (phosphonic acid). [h] Octyl phosphonic acid. [i] Purification by chromatography on silica gel.

In Table 2.3 (entries 1-15), we observe that both the acid-base character and steric hindrance of the amine in hypophosphorous acid salts influences the reaction. An aniline-like substrate (pK_a 4.5, entry 1) did not participate successfully in the reaction, which could be due to the steric hindrance from the amino group in the ortho position, contrary to anilinium hypophosphite (AHP), which yields 93% of product (Ref. 33). Salts of the more basic aniline 4-DMAP (pK_a 9.5, entry 2), and of alkyl, allylic and benzylic primary amines (pK_a 9-11) (entries 3-8) furnished low yields of products and their solubility was quite low in DMF, which is reflected in the high NMR yields compared to the isolated ones. However, the more basic tertiary benzylic amine from entry 9 did undergo the reaction in good yield. Interestingly, the sterically hindered *t*-BuNH_2 (entry 5) reacted better that Bu-NH_2 (entry 6), which is somewhat unexpected. With ammonium hypophosphite or tertiary amines (entries 11 and 12) the yields of product were also very low. Finally, the hydrophosphinylation with salts of *N*-heterocycles (entries 13 and 14) gave low to moderate yields of products, but interestingly, with pyridinium hyposphosphite (entry 13), the oxidized product (octyl phosphonic acid) was obtained instead. This finding served as a precedent for the development of an *in situ* oxidation of *H*-phosphinic acids (Chapter Six).

Looking towards the development of an asymmetric version of this process by means of a combination of chiral catalysts and hydrogen-bonding participation, we examined the stability of an alkyl phosphinate bearing a primary amide (entry 17), however we observed that these compounds were not very stable and tended to hydrolyze into the corresponding acids under the reaction conditions (entry 16 *vs* 17). This finds precedents in the literature.[135b] We also confirmed that the one-pot tandem esterification-hydrophosphinylation reaction occurs uneventfully in CH_3CN (entry 18).

Related to this work, a series of control experiments were tried on pinacol-*H*-phosphonate[146] (introduced by Tanaka, see Scheme 1.6),[31a-d] using our catalytic conditions (Table 2.4). It should be noted that this phosphonate is not a convenient synthon to access phosphonic acids because its cleavage requires very harsh conditions.[32] Pursuant to the design of a phosphonate synthon possessing a more labile protecting group, benzopinacol-*H*-phosphonate was prepared,[147] and reacted under the hydrophosphorylation conditions reported by Pagenkopf (Table 2.4).[31e] Even though the results were not good, we devised later a highly efficient methodology to prepare phosphonic acids directly starting from H_3PO_2 (Chapter Six).

Table 2.4 Hydrophosphorylation of pinacol-*H*-phosphonates[a]

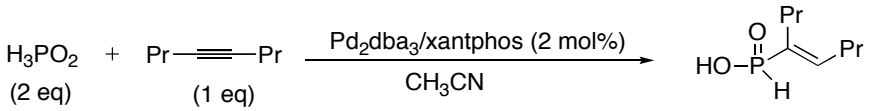


Entry	$(RO)_2P(O)(H)$ R (eq)	R' (1 eq)	Catalyst (%)	Solvent	^{31}P NMR Yield, %
1	Me (1)	Oct	Pd_2dba_3/xantphos (2)	CH_3CN	19
2	Me (2)	Oct	Pd_2dba_3/xantphos (2)	Toluene	0
3	Me (2)	Oct	Pd_2dba_3/xantphos (2)	THF	47
4	Ph (1)	Hex	$Cl(PPh_3)_3Rh$ (1.25)/dppb (5)	Dioxane	54[b]

[a] The reactions were run under N_2 between 14-42 h. [b] Several peaks were observed in ^{31}P NMR, probably due to hydrolysis and/or formation of the branched isomer.

Next, we investigated and optimized the conditions to achieve the Pd-catalyzed hydrophosphinylation under microwave irradiation. As for the unsaturated substrate, an internal alkyne was used (Table 2.5). The reaction was very fast and good yields of product were obtained, comparable to the results achieved with normal heating (Isolated yield = 90%).

Table 2.5 Pd-catalyzed hydrophosphinylation of 4-octyne with microwave heating[a]



Entry	Temperature (°C)	Power (W)	Time (min)	Pressure (psi)	^{31}P NMR yield, % (Isolated yield, %)
1	100	35	5	22	97 (90)
2	100	35	2	20	92
3	125	65	5	63	83

[a] Concentrated acid was used.

The influence of the electronic and steric character of various monodentate phosphine ligands, and the catalytic activity of a different source of Pd were briefly investigated in the hydrophosphinylation of 1-octene (Table 2.6). The use of monodentate phosphines produced low yields of the hydrophosphinylation product, which decreased as expected, as a result of increasing the number of electron-donating substituents on the aromatic ring. These low yields can be explained by a faster transfer hydrogenation than hydropalladation pathway (Scheme 1.7). As expected, the success of the bisphosphine xantphos (100% yield of product, Ref. 33) is probably related to its tendency to be *trans*-chelating in Pd-complexes, which has been demonstrated experimentally by X-ray crystallography (P-Pd-P, bite angle=150.7°).[148] Xantphos appears to slow down the reductive elimination of the phosphinyl-Pd-hydride complex into Pd-dihydride (**2b-2a**, Scheme 1.6). Nonetheless, when using $PdCl_2$ in the absence of ligand, in refluxing toluene (entry 7), a high yield of product was obtained. This last result has implications in the development of an asymmetric variant of this reaction using chiral ligands (Chapter VII).

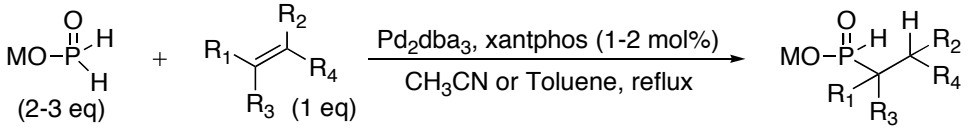
Table 2.6 Influence of the ligand in the Pd-catalyzed hydrophosphinylation of 1-octene[a]

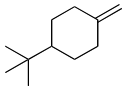
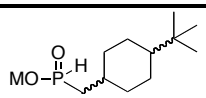
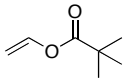
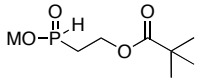
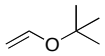
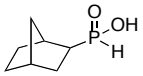
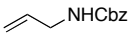
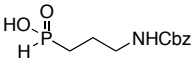
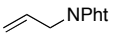
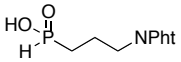
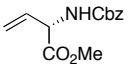
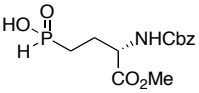
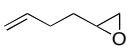
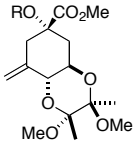
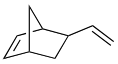
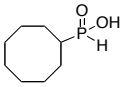
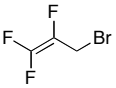
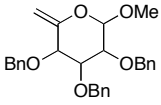
Entry	ROP(O)H_2[b] R (eq)	Catalyst (%)	Solvent	^{31}P NMR Yield, %
1	Bu (3)	Pd_2dba_3, PPh_3 (1)	CH_3CN	27
2	Bu (3)	Pd_2dba_3, $Ph_2P(2\text{-}OMeC_6H_4)$ (1)	CH_3CN	27
3	Bu (3)	Pd_2dba_3, $P(2\text{-}OMeC_6H_4)_3$ (1)	CH_3CN	22
4	Bu (3)	Pd_2dba_3, $P(4\text{-}OMeC_6H_4)_3$ (1)	CH_3CN	15
5	Bu (3)	Pd_2dba_3, PPh_3 (1)	Toluene	0
6	Et (2)	$PdCl_2$ (2)	CH_3CN	30
7	Et (2)	$PdCl_2$ (2)	Toluene	77

[a] The reactions were run at reflux temperature of the corresponding solvent for 12 h under N_2. [b] 0.5 M Stock solutions of alkyl phosphinates were used.

We complemented this project with a general study of the reactivity of various cyclic and functionalized alkenes, allenes, allenols, and 1,3-dienes as substrates. The results are summarized in the following tables.

Table 2.7. Reactivity of cyclic and functionalized alkenes in the hydrophosphinylation reaction[a]



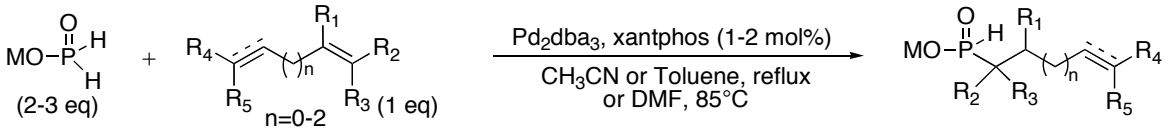
Entry	$MOP(O)H_2$ M (eq)	Substrate	Solvent (85°C)	Product (Outcome of the Reaction)	NMR yield, % (Isolated Yield, %)[b]
1	H (3)		DMF		100 (73)
	Et (3)		CH_3CN	(Mixture isomers, r=7.3/1)	45
2	H (3)		CH_3CN		100 (98)
	Bu (3)				100 (100)
3	H (3)		CH_3CN	(Mixture of products)	44
	Bu (3)			(No product)	-
4	H (2)		CH_3CN		100 (100)
5	H (2)		CH_3CN		100 (100)
6	H (2)		CH_3CN		100 (83)
7	H (3)		CH_3CN		100 (80) and 100 (36)[c]
8	H (2)		CH_3CN	Unidentified	41 (3)
	Bu (3)		CH_3CN	(Mixture of products)	-
9	H (3)	 R=H	CH_3CN	(Mixture of products)	29
	H (3)	R=MOM	CH_3CN	(Mixture of products)	42
	Et (3)			(No product)	-
10	H (2)	 (mixture endo/exo)	CH_3CN	(Mixture of products)	100
11	H (2)		CH_3CN		10
12	H (2)		CH_3CN	(No product)	-
13	H (2)		CH_3CN	(No product)	-
14	H (3)		CH_3CN	(No product)	-
15	H (2)		CH_3CN	(No product)	-
16	H (2)		CH_3CN	(No product)	-

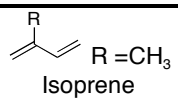
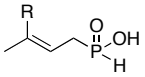
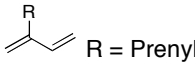
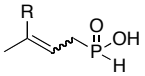
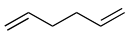
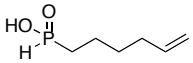
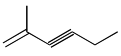
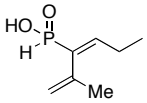
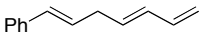
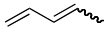
[a] Concentrated H_3PO_2 and stock solutions of alkyl phosphinates were used. The reactions were run for 8-20 h under N_2. [b] When using H_3PO_2, the products were isolated as acids by acidic workup, unless otherwise noted. When using alkyl phosphinates, the products were purified by chromatography on silica gel. [c] Isolated as butyl ester from *in situ* esterification with $(BuO)_4Si$, followed by chromatography on silica gel.

As observed in Table 2.7, an extensive study on the reactivity of various alkenes in this Pd-catalyzed hydrophosphinylation reaction was performed. The reaction is highly convenient, as it does not require anhydrous or anaerobic conditions; additionally, when using hypophosphorous acid, the products can be isolated by an aqueous workup (>95% purity). Various cycloalkenes were reacted under the previously established conditions, using relatively low catalyst loading of Pd_2dba_3/xantphos (as little as 0.02 mol%).[33] The results indicate that, in general, the reaction is limited to terminal alkenes, where the insertion of the Pd occurs at the least hindered primary carbon atom. In addition to terminal alkenes, a disubstituted olefin prepared using the Takai procedure[149] (entry 1) participated successfully in the reaction, furnishing a mixture of isomers, in a similar ratio to the one obtained by our radical reaction (7.3:1 *vs* 9:1-radical).[25] Furthermore, a very reactive cyclic internal alkene undergoes effectively the phosphinyl addition (entry 4) to afford exclusively the exo-*H*-phosphinic acid in quantitative yield. Gratifyingly, the vinyl pivalate from entry 2 is able to react with H_3PO_2 and with an alkyl phosphinate in very high yields, contrary to the vinyl ether (entry 3) or to hex-5-enopyranose[150] (entry 15). *N*-protected allylamines provide as well good yields of the corresponding *H*-phosphinic acids (entries 5 and 6). The reaction was also applied in the synthesis of an intermediate of the phosphinylated α-aminobutyric acid-based herbicide (phosphinothricin) through hydrophosphinylation of α-vinyl glycine, which was prepared according to the procedure reported by Coward (entry 7).[151] Pursuant to the synthesis of an analog of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP), we tried the reaction on an olefin derived from quinic acid (entry 9), as described by Frost *et al.,*[3g] however we did not get good results. Vinylnorbornene (entry 10) participated in the reaction but there was addition to both the cyclic and vinylic double bonds. Cyclooctene (entry 11) reacts very sluggishly, in the same way as cyclohexene;[33] this can be due to a fast and reversible hydropalladation step (Scheme 1.7).

Neither α- and β-pinene (entries 12 and 13) nor an olefin possessing fluoro substituents across the double bond (entry 14) participated in the reaction.

Table 2.8. Reactivity of dienes in the hydrophosphinylation reaction[a]



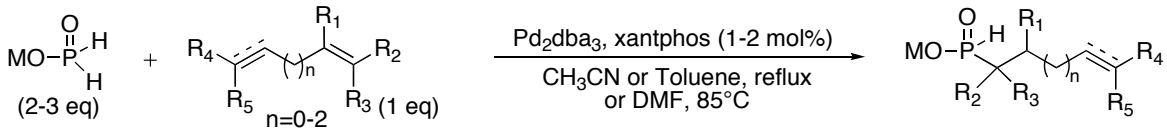
Entry	MOP(O)H_2 M (eq)	Substrate	Solvent (85°C)	Product (Outcome of the Reaction)	NMR yield, % (Isolated Yield, %)
1	$PhNH_3$ (3)	 R =CH_3 Isoprene	DMF		100 (56)
2	$PhNH_3$ (3)	 R = Prenyl Myrcene	DMF	 (Mixture isomers)	59 (59)[b]
3	H (3)		CH_3CN		100 (70)
	$PhNH_3$ (3)		DMF	(Mixture of products)	100 (72)
4	H (3)		CH_3CN		100 (100)[c]
	$PhNH_3$ (3)		DMF		
5	H (3)		DMF	(No product)	-
6	H (3)		CH_3CN	(No product)	-
7	H (2)		CH_3CN	(No product)	-

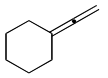
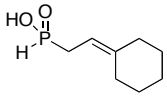
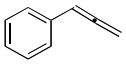
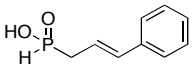
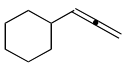
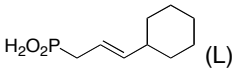
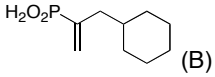
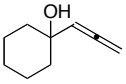
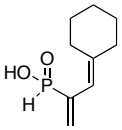
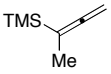
[a] Concentrated H_3PO_2 was used. The reactions were run from 8-14 h under N_2. The products were isolated by acidic workup. [b] 1:1 mixture of isomers. [c] The main isomer (64%) is shown on the table, however, two more isomers (36%, 1/1 ratio) were obtained from addition to the internal alkyne.

Again, to gain insight into the scope of the reaction, several dienes were screened; some representative results are shown in Table 2.8. In general, conjugate dienes, including indene, do not undergo the hydrophosphinylation reaction (entries 5-7), with the exception of isoprene or its derivatives (entries 1 and 2) where a rearrangement takes place leading to the more stable allylic *H*-phosphinic acid. Interestingly, in the case of 1,5-hexadiene (entry 3) the mono-*H*-phosphinic acid product is obtained, which results from selective addition to one of the double bonds, but there are no signs of formation of cyclization product. This is also a good indication that the

reaction goes via hydropalladation and not through phosphinylpalladation.[145a-b] Selective addition to the more reactive internal alkyne occurs in the substrate from entry 4.

Table 2.9 Reactivity of allenes in the hydrophosphinylation reaction[a]



Entry	$MOP(O)H_2$ M (eq)	Substrate	Solvent (85°C)	Product	NMR yield, %, Outcome of Reaction (Isolated Yield, %)
1	$PhNH_3$ (2)		DMF		77 (64)
	H (3)		DMF		63 (74)
	H (2)		CH_3CN		56 (44)
2	$PhNH_3$ (2)		DMF		100 (98)
	H (2)		CH_3CN		100 (100)
	Bu (3)		Toluene		54 (30)[b]
3	$PhNH_3$ (2)		DMF	 (L)	40, L (52)[c]
	H (3)		DMF		92, L/B = 2.3/1(100)[d]
	H (3)		CH_3CN	 (B)	60, mixture of three isomers
4	H (2)		CH_3CN		8
	$PhNH_3$ (2)		DMF		100, mixture of products
	NH_4 (3)		DMF		100 (71)[e]
5	H (2)		CH_3CN		0
	$PhNH_3$ (2)		DMF	Unidentified product	17
	NH_4 (3)		DMF		14

[a] Concentrated H_3PO_2 was used. The reactions were run from 8-14 h under N_2. The products were isolated by acidic workup. [b] The product with the reduced double bond was obtained. [c] 90% of the linear isomer and 10% of another isomer. [d] 67% of linear/branched products and 33% of other two isomers. [e] 80% of the product shown on the table and 20% of three other products.

As exemplified by Table 2.9, various allenes were synthesized by homologation of acetylenes[152] or by Pd-catalyzed hydrogenolysis of alk-2-ynyl carbonates with ammonium formate,[153] however low yields of products were usually obtained (around 20%), which was probably due to the fact that we did not reach an adequate reduced pressure during distillation, or to the inefficiency of the synthetic methods. Even though some of them participated selectively in the reaction to afford the corresponding allylic-*H*-phosphinic acids (entries 1 and 2) in good yields, their use is acceptable only if there is not another available methodology to prepare the target compound. The use of an allenol (entry 4) generally gave mixtures of products, however

when using the strong reductant ammonium hypophosphite, the major product corresponds to the one observed in dehydrative allylation reactions (Chapter V).

2.3 Ni-catalyzed hydrophosphinylation

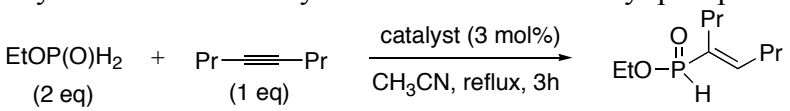
2.3.1 $NiCl_2$-catalyzed addition of alkyl phosphinates to alkynes

From our studies on metal-catalyzed hydrophosphinylation processes with hypophosphorous acid derivatives we discovered that $NiCl_2$ was an excellent catalyst for the addition of alkyl phosphinates to terminal alkynes, and even more interesting, to internal alkynes (Eq. 1.12, Chapter 1 and Scheme 2.3).[35] More notably, the reaction is very convenient from an economical point of view as it does not require the addition of any ligand, and relatively low catalyst loading (as low as 0.5 mol%) furnishes the products *H*-phosphinates in moderate to excellent yields. Presumably the alkyl phosphinates function not only as reducing agents generating *in situ* Ni(0), but they also form the active catalytic species through complexation of Ni(0). Indeed, a preactivation procedure with $NiCl_2$ and alkyl phosphinates supports this hypothesis (Section 2.3.3).[35] Overall, this process is a very efficient approach to alkenyl-*H*-phosphinates, given the fact that the highly air-sensitive $Ni(cod)_2$ is not necessary, that it does not require strict anhydrous conditions, and that all of the reagents can be manipulated in air. Furthermore, the use of TFA salts of aminosilicates as esterifying agents[18] allows the isolation of pure products in very high yields by a simple extractive workup, while a tandem esterification-hydrophosphinylation process also works uneventfully.[35]

As demonstrated in Table 2.10, and consistent with our previous results on hydrophosphinylation,[33] $PdCl_2$ catalyzed the reaction sluggishly. Dramatically, when various nickel chloride precatalysts (entries 1-6), and even their hydrates were used (entry 2), the addition took place readily to afford the *H*-phosphinate products in less than 3 h. It is also clear that the presence of water or air does not affect the catalyst's activity (entries 13-15). On the

other hand, alkynes are by far more reactive than both terminal an internal alkenes under the present conditions.[35]

Table 2.10 Reactivity of various Ni-catalysts in the addition of ethyl phosphinate to 4-octyne

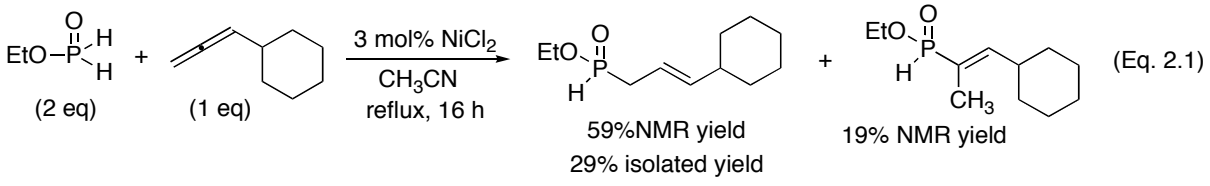


Entry	Catalyst	Additive	NMR yield, %[a]
1	$NiCl_2$	None	100
2	$NiCl_2.6H_2O$	None	99
3	$NiBr_2$	None	97
4	NiI_2	None	99
5	$NiCl_2(PPh_3)_2$	None	100
6	$NiBr_2(PPh_3)_2$	None	100
7	$Ni(acac)_2$	None	94
8	$Ni(OAc)_2.H_2O$	None	47
9	$NiCp_2$	None	15
10	Ni powder	None	11
11	Ni on SiO_2/Al_2O_3[b]	None	8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

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

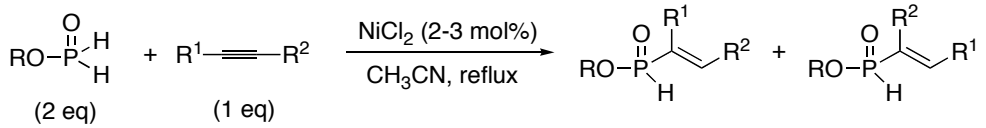
Thus, in the presence of catalytic amounts of $NiCl_2$, the reaction proceeds rapidly in acetonitrile or toluene at reflux, however, acetonitrile was more generally used and often provided the best results. As for the hypophosphorous compound (Table 2.11), various alkyl phosphinates ($AlkOP(O)H_2$), prepared using our silicate-based methodology (alkoxysilanes or aminosilicates salts)[18] can effectively undergo the addition reaction, contrary to H_3PO_2 or its anilinum salt (AHP), which produce only low yields of products (< 20%). In order to optimize the time and facilitate the manipulation, stock solutions of alkyl phosphinates can be used,[35] and an even more convenient one-pot process, where the alkyl phosphinate is formed *in situ*, furnishes the product in good yield (Table 2.11, entry 1d). Moreover, the use of aminosilicates facilitates the purification, increasing also the isolated yields (Table 2.11, entries 2b, 6b, 7b, 11 and 12). As illustrated in Table 2.11, a broad study was performed in which diverse internal and

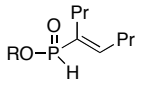
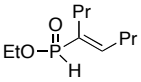
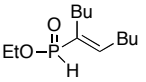
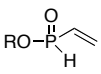
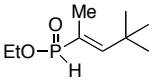
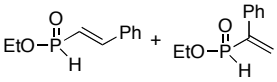
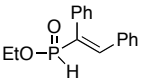
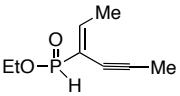
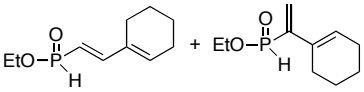
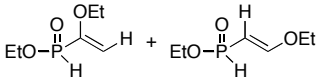
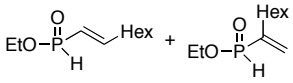
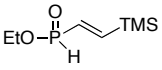
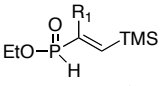
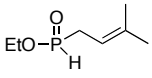
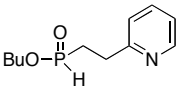
terminal alkynes were reacted in the presence of alkyl phosphinates.[35] Gratifyingly, it was found that the hydrophosphinylation reaction is highly general and stereospecific for the formation of *E*-adducts as a result of a *syn* addition. Usually, poor regiocontrol is observed with unsymmetrical alkynes (1:1 - 3:1, from entries 6, 9-11), with a tendency to preferentially form the linear isomer over the branched (entry 11), however, this trend seems to be inverted with the presence of phenyl, alkene, or alkoxy substituents (entries 6, 9 and 10). Nevertheless, an exception to the previous behavior occurs with alkynes bearing a terminal bulky substituent, where the *β*-substituted alkenyl-*H*-phosphinate is obtained exclusively (entries 5, 12 and 13). As exemplified in entry 8, 2,4-hexadiyne did undergo the hydrophosphinylation reaction with good regiocontrol. In the particular case of terminal alkynes, our Pd-catalyzed version of this process is superior in terms of regioselectivity (see Section 2.2.1.1).[33] Although alkenyl-*H*-phosphinates have also been prepared stereo- and regiospecifically through cross-coupling of alkenyl halides (see Section 3.2.2, Chapter 3),[63] the present addition reaction represents an atom-economical approach,[154] since alkynes are basic feedstocks, and hence more readily available.[35] Notably, it was found that acetylene gas can be employed as the substrate (entry 4), but we were unable to isolate the product in good purity due to the fact that low molecular weight vinyl-*H*-phosphinates are highly water soluble and sensitive to hydrolysis. This fact was not surprising as we faced the same problem during the development of our cross-coupling reaction (see Chapter 3).[63] Note that with a propargyl chloride (entry 14), a rearrangement via an allene intermediate takes place, and allenes are effective partners in this reaction (Eq. 2.1). Additionally, with 2-ethynylpyridine (entry 15), the product from hydrophosphinylation followed by reduction is obtained.



(Eq. 2.1)

Table 2.11. Scope of the $NiCl_2$-catalyzed hydrophosphinylation of alkynes



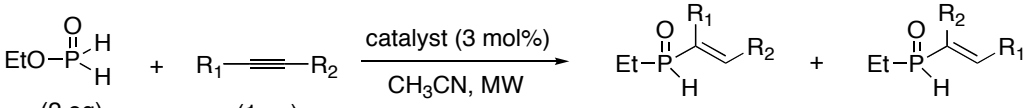
Entry	R^1	R^2	R	Time (h)	Reagent for $ROP(O)H_2$ formation	Product(s)	Isolated Yield %[a]
1a	Pr	Pr	Me	38	$(MeO)_4Si$		90
1b			*i*-Pr	13	$(i\text{-}PrO)_4Si$		96
1c			Bu	2.5	$(BuO)_4Si$		100
1d			Bu	16[b]	$(BuO)_4Si$[b]		90[b]
2a	Pr	Pr	Et	7	$Me_2Si(OEt)_2$		75
2b				13	$(EtO)_3Si(CH_2)_3NH_2$		100
3	Bu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

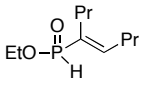
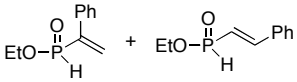
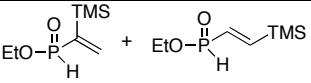
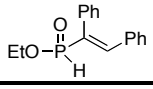
[a] All yields are isolated. Ratios in parentheses indicate regioselectivity determined on the crude reaction mixture. All reactions were conducted in refluxing reagent grade CH_3CN. Details can be found in the Experimental Section. [b] One-pot process, where esterification and hydrophosphinylation take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

The reactivity of various propargylic electrophiles (i.e. acetate, tosylate, phenyl ether) was investigated. Although they did undergo the addition in moderate to good yields, we did not succeed in the isolation of the products as a result of their easy-hydrolysis, even when we used our aminosilicate-methodology[18] to avoid in this way the purification over silica gel. On the other hand, we also tested the hydrophosphorylation reaction on pinacol-*H*-phosphonate with terminal alkynes using $NiCl_2$ as catalyst, however no addition took place under these conditions.

Over the last few years using microwave energy to heat and drive chemical reactions has become very popular. One of the main advantages of this technique is the dramatic reduction of reaction times.[155] We envisioned that our alkyne hydrophosphinylation could be performed with microwave irradiation as the heating source. As revealed by the results (Table 2.12), the microwave-assisted addition of alkyl phosphinates to alkynes sucessfully leads to alkenyl-*H*-phosphinates, but no improvement in the regioselectivity with terminal alkynes was observed.[35]

Table 2.12 Ni-Catalyzed hydrophosphinylation of alkynes with microwave heating[a]



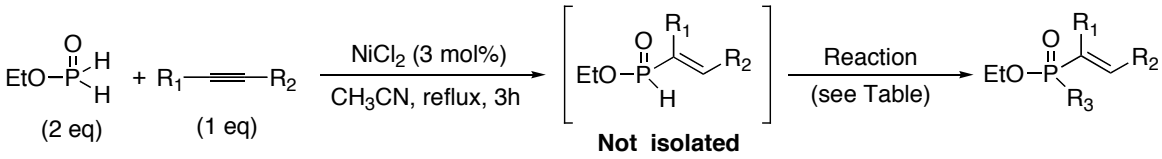
R_1	R_2	Catalyst	Time (min)	Temp (°C)	Power (W)	P (bars)	Product(s)	NMR yield, % [Ratio isomers] (Isolated yield, %)
Pr	Pr	$NiCl_2.6H_2O$	5	100	20	0		100 (73)
Pr	Pr	$NiCl_2$	5	100	25-30	1		100 (81)
Pr	Pr	$NiCl_2$	5	125	25	2		96
Pr	Pr	$NiCl_2$	1	125	25	2		93
Pr	Pr	$NiCl_2$	10	125	30	2		92
Pr	Pr	$NiCl_2$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

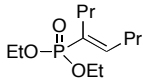
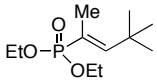
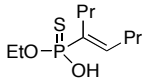
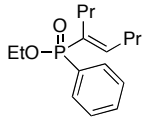
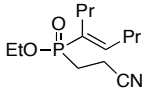
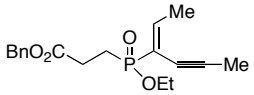
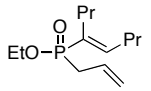
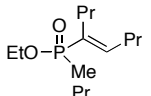
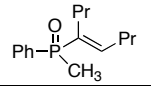
[a] See Experimental Section for details of the procedures. [b] Branched only

2.3.2 Tandem one-pot alkyne hydrophosphinylation-functionalization reactions

The development of tandem or "domino" processes is attracting a lot of attention in synthetic chemistry as they represent a "Green Chemistry" approach to more complex, functionalized molecules.[154,156] Considering the versatility of *H*-phosphinates as synthons for the preparation of a wide variety of organophosphorus compounds, as discussed in the first chapter of this dissertation (Section 1.3); we decided to look into the possibility of conducting these transformations via *in situ* functionalization of the *H*-phosphinates prepared by means of our Ni-catalyzed hydrophosphinylation.[35] Moreover, upon avoidance of the purification of the sensitive *H*-phosphinates, we could potentially increase the overall synthetic yields. Some of the results are summarized in Table 2.13. As shown in entries 1 and 2, *in situ* oxidation of alkenyl-*H*-phosphinates under Atherton-Todd reaction conditions[113-115] leads to the corresponding phosphonates in moderate yields. Another interesting transformation is the oxidation with elemental sulfur (entry 3),[119] which allows the one-pot preparation of phosphonothioic acids, which are an important source of *P*-chiral organophosphorus compounds via resolution with chiral amines (see Section 1.3.9).[120] Of greater interest, disubstituted phosphinic acids are prepared in acceptable yields through various tandem reactions such as cross-coupling (entry 4),[60] base-promoted conjugate addition (entries 5 and 6),[85] and alkylation under Arbuzov-like conditions involving silyl alkyl phosphonite intermediates (entries 7 and 8).[94] Finally, as illustrated by the remarkable transformation in entry 9, functionalized tertiary phosphine oxides can be generated in good yields through a one-pot, three-step carbon-phosphorus bond forming sequence, involving hydrophosphinylation of an internal alkyne with the precatalyst $NiCl_2$,[35] displacement by a Grignard reagent,[116] and trapping of the resulting secondary phosphine oxide anion with an electrophile. This straightforward approach to tertiary phosphine oxides could find application in the synthesis of phosphines via known reduction methods.[128]

Table 2.13 Tandem one-pot alkyne hydrophosphinylation-functionalization

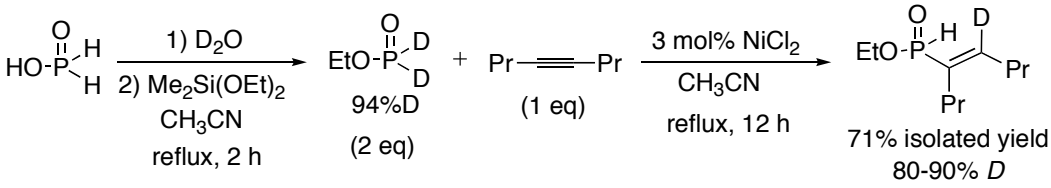


Entry	R_1	R_2	Reaction[a]	Temperature, Time	Product	Isolated Yield, %
1	Pr	Pr	EtOH, CCl_4, Et_3N	rt, 12 h		48
2	Me	*t*-Bu	EtOH, CCl_4, Et_3N	rt, 12 h		57
3	Pr	Pr	S_8, Et_3N	rt, 12 h		70
4	Pr	Pr	PhI, Et_3N 2% $Cl_2Pd(PPh_3)_2$	reflux, 12 h		58
5	Pr	Pr	Acrylonitrile, DBU	rt, 6 h		63
6	C≡CMe	Me	Benzyl acrylate, DBU	rt, 6 h		32
7	Pr	Pr	Allyl chloride, BSA	reflux, 3 h		76
8	Pr	Pr	Me_2SO_4, BSA	rt, 3 h		62
9	Pr	Pr	1) PhMgBr, THF 2) MeI, THF	reflux, 1.5 h rt, 1h		53

[a] See Experimental Section for details of the procedures.

2.3.3 Mechanistic considerations and kinetic experiments

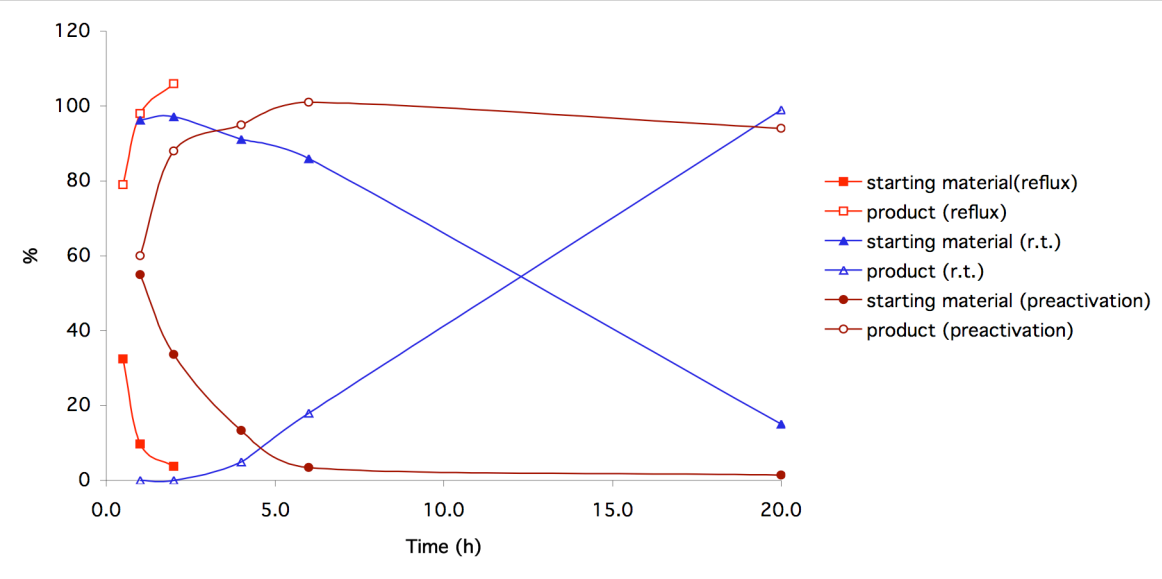
The mechanism of this Ni-catalyzed addition reaction was not studied in detail, but it probably proceeds in the same way as the Pd-catalyzed version, through hydrometallation followed by reductive elimination (See Chapter 1, Scheme 1.7).[33] This finds support in an isotopic labeling experiment (Eq 2.2) where we observed incorporation of deuterium into the double bond (via *syn* addition) in the reaction of deuterated ethyl phosphinate with an internal alkyne (prepared by esterification of D_3PO_2 with alkoxysilanes).[35]



(Eq. 2.2)

On the other hand, some kinetic evaluation experiments of this transformation support the *in situ* formation of the catalytically active Ni(0) species by reduction of the precatalyst $NiCl_2$ with the starting hypophosphorous compounds (Scheme 2.4).[35] Our approach consisted of performing a preactivation process where a mixture of the alkyl phosphinate and the alkyne was heated for 15 min, accelerating in this way the catalyst formation. After this time, the solution was cooled to room temperature, the alkyne was added, and the reaction was then continued at room temperature. We observed, through monitoring by ^{31}P NMR (product formation) and by GC chromatography (consumption of the alkyne) that the reaction was completed in 6 h (see also Table 2.11, entry 4). This time is significantly shorter than what we detected when the whole process was done at room temperature (20 h). In addition, we obtained a good match between the data obtained from GC and from ^{31}P NMR, which validates the NMR yield measurements.

Scheme 2.4 Kinetics profile for the hydrophosphinylation of 4-octyne with $EtOP(O)H_2$

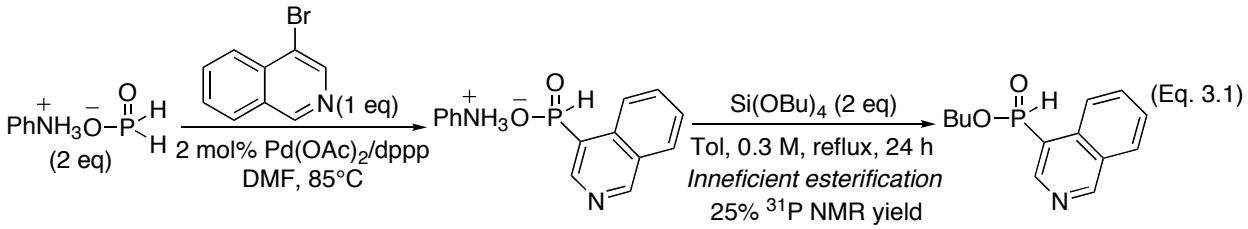


Chapter Three: Cross-coupling reaction of alkyl phosphinates with aryl, benzyl and alkenyl electrophiles

3.1 Introduction

The use of organometallic catalysis for the execution of bond forming reactions in chemistry has revolutionized organic synthesis. Metal-catalyzed cross-coupling reactions constitute a popular and reliable carbon–carbon bond forming methodology.[157] Recently, palladium, and to a lesser extent other metals, have demonstrated their utility for the creation of carbon bonds to nitrogen, oxygen and sulfur.[158] The success of these cross-coupling reactions depends in great part on the selection of the adequate ligand around the metal, which is generally a phosphine. However, the formation of C-P bonds through metal-catalyzed cross-coupling processes has not received widespread attention,[29a] which is somewhat contradictory because synthesis of phosphine ligands via cross-coupling goes hand in hand with the development of novel bond-forming methodologies.[67] Pioneering work in this area was performed by the Hirao group, who reported the palladium catalyzed cross-coupling of aryl and vinyl bromides with dialkyl phosphites $(RO)_2P(O)H$.[159] Recent efforts have been directed towards the preparation of phosphines, particularly *P*-chiral ones, either by cross-coupling of phosphine oxides or phosphine-borane complexes, which require an additional reduction step, or by the direct coupling of air-sensitive primary or secondary phosphines.[160] Since the work by Hirao *et al.*, the cross-coupling of phosphonic acid derivatives has been expanded and found important applications in the synthesis of enzymatic inhibitors,[161] and in the fabrication of hydrolytically-stable oligonucleotides.[162] Though, not less interesting, the cross-coupling of phosphinic acids (see Chapter I, Section 1.3.1 and references in therein) and in particular, of hypophosphorous acid derivatives has been by far less studied (Chapter I, Section 1.2.11), and few successful cross-couplings with these compounds have been reported due to their thermal instability[10] and/or possibility for competing transfer hydrogenation (Scheme 1.10, Pathway B).[30] In this

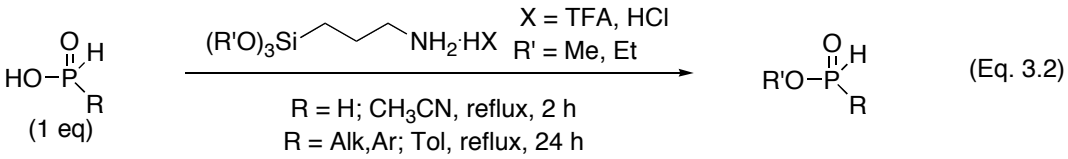
context, Montchamp and coworkers reported a remarkably efficient Pd-catalyzed cross-coupling of amine salts of hypophosphorous acid, particulary anilinium and ammonium salts, with a broad range of aryl and alkenyl electrophiles (Eq. 1.24).[41,61] The products of these reactions can be isolated as *H*-phosphinic acids after acidifying the reaction mixtures, or as the corresponding esters after a separate esterification step, i.e. with alkoxysilanes[163] or activating agents.[164,89,106e] Nonetheless, in some cases, it would be preferable to directly obtain the *H*-phosphinate esters, minimizing in this way reaction time and manipulation. This is particularly important in the case of highly water-soluble *H*-phosphinic acids, or when using substrates containing basic functionalities, i.e. nitrogen heterocycles, which after acidification of the reaction mixture may undergo protonation at the *N*-atom, forming water-soluble phosphinic acid intermediates that require time-consuming ion-exchange purification. Additionally, previous studies in the Montchamp group indicate that the silicate-based esterification of the crude salts of *N*-containing heteroaryl-*H*-phosphinic acids does not work effectively (Eq. 3.1).[62]



(Eq. 3.1)

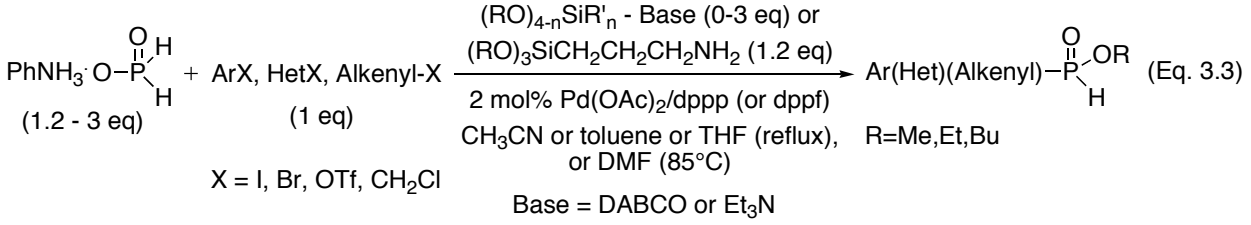
As mentioned in Section 1.2.11, Schwabacher first reported the cross-coupling reaction of aryl iodides with methyl and *tert*-butyl phosphinates (Eq. 1.23).[15a,60] Aside from the competing transfer hydrogenation, this reaction is extremely limited by the reactivity of the electrophiles, due to the thermal decomposition of alkylphosphinates prepared by the Fitch's orthoformate method.[10,12] However, the Montchamp group recently established an efficient and general methodology for the synthesis of alkylphosphinates (Eq. 1.4) via esterification of H_3PO_2 and some of its salts with alkoxysilanes. This reaction works efficiently in several solvents and it

does not require strict anhydrous conditions. Interestingly, alkyl phosphinates prepared by this method show an unprecedented thermal stability (Section 1.2.1).[18] Montchamp *et al.* also introduced salts of commercially-available aminosilicates as esterifying agents for hypophosphorous and *H*-phosphinic acid derivatives. These reagents offer an additional advantage in terms of purification of the products because the silicate-byproducts can be removed by an acidic extractive workup (Eq. 3.2).[18,163]



(Eq. 3.2)

Taking into account the advantages and generality of the previously described cross-coupling and esterification methodologies developed by Montchamp, we considered studying the cross-coupling reactions of alkylphosphinates with a variety of electrophiles, including the less reactive bromides and triflates, expecting that they might have enough time to react prior to the decomposition of their precursors, alkyl phosphinates. Two papers have been published regarding this reaction, a preliminary communication and a full paper (Eq. 3.3).[62,63]



(Eq. 3.3)

3.2 Results and discussion

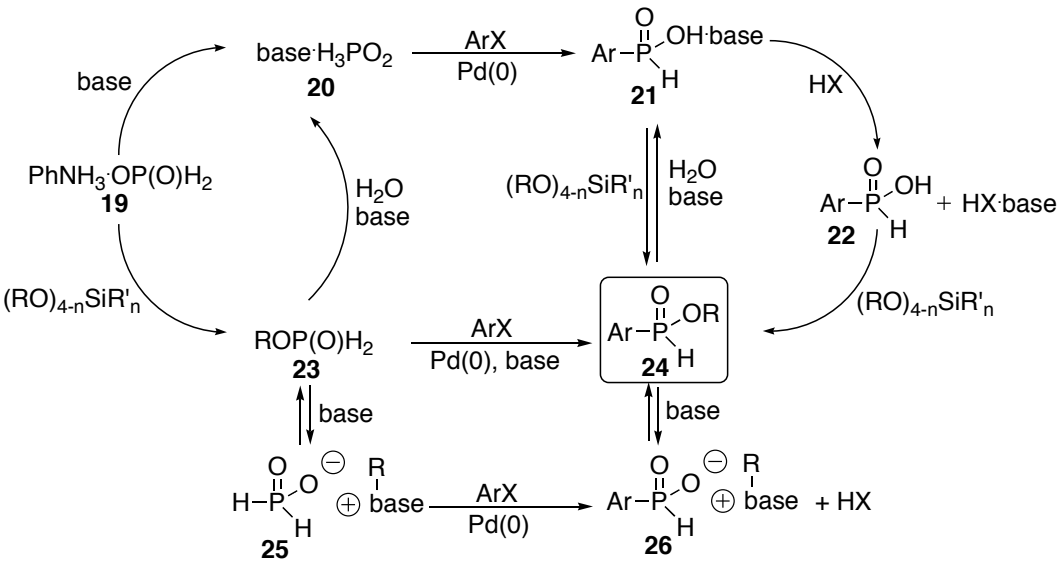
3.2.1 Reaction conditions

Our approach to this project started with the selection of ligands and reaction conditions. According to previous cross-coupling studies with hypophosphorous compounds,[41,61] $Pd(OAc)_2$ was generally used as the source of palladium, with mono and bisphosphines as ligands. The initial screening of conditions consisted of performing the alkyl phosphinates through the

reaction of anilinium hypophosphite and a silicate, and then adding the electrophile, base, and catalyst *in situ*. However, aryl iodides were the only electrophiles that reacted successfully under these conditions, using anhydrous Et_3N as the base and $PdCl_2(PPh_3)_2$ as catalyst. Gratifyingly, it was found later that less reactive electrophiles (bromides and triflates) did undergo this cross-coupling reaction in presence of DABCO [1,4-diazabicyclo[2.2.2]octane] as the base, using $Pd(OAc)_2$ ligated by dppp (1,3-bis(diphenylphosphino)propane). Nevertheless, more experimental studies confirmed that the base was not responsible for the previous results, but the water in the batch of DABCO we used. This suggests that a straightforward cross-coupling of alkyl phosphinates occurs only with aryl iodides (**23**-**24**), but with less reactive electrophiles the process should be more complicated. It was likely that in the latter case the water hydrolyzed the preformed alkyl phosphinate **23** to the corresponding hypophosphite DABCO salt **20**, which could then undergo cross-coupling to generate **21**, followed by *in situ* esterification with the alkoxysilane, yielding the product **24** (Scheme 3.1).[62] These preliminary findings made us turn our attention to the development of a more convenient, one-pot process, where anilinium hypophosphite, an alkoxysilane, a base, and the aryl electrophile were reacted in the presence of catalytic amounts of Pd/ligand. Through optimization, it was found that the direct cross-coupling of alkylphosphinates with aryl halides furnishes a wide range of aryl-*H*-phosphinate esters in moderate to good yields, after purification by chromatography over silica gel. We further studied the mechanistic pathways and extended the scope of the reaction to heteroaryl, alkenyl and benzylic electrophiles.[63] In terms of ligands, dppp gave the best results with the majority of substrates, and dppf (1,1'-bis(diphenylphosphino)ferrocene) was preferred with sterically hindered alkenyl halides (*Z*-substituted) and with benzylic chlorides, while triphenylphosphine [$PdCl_2(PPh_3)_2$] worked well exclusively with activated aryl iodides. Several solvents could be employed, but acetonitrile often gave the best results. The base DABCO generally improved the

yields of products compared to Et_3N. Interestingly, we also observed that when using aryl iodides as electrophiles, the base is not required because the alkyl phosphinates not only scavenge the HI produced during the coupling step, but also reduce the Pd(II) back to Pd(0).[63] This also supports the fact that the P(III) form of the alkyl phosphinate should oxidatively add palladium, without deprotonation of the phosphorus nucleophile, as previously proposed in the cross-coupling reaction of anilinium hypophosphite salt (AHP) (Scheme 1.10).[41]

Scheme 3.1 Proposed mechanistic pathways in cross-coupling reactions of alkyl phosphinates

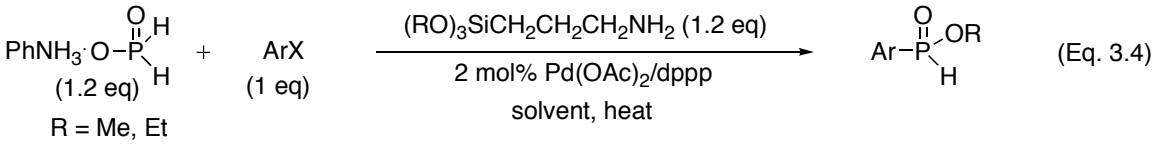


3.2.2 Scope of the reaction

Aromatic and heteroaromatic halides were studied as cross-coupling partners, using the one-pot process (Table 3.1).[62] A variety of commercially-available aryl iodides, bromides and triflates participate in the reaction providing aryl-*H*-phosphinate esters in moderate to good yields (entries 1-9). Iodobenzene (even in the absence of base) (entry1), and iodoanisole (entry 4) which is deactivated towards oxidative addition, react successfully. 4-Nitroiodobenzene undergoes cross-coupling, followed by reduction of the nitro group (entry 5). However, 4-nitrobromobenzene produces only 24% of product. Bromobenzene and aryl chlorides follow the same trend and are unreactive under the present conditions, probably due to a faster competing

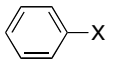
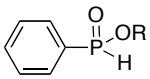
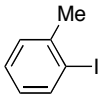
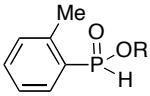
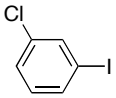
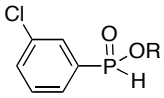
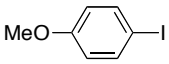
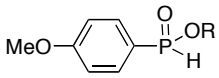
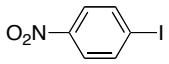
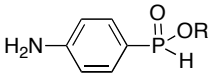
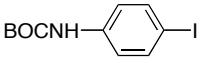
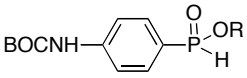
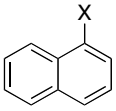
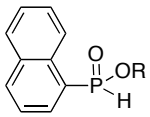
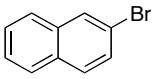
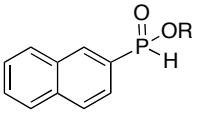
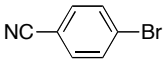
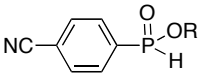
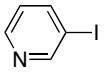
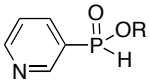
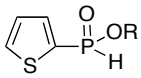
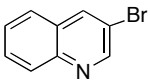
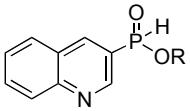
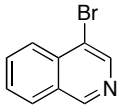
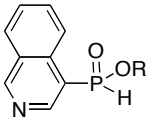
transfer hydrogenation pathway (Scheme 1.10). We also tried several aryl chlorides with electron withdrawing groups i.e. trifluoromethyl, however no successful cross coupling was observed. In the case of 4-bromoacetophenone, mixtures of products from addition to the carbonyl and cross-coupling are obtained. Of greater interest, heterocyclic substrates participate in the coupling (entries 10-13) to afford the corresponding heteroaryl-*H*-phosphinate esters. In spite of the fact that the heterocyclic halides we tested did react in the cross-coupling with AHP (Eq. 1.24),[41] the isolation of the products was very complicated. Hence, the present methodology circumvents not only transfer hydrogenation with alkyl phosphinates, but also purification issues with *N*-heteroaryl-*H*-phosphinates, permitting access to previously inaccessible compounds.

Next, we investigated the use of aminosilicates as esterification partners, in order to increase the yields of products by simplifying the purification process (Table 3.1, Method C).[63] *H*-Phosphinates are sensitive to hydrolysis over silica gel. This is evidenced by the higher NMR yields (^{31}P NMR from the reaction mixtures) with respect to the isolated yields.[35] Remarkably, aminotrialkoxysilanes worked efficiently, and they did not only replace alkoxysilanes, but also functioned as the base for the Pd-catalyzed cross-coupling reaction (Eq. 3.4). These reagents have proved to be efficient only when the amino group is protonated, which requires the addition of a strong acid (HCl or TFA).[18,163] Notably, in this particular reaction the HX generated during the coupling step does the work. With a simple acidic workup the silicate byproducts are removed in the aqueous phase, while the *H*-phosphinates along with some dialkyl phosphites $(RO)_2P(O)H$ remain in the organic phase. The latter can be removed in vacuo (if methyl or ethyl) and the corresponding products are then isolated in more than 95% purity.[63]



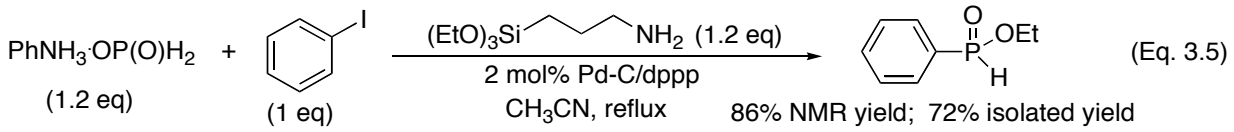
(Eq. 3.4)

Table 3.1 Cross-coupling scope with (hetero)aromatic electrophiles

Entry	Electrophile	*H*-Phosphinate Product	R	X	Method[a]	Isolated Yield,[b] %
1			Bu	I	A[c]	80
			Et	I	A[d]	77
			Et	I	B[e]	61
			Et	I	C[c]	72
			Et	Br	B[e]	40[f]
2			Bu	-	B[c]	83
3			Bu	-	B[c]	63
4			Bu	-	B[c]	78
5			Bu	-	B[c]	53
6			Bu	-	B[c]	82
7			Me	Br	C[c]	100
			Bu	OTf	B[g]	80
8			Et	-	B[e]	69
			Et	-	C[c]	88
			Et	-	C[e]	74
9			Bu	-	B[g]	51
			Et	-	C[c]	92
10			Bu	-	B[c]	64
11			Bu	-	B[c]	36
12			Bu	-	B[g]	65
13			Bu	-	B[g]	78

[a] Method A: 3 eq AHP, 3 eq $(BuO)_4Si$, 3 eq Et_3N, 2 mol% $Cl_2Pd(PPh_3)_2$; Method B: 3 eq AHP, $(RO)_{4-n}SiR'_n$, 3 eq DABCO, 2 mol% $Pd(OAc)_2$/dppp; Method C: 1.2 eq AHP, 1.2 eq $(RO)_3Si(CH_2)_3NH_2$, 2 mol% $Pd(OAc)_2$/dppp. [b] Unless otherwise noted, yields are for isolated product with satisfactory spectral data (>95% purity). [c] CH_3CN, reflux. [d] No base. [e] Toluene, reflux. [f] ^{31}P NMR yield. [g] DMF, 85°C.

Aminosilicates also permit a reduction in the amount of hypophosphorous acid derivative (from 3 eq to 1.2 eq), which could be a result of a more effective suppression of the competitive reductive pathway or a better esterification. However, it is not convenient to use aminosilicates with *N*-containing heterocycles, as the acidic workup would protonate them as well. As for the Pd sources, Pd-C could replace $Pd(OAc)_2$ (Eq. 3.5), which represents a cost-effective alternative. Thus the aminosilicate method furnishes various *H*-phosphinate esters in high yields.[63]

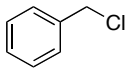
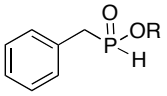
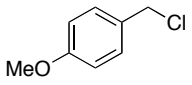
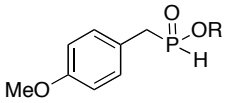
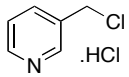
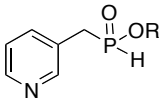
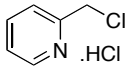
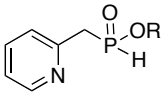
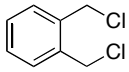
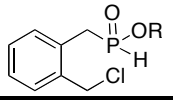


(Eq. 3.5)

Attempted couplings to benzylic and heterobenzylic electrophiles were problematic initially under the previously described conditions for aryl halides. However, a ligand change from dppp to dppf increased substantially the yields of products (Table 3.2).[62] In this particular case, the aminosilicate methodology did not improve the results, and neither did a change of base from DABCO to Et_3N or *i*-Pr_2NEt. In terms of scope, benzylic chlorides provided moderate yields of cross-coupling products. With α,α'-dichloro-*o*-xylene, we could achieve the selective functionalization of one of the two chlorine atoms, however no second C-P bond formation was observed (cyclization) neither via cross-coupling nor under Arbuzov-like conditions (using BSA). Benzylic bromides (benzyl bromide and α,α'-dibromo-*o*-xylene) did not undergo the coupling, presumably because of the faster transfer hydrogenation, even though we did not observe the formation of the reduction products (toluene and xylene) by GC analysis. One possible reason for this finding is the formation of an ammonium salt upon reaction with the base. Both 2- and 3-chloromethylpyridines couple to alkyl phosphinates, and they can be used directly as their commercially available hydrochlorides salts in the presence of an additional equivalent of base. With 3-chloromethylpyridine, we observed the formation of a disubstituted phosphinate (^{31}P NMR δ: 49 ppm, singlet, ~20 %) in the crude reaction mixture; the reason for

this fact is unclear at this moment. One conceivable explanation is the increased reactivity of the first product (monosubstituted aryl-*H*-phosphinate) with respect to the starting material (hypophosphorous compound), due to the 'directing' group effect provided by the nitrogen atom of the pyridine ring due to a chelation-assisted metallation,[165] however we did not observe the same result with the 2-isomer (entry 4). The low isolated yields with the benzylic pyridines are probably related to the increased polarity and easy hydrolysis of the products. 4-Chloromethylpyridine did not react as expected; neither did benzylic chlorides bearing an alkene in the *para* position, which produced low yields of the cross-coupling product (18%) and the same amount of the product from addition of the alkyl phosphinate to the double bond.[63]

Table 3.2 Cross-coupling scope with benzylic chlorides[a]

Entry	Electrophile	*H*-Phosphinate Product	R	Ligand	Isolated Yield, % (NMR yield, %)
1			Bu	dppf	88 (100)
				dppp	(21)
2			Bu	dppf	53 (65)
3			Bu	dppf	46 (60)
4			Bu	dppf	24 (38)
5			Bu	dppf	(100)

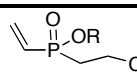
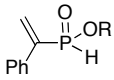
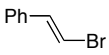
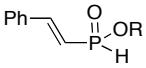
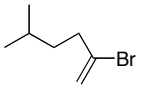
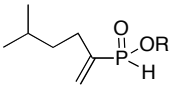
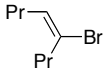
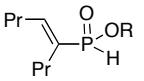
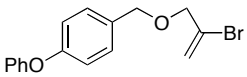
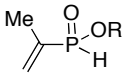
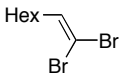
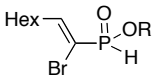
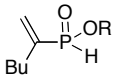
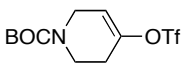
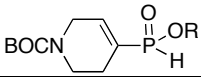
[a] The yields reported are for isolated compounds with satisfactory spectral data (~95% purity). The yield in parentheses is determined by ^{31}P NMR. Conditions: 3 eq AHP, 3 eq $(RO)_4Si$, DABCO 3 eq (4 eq for hydrochlorides), 2 mol% $Pd(OAc)_2$/dppf, CH_3CN, reflux.

Finally, the reactivity of alkenyl halides and triflates in this reaction was also explored.[63] As listed in Tables 3.3 and 3.4, various alkenyl electrophiles possessing different substitution patterns participated in the cross-coupling with alkyl phosphinates. The choice of solvent also proved to be crucial for determining the outcome of the reaction. The use of CH_3CN at reflux temperature (82°C) gave satisfactory results in most cases, reaching up to 100% NMR yield

(95% isolated, entry 9, Table 3.3). However, THF at reflux (66°C) furnished higher yields with some low molecular weight alkenyl halides (entries 3 and 4, Table 3.4), with α- and β-bromostyrene, which are prone to competing thermal conjugate addition reactions, and with a conjugated ketone, which can undergo addition of the alkyl phosphinate into the carbonyl moiety (entry 7, Table 3.4). As mentioned before, dppf in general gave better results with *Z*-substituted alkenes. The reaction times were not optimized, however no significant difference in yields was observed between 7 to 15 h. This reaction occurs with complete regio- and stereo-control. In an alternative synthesis of these compounds, via metal- catalyzed hydrophosphinylation of alkynes (see Section 1.2.3, Eq. 1.10 and 1.12),[33,35] the regioselective formation of the linear *versus* the branched isomer is often more difficult to achieve (as discussed in Chapter Two). However, in certain cases, alkynes are more readily available than alkenyl halides. In fact, when we started the screening, some commercially available alkenyl halides were screened (entries 1-5, Table 3.4); even though they participated in the coupling, the high water solubility and fast hydrolysis of the cross-coupling products did not permit their isolation. One representative example is vinyl bromide, which reacted smoothly with alkylphosphinates (^{31}P-NMR, ~80-90%), however vinyl-*H*-phosphinate was not isolated pure and its *in situ* functionalization led to the more stable and easily handled disubstituted phosphinate in low yield (entry 1, Table 3.3). The olefin in entry 8[166] from Table 3.4 contains bromine and fluorine substituents in the 1-position and gave a significant amount of the product from cross-coupling followed by reduction of the double bond. We then turned our attention to less polar alkenyl halides (bromides and triflates) as cross-coupling partners. These are not commercially available and, although their synthesis is quite simple,[167] we faced a lot of problems during their purification as they can be easily isomerized during distillation (i.e. entry 5,[167c] Table 3.3 and entry 6,[167b] Table 3.4). These compounds furnished moderate to good yields of products as shown in Table 3.3. In the case of the olefin

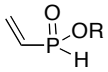
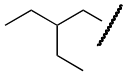
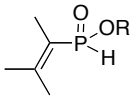
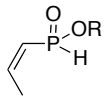
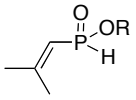
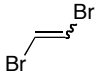
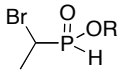
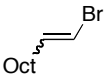
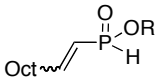
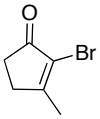
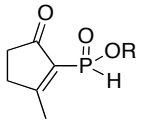
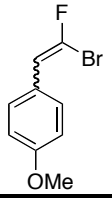
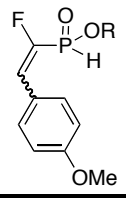
from entry 6 in Table 3.3, containing an allylic ether moiety, cross-coupling and simultaneous carbon-oxygen bond cleavage takes place. The reaction of a 1,1-dibromoolefin[167a] (entry 7, Table 3.3) proceeds stereospecifically to yield substitution of the bromine atom in the *E*-configuration. Of greater interest, an intermediate in the synthesis of TPMPA (1,2,3,6-tetrahydropyridin-4-yl)-methylphosphinic acid), which is a selective antagonist for $GABA_C$ receptors, was also synthesized in excellent yield (entry 8, Table 3.3).[63] The corresponding acid of this compound was previously prepared via the AHP coupling, however the cross-coupling yield was lower (64%) and its purification required a tedious ion-exchange chromatography.[61] In summary, we have demonstrated a facile and convenient C-P bond formation methodology. The reaction requires low catalyst loading (2 mol%) and leads to vinylic-*H*-phosphinates, which can find applications to the synthesis of biologically-active compounds.

Table 3.3 Cross-coupling scope with alkenyl electrophiles (First Part)

Entry	Electrophile	*H*-Phosphinate Product	R	Solvent	Method[a]	Isolated Yield, %
1			Et	CH_3CN	A	30
2			Bu	THF	B	79
3			Bu	THF	B	95
4			Bu	CH_3CN	B	63
5			Bu	CH_3CN	B	77
6			Bu	CH_3CN	B	57
7			Et	CH_3CN	A	48
8			Bu	CH_3CN	B	58
9			Bu	CH_3CN	B	95

[a] Method A: 2 eq AHP, 2 eq $(RO)_3Si(CH_2)_3NH_2$, 2 mol% $Pd(OAc)_2$/dppf [for entry 7, 3 eq AHP + 3 eq $(RO)_3Si(CH_2)_3NH_2$]; Method B: 3 eq AHP, 2.1 eq $(BuO)_4Si$, 1.0 eq Et_3N, 2 mol% $Pd(OAc)_2$/dppp.

Table 3.4 Cross-coupling scope with alkenyl electrophiles (Second Part)

Entry	Electrophile	*H*-Phosphinate Product	R	Solvent	Ligand	Method[a]	Isolated Yield, % (NMR yield, %)[b]
1			Et	CH_3CN	dppf	A	(80)[c]
			Et	CH_3CN	dppp	A	44[d] (100)
			Bu	THF	dppf	B	(36)
			Bu	CH_3CN	dppp	B	50[d] (56)
				CH_3CN	dppp	B	20 (90)
			Et	THF	dppp	B	(19)
2			Bu	THF	dppf	B	(40)
			Et	CH_3CN	dppf	A	0 (53)
			Bu	CH_3CN	dppf	B	(0)
3			Bu	THF	dppf	B	18
			Bu	THF	dppp	B	(24)
4			Bu	THF	dppf	B	(42)
			Bu	CH_3CN	dppf	B	(0)
			Et	CH_3CN	dppf	A	0 (46)
			Bu	CH_3CN	dppp	B	(0)
5			Bu	CH_3CN	dppf	B	(0)
			Et	CH_3CN	dppf	A	(43)
6			Bu	CH_3CN	dppp	B	40[e] (50)
7			Bu	THF	dppf	B	(74)[f]
			Bu	CH_3CN	dppf	B	(0)
8			Bu	CH_3CN	dppp	B	(58)[g]

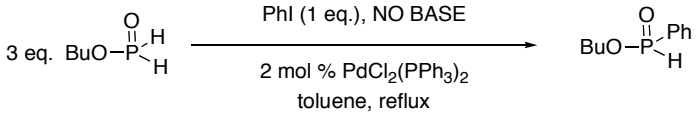
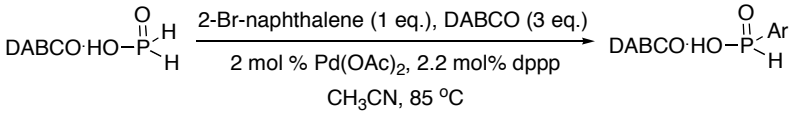
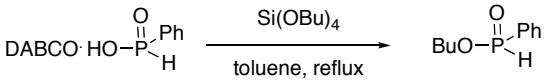
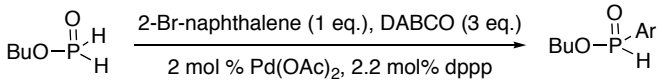
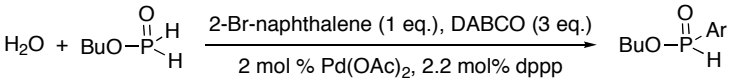
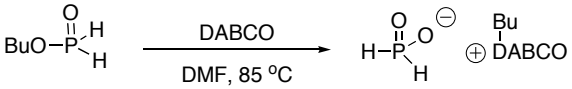
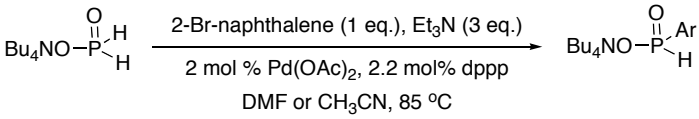
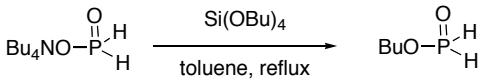
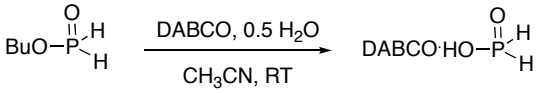
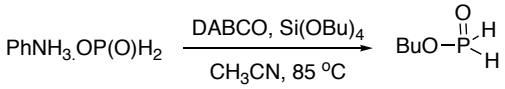
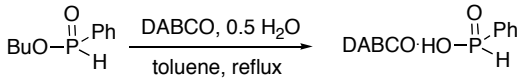
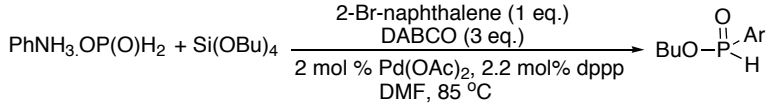
[a] Method A: 2 - 3 eq AHP, 2 - 3 eq $(RO)_3Si(CH_2)_3NH_2$, 2 mol% $Pd(OAc)_2$/ligand; Method B: 3 eq AHP, 2.1 eq $(BuO)_4Si$, 1 - 3 eq Et_3N, 2 mol% $Pd(OAc)_2$/ligand. [b] Unless otherwise noted, NMR yields were low and/or isolation of pure products was not successful. [c] 20% of disubstitution product was formed. [d] Product was isolated with 80% purity. [e] Product was pure. [f] 37% of the product from addition to the carbonyl group was observed. [g] 28% of the product from reduction of the alkene was observed.

3.2.3 Mechanistic studies

Inspired by the experimental results obtained in the alkyl phosphinate – aryl halide cross-coupling reactions, and in order to support the previous mechanistic hypotheses, a series of control experiments were conducted The results are summarized in Table 3.5.[63] Iodobenzene cross-couples efficiently with butyl phosphinate in the absence of base and water (entry 1) (**23-24**). Whereas, a less reactive electrophile (2-bromonaphthalene) does not undergo the coupling in the presence of DABCO under anhydrous conditions (entry 4), however the results are reversed in the presence of water (entry 5) (**23-20-21-22-24**), where the napthyl-*H*-phosphinate ester is obtained in 78% yield. We also proved that DABCO promotes the hydrolysis of butyl phosphinate effectively to the DABCO salt, even at room temperature if water is present (entry 9) (**23-20**), and it is not reversible (entry 10) (**20-23**). Furthermore, the corresponding DABCO salt participates successfully in the coupling with 2-bromonaphthalene (entry 2) (**20-21**). Additionally, the alkoxysilane-based esterification of the isolated DABCO salt of an aryl-*H*-phosphinate does not occur efficiently (entry 3) (**21-24**), which confirms the importance of the HX generated during the coupling step in the outcome of the reaction. In the absence of water, it is conceivable that dealkylation of the ester is taking place (entry 6) yielding quaternary ammonium salts of hypophosphorous acid (**23-25**), which do not undergo cross-coupling with 2-bromonaphthalene (entry 7) (**25-26**), and do not esterify with silicates (entry 8) (**25-23**). Indeed, a transfer hydrogenation reaction was confirmed by the detection of naphthalene by gas chromatography in the reaction from entry 7. The resulting aryl-*H*-phosphinate product is by far more stable with respect to hydrolysis than its precursor alkyl phosphinate (entry 11) (**24-21**). Overall, the one-pot tandem cross-coupling–esterification is optimal if the reactions are run under anhydrous conditions, and it is also more convenient in terms of manipulation and reaction time (entry 12) (**19-20-21-22-24**). This suggests that the development of an asymmetric variant

of this reaction might only be possible with aryl iodides, since in the case of less reactive halides, all the intermediates are achiral.

Table 3.5 Control experiments related to the mechanistic pathways in cross-coupling[a]

Entry	Reaction	Model	31P NMR yield,%[b]
1		23 → 24	100%
2		20 → 21	100%
3		21 → 24	11%
4		23 → 24	no *H*-phosphinate ester
5		23 → 21 22 → 24	78%
6		23 → 25	65%
7		25 → 26	no cross-coupling product
8		25 → 23	no esterification
9		23 → 20	92%
10		20 → 23	17%
11		24 → 21	15%
12		19 → 24	74%

[a] See **Scheme 3.1.** [b] NMR yields are determined by integrating all the signals in the spectrum.

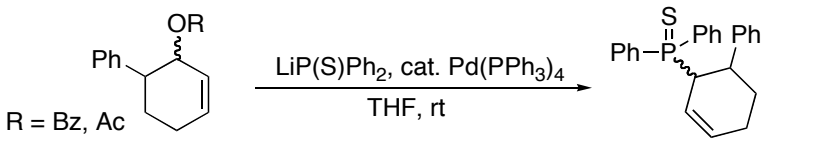
Chapter Four: Metal-catalyzed reactions of hypophosphorous acid derivatives with allylic electrophiles

4.1 Introduction

Palladium catalyzed allylic substitutions constitute an efficient and highly chemo-, regio-, and stereoselective methodology for constructing carbon-carbon bonds and carbon-heteroatom bonds. Their synthetic utility has been soundly demonstrated since it was introduced, more than four decades ago.[168] The catalytic cycle for these processes demands oxidative addition of Pd(0) species to allylic electrophiles with *in situ* formation of π-allylpalladium(II) intermediates, which then can react with nucleophiles at both termini of the allylic cation equivalent. As for the nucleophilic partner, carbon, nitrogen, oxygen and sulfur species have been extensively investigated while halides, acetates, carbonates, phosphates, carbamates, and some other related derivatives from allylic alcohols are normally used as electrophiles rather the parent allylic alcohols which are less prone to undergo C-O bond cleavage under these conditions due to the poor ability of the hydroxyl group as living group.[168] However, as a result of the more recent quest for Green Chemistry, significant efforts are currently being devoted to the development of allylation processes that use allylic alcohols directly.[169,170]

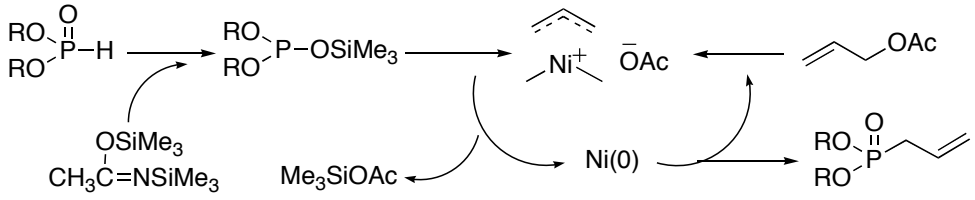
On the other hand, despite the enormous biological and synthetic impact of organophosphorus compounds, the development of novel metal catalyzed allylation processes involving C-P bond formation has been slow and just a few examples have been reported. Fiaud demonstrated that lithium salts of thiophosphides react with allylic acetates using Pd-catalysts, but only limited yields were obtained (Eq. 4.1),[171] while Lu *et al.* developed an allylation process where *O*,*O*-dialkyl phosphonates, or ethyl phenyl- and ethyl methyl-*H*-phosphinates cross-couple with allylic acetates or carbonates in the presence of stoichiometric amounts of bis(trimethylsilyl)acetamide (BSA) as silylating agent and using the highly air-sensitive $Ni(cod)_2$ as a catalyst (Scheme 4.1, see also Eq. 1.27 and 1.30).[65] This last approach is not convenient, as

it is an neither atom-economical process (produces molar amounts of silicate byproducts), nor a cost-effective transformation. In addition, it requires the manipulation of air- and water-sensitive compounds.



(Eq. 4.1)

Scheme 4.1 Mechanism for the Ni-catalyzed allylation of phosphonates with allylic electrophiles



Given the broad scope of our previously developed Pd-catalyzed cross-coupling reactions of aryl, benzylic and allylic electrophiles with hypophosphorous compounds, and considering the critical need to develop new methodologies particularly suited to access functionalized organophosphorus compounds, as well as the special versatility of *H*-phosphinates as synthons (Scheme 1.3), we focused our research on the development of catalytic allylation reactions. We initiated our study with allylic halides, where we discovered that, depending on the catalytic system and reaction conditions, alkyl phosphinates could behave as formates, promoting the hydrogenolysis of allylic electrophiles, or undergo a cross-coupling reaction directly. Part of this work was published in a full paper in 2005.[63] Later, we developed a general approach for allylic-*H*-phosphinic acids and *H*-phosphinate esters through a Pd-catalyzed allylation of hypophosphorous acid derivatives with various allylic electrophiles.[164a]

4.2 Cross-coupling *vs* hydrogenolysis-hydrophosphinylation with allylic electrophiles

First, we attempted our cross-coupling reaction with simple allyl chloride or bromide as substrates under our optimized conditions for the cross-coupling of aryl or alkenyl electrophiles

with hypophosphorous compounds. However, no C-P bond formation was detected. Next, we examined the reactivity of various allylic halides possessing longer carbon chains. A summary of the results is provided in Table 4.1.[63] Cinnamyl chloride was reacted with alkyl phosphinates in the presence of catalytic amounts of $Pd(OAc)_2$ and dppf in acetonitrile generating C-P bond formation. However, the product of the reaction proved to be the corresponding cross-coupling product but with the reduced double-bond (entries 1a, 1b). Through an assay of reaction conditions, it was found that the expected coupling product, cinnamyl-*H*-phosphinic acid (entry 1c, 1d), was formed effectively using alkyl phosphinates and $NiCl_2$ or $NiCl_2(PPh_3)_2$ in toluene. Geranyl chloride (entry 2) and 3-chloro-1-butene (entry 3) participated in the reaction with the Pd-catalyst furnishing the reduced products in low to moderate yields, but they did not couple using Ni-catalysts. On the other hand, cinnamyl formate (entry 4) (prepared by formylation with chloral)[172] and cinnamyl carbonate (entry 5) furnished lower yields of the reduced products under palladium catalysis. In analogous experiments using propargylic chlorides as electrophilic partners, we did not observe a clean transformation, i.e. entry 6, while H_3PO_2 or AHP did not undergo the expected C-P bond formation. Stimulated by these preliminary findings, gas chromatography studies were performed, which led us to propose some mechanistic pathways that might be involved in these transformations (Scheme 4.2).[63] Our studies suggest that with the Pd-catalyst, alkyl phosphinates are promoting the reduction of allylic electrophiles, particularly of allylic chlorides, similar to the well-established formate-promoted hydrogenolysis of these substrates (Eq. 4.2).[173] To further probe our hypotheses, we performed an isotopic labeling experiment with $EtOP(O)D_2$ and cinnamyl chloride in the presence of $Pd(OAc)_2$/dppf (2%). In this case, the ^{31}P NMR from the crude reaction mixture showed four different products resulting from C-P bond formation; after workup only two products were present, but unfortunately we did not succeed in their isolation.

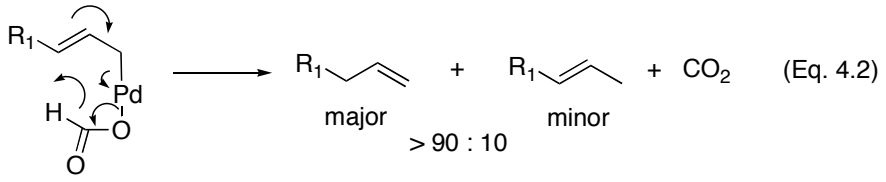
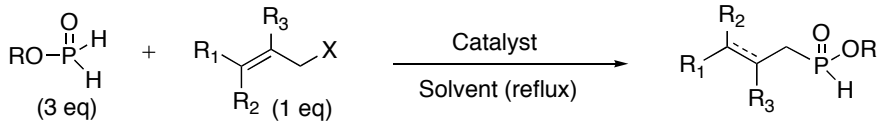
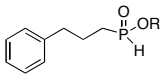
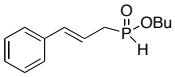
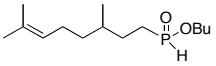
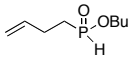
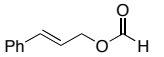
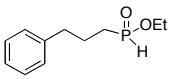
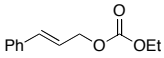
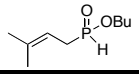


Table 4.1 Reactions of allylic electrophiles with alkyl phosphinates[a]



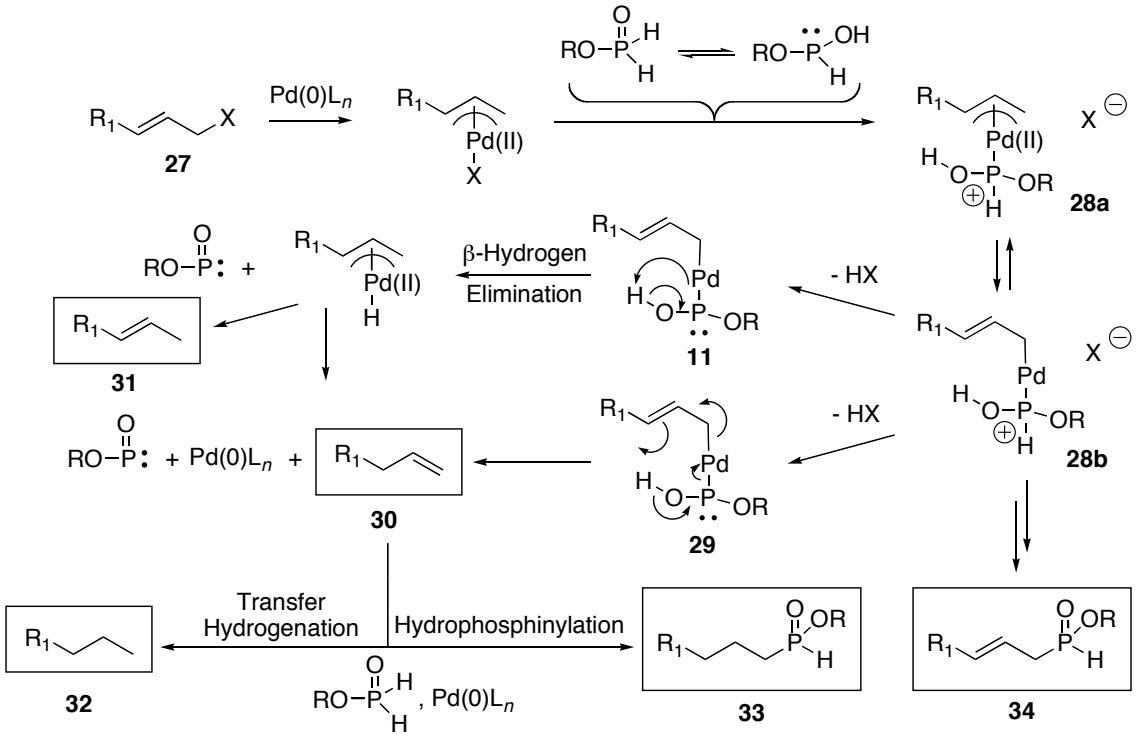
Entry	ROP(O)H_2 R =	Allylic substrate	Catalyst (mol%)	Solvent	Product	NMR yield, % (Isolated yield, %)
1a	Et	Cinnamyl-Cl	$Pd(OAc)_2$, dppf (2)	CH_3CN		95 (62)
1b	Bu					100 (73)
1c	Bu		$NiCl_2$ (4)	Toluene		100 (70)[b]
1d	Bu		$NiCl_2(PPh_3)_2$(2.5)			100 (88)[b]
2	Bu	Geranyl-Cl		CH_3CN		86 (46)
3	Bu			CH_3CN		33
4	Et		$Pd(OAc)_2$, dppf (2)	CH_3CN		33
5	Et			CH_3CN		13
6	Bu			CH_3CN		100 (74)[c]

[a] See Experimental Section for details of the procedures. [b] Isolated in 95% purity, contains 5% of the product with the reduced double bond. [c] Isolated with 75% purity, contains 25% of two other isomers.

As illustrated in Scheme 4.2, the Pd-catalyzed reaction of cinnamyl chloride with butyl phosphinate (Table 4.1, entry 1b) was monitored by GC (consumption of reagents) and ^{31}P NMR (product formation).[63] After 35 min, we observed 87% conversion of the cinnamyl chloride (**27**) to allylbenzene (**30**), and ^{31}P NMR spectra indicated the presence of 13% of the product **33**, however, no β-methylstyrene was detected (**31**), which rules out β-hydrogen elimination as the major pathway. After 2.5 hours, a 33% yield of allylbenzene was detected, while product **33** reaches a 65% NMR yield. The reaction was continued and after 8 h, quantitative formation of product **33** was measured, while only traces of allylbenzene (**30**) and propylbenzene (**32**) were

detected (1 and 2%, respectively). These results indicate that the reduced product **33** is formed upon hydrophosphinylation of **30** with the excess of alkyl phosphinate.

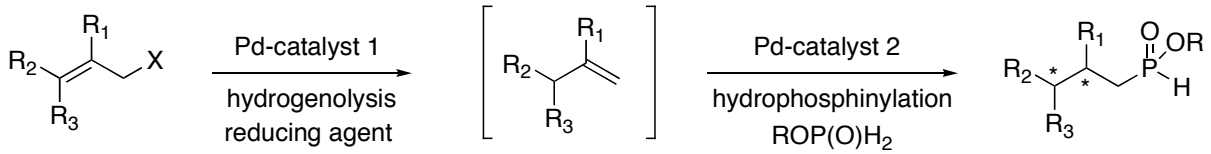
Scheme 4.2 Mechanistic pathways involved in metal-catalyzed reactions of alkyl phosphinates and allylic electrophiles



In contrast to the previously described pathway with Pd-catalysts, monitoring of the Ni-catalyzed version of this reaction (Table 4.1, entry 1c & 1d) showed that cinnamyl chloride (**27**) disappears slowly over time, reaching completion after 4 h; while only traces of allylbenzene (**30**) or propylbenzene (**32**) are present at any given time.[63] One conceivable explanation for this behavior is a faster reductive elimination (**28**/**29** to **34**) than reductive isomerization (**29** to **30**). In agreement with our postulated mechanism, the reaction of some other electrophiles, including formates and carbonates, provided similar results, although the yields of products were lower (Table 4.1, entries 2 to 5). These observations showed great potential for establishing a new general methodology for C-P coupling using various allylic electrophiles and hypophosphorous acid derivatives, which will be discussed in the next section.

Moreover, inspired by the results obtained in the allylation reactions with alkyl phosphinates, we speculated that two-step processes consisting of a hydrogenolysis-hydrophosphinylation sequence might be possible if an appropiate combination of catalyst and allylic electrophile (Scheme 4.3) were chosen.

Scheme 4.3 Possible tandem hydrogenolysis-hydrophosphinylation processes



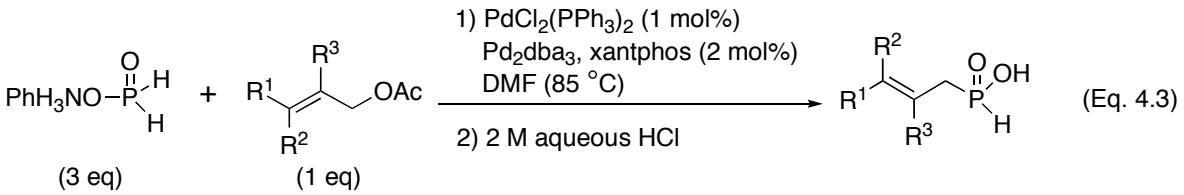
catalyst1: $Cl_2Pd(PPh_3)_2$, $Pd_2dba_3(Pd(acac)_2)/Bu_3P$

reducing agent: HCO_2NH_4, $ROP(O)H_2$, $HCO_2H{\cdot}Et_3N$, PMHS

R = H, $PhNH_3$, Alk

catalyst2: Pd_2dba_3/xantphos, $Pd(OAc)_2$/dppf

Our initial studies in this project consisted of investigating the optimized conditions for the hydrogenolysis of acetates with $PhNH_3OP(O)H_2$ (AHP) as reducing agent, using some common catalysts for this reaction.[173] After some screening, we did not find the optimum conditions. On the other hand, various mixtures of catalysts (catalyst1/catalyst2, Scheme 4.3) were tried in a "dual catalysis" approach to this tandem process. Surprisingly, when we used a combination of $PdCl_2(PPh_3)_2$, Pd_2dba_3 and xantphos in the reactions of geranyl and cinnamyl acetate with AHP in DMF (85°C), quantitative formation of the cross-coupling products, (geranyl- and cinnamyl *H*-phosphinic acids) was observed, instead of the expected reduced products (Eq. 4.3).[164a] Gas chromatography analyses revealed after just 1 h, complete disappearance of the acetate starting material, along with traces of the transfer hydrogenation product β-methylstyrene (4%) (**31**, Scheme 4.2), while ^{31}P NMR indicated formation of the coupling product (100%). Indeed, we later found that $PdCl_2(PPh_3)_2$ was not necessary, and that as low as 0.2 mol% of Pd_2dba_3/xantphos efficiently catalyzes this cross-coupling.[164a] We will discuss the scope and mechanism for this transformation in more detail in the next section of this chapter.



4.3 Cross-coupling of hypophosphorous acid derivatives with allylic electrophiles

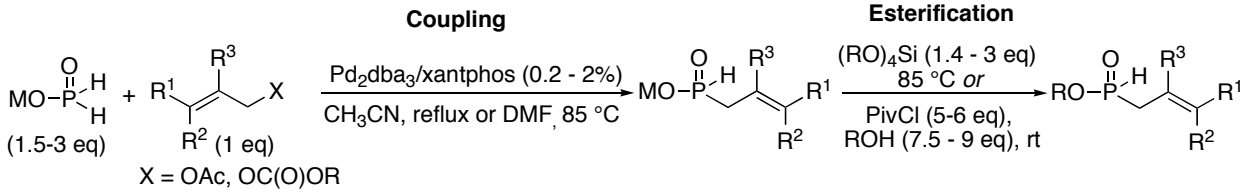
We first examined the reactivity of various allylic acetates with anilinum hypophosphite (2-3 eq) using 2 mol% of our best catalytic system (Pd_2dba_3/xantphos).[164a] The reactions were carried out in DMF at 85°C under a nitrogen atmosphere, however, no strict anhydrous or oxygen-free conditions were required (Table 4.2). DMF proved to be the best solvent for this reaction, while CH_3CN and THF (at reflux) were also effective in some cases. The isolation of the products allylic-*H*-phosphinic acids was performed by a simple aqueous acid workup. Several aqueous solutions of $NaHSO_4$, H_2SO_4 and HCl with different concentrations, as well as an acidic resin (amberlite) were tried for the workup. Even though the best results were obtained with 1–2 M solutions of HCl or $NaHSO_4$, we were unable to remove traces of aniline from the reaction mixture. Thus, we reasoned that a hypophosphorous acid salt of a more basic amine might substantially improve the isolation of pure products due to a more efficient acid-base reaction. Indeed, triethylammmonium hypophosphite (2-3 eq) turned out to be the most general starting material. Representative results for this cross-coupling reaction are summarized in Table 4.2. Ammonium hypophosphite (prepared from ammonium carbonate and H_3PO_2),[38e] and the commercially available, but hard to manipulate, highly hygroscopic, ethylpiperidinium hypophosphite also furnished the products in good yields (entries 3e and 3f). For our surprise, H_3PO_2 cross-couples with the very reactive electron-poor cinnamyl acetate efficiently in CH_3CN, in the absence of base (entry 2e), producing the corresponding cinnamyl-*H*-phosphinic acid in excellent yields and in high purity. However, with aliphatic allylic acetates, addition of a base

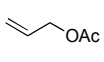
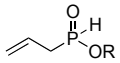
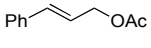
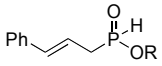
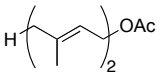
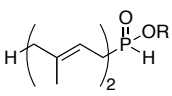
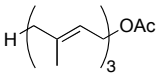
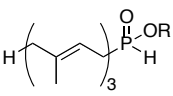
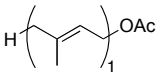
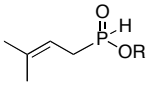
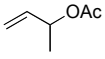
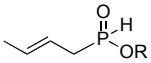
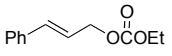
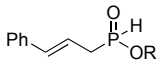
(Et_3N, 0.1-1 eq) played a key role in the success of the reaction when this was conducted in CH_3CN. A representative example of this behavior is geranyl acetate (entry 3j *vs* 3k). According to the postulated mechanism in Scheme 4.4, this basic additive may serve to: (a) drive the tautomeric equilibrium towards the P(III) form of the hypophosphorous compound (**36-37**), (b) promote the rearrangement of the phosphinyl-Pd-intermediate (**39-40**), and/or (c) accelerate the formation of the active catalyst through reduction of Pd(II) back to Pd(0). Of greater interest, we discovered that when DMF was used as a solvent, there was no need to add an extra base, i.e. geranyl acetate did react successfully (entry 3i). However, with another aliphatic allylic acetate, we observed the formation of the *H*-phosphinic acid product in low yield in DMF in the absence of base (entry 4e), and this result was significantly improved when adding a catalytic amount of Et_3N (0.1 eq) (entry 4f). A plausible explanation for this behavior is the slow formation of catalytic amounts of dimethylamine from DMF upon acid catalysis (H_3PO_2) and heating (85°C). Further optimization of this particular variant of the reaction is required in order to establish a particular set of conditions. As for the allylic electrophiles, we focused mainly on acetates, but a few examples of carbonates and benzoates were also screened and they did undergo the reaction in good yields. When using benzoates, *in situ* esterification of the acid products was required for their isolation (entries 7-9). It should be noted that a good indication of a π-allyl intermediate is denoted by the formation of a primary *H*-phosphinic acid in the case of the substrate from entry 6 due to the attack of the phosphorus nucleophile at the least hindered position in the η^3-complex. We also noticed that 2-substituted allylic acetates bearing electron withdrawing substituents did not participate effectively in this transformation. A representative case of this behavior is the reaction of 2-methallyl acetate (entry 12), which yields 63% of the product, versus 2-(acetyloxy)methyl-2-propenenitrile (entry 13), which produces only 5% of the *H*-phosphinic acid. The latter substrate was prepared by acetylation of the parent alcohol, itself synthesized

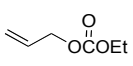
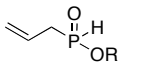
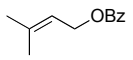
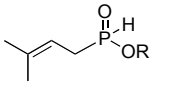
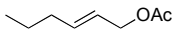
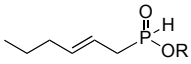
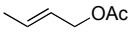
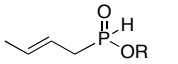
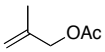
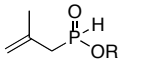
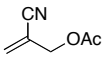
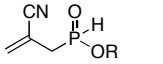
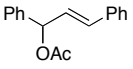
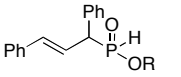
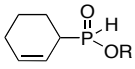
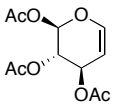
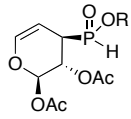
through a condensation of (*O,O*-diethylcyanomethyl)phosphonate (prepared by Arbuzov reaction)[174] with formaldehyde, followed by base-promoted elimination of the phosphonate.[175] Unfortunately, secondary allylic acetates reacted very sluggishly or not at all. That is the case of *trans*-1,3-diphenyl-2-propen-1-yl acetate (entry 14), which did not couple with $Et_3NHOP(O)H_2$ and produced a low yield of the corresponding *H*-phosphinic acid with H_3PO_2 (20%), while 2-cyclohexenyl acetate (entry 15) yielded only 20% of the product with the triethylamine salt, and no product with H_3PO_2. In addition, given the impact of glycosides as a result of their interesting pharmacological properties,[176] the reactivity of a peracetylated glycal (entry 16) in our cross-coupling reaction was investigated, but it followed the same trend as other secondary acetates and it did not participate in the coupling. On the other hand, terminal or substituted propargyl acetates furnished mixtures of several products resulting from C-P bond formation.

We also demonstrated the effectiveness of one-pot tandem cross-coupling-esterification processes for the generation of *H*-phosphinate esters (Table 4.2). The reactions consist of an *in situ* esterification of allylic *H*-phosphinic acids or of their corresponding amine salts with alkoxysilanes,[163] or using pivaloyl chloride as an activating agent in presence of an alcohol.[164] As shown in table 4.2, a wide range of *H*-phosphinates were obtained in moderate to good yields after isolation by column chromatography over silica gel. Of particular relevance, there is no need for a solvent change from DMF or CH_3CN to toluene, nor an increase in the esterification temperature to prepare the ester products in acceptable yields when using orthosilicates.[164a]

Table 4.2 Scope for the cross-coupling and cross-coupling–esterification with allylic electrophiles[a]



Entry	$MOP(O)H_2$ M= (eq)	Substrate	Product	Solvent	Isolated Yield (R=H) %	Esterification $(RO)_4Si$ *or* ROH-PivCl	Isolated Yield (R=Alk) %
1a	Et_3NH (2.5)			DMF	62		
1b	Et_3NH (2.5)			DMF		BuOH	57
2a	$PhNH_3$ (3)			DMF	>100[b]		
2b	$PhNH_3$ (3)			CH_3CN		$(BuO)_4Si$	91
2c	$PhNH_3$ (2)			CH_3CN		$(BuO)_4Si$	74
2d	Et_3NH (3)			DMF	86		
2e	H (1.5-3)			CH_3CN	100		
2f	H (2)			CH_3CN		$(BuO)_4Si$	67
2g	D(2)			CH_3CN	95		
3a	$PhNH_3$(2-3)			DMF	>100[b]		
3b	$PhNH_3$(2)			CH_3CN	>100[b]		
3c	$PhNH_3$ (3)			DMF		BuOH	70
3d	Et_3NH (2.5)			DMF		BuOH	58
3e	NH_4 (2.5)			DMF	85		
3f	Et-Piperidinium (3)			DMF	63		
3g	Et_3NH (3)			DMF	100		
3h	Et_3NH (2)	Geranyl-OAc		DMF	81		
3i	H (3)			DMF	99		
3j	H (3)			CH_3CN	0		
3k	H (3)[c]			CH_3CN	100[d]	$(BuO)_4Si$	58
3l	$PhNH_3$ (3)			CH_3CN		$(BuO)_4Si$	75
4a	Et_3NH (3)			DMF	100		
4b	$PhNH_3$ (3)			CH_3CN		EtOH	66[e]
4c	$PhNH_3$ (3)			CH_3CN		$(BuO)_4Si$	62
4d	$PhNH_3$ (3)			THF	100		
4e	H (3)	Farnesyl-OAc		DMF	45[d]		
4f	H (3)[f]			DMF	89[g]		
5a	$PhNH_3$ (2)			DMF	>100[b]		
5b	$PhNH_3$ (2)			CHCN	>100[b]		
5c	Et_3NH (3)			DMF	88[h]		
5d	$PhNH_3$ (3)	Prenyl-OAc		CH_3CN		$(BuO)_4Si$	88
6a	$PhNH_3$ (2)			CH_3CN	78[h]		
6b	$PhNH_3$ (2)			DMF	>100[b,h]		
6c	Et_3NH (2.5)			DMF	58[h]		
7	Et_3NH (3)			DMF	94[d]	$(BuO)_4Si$	54

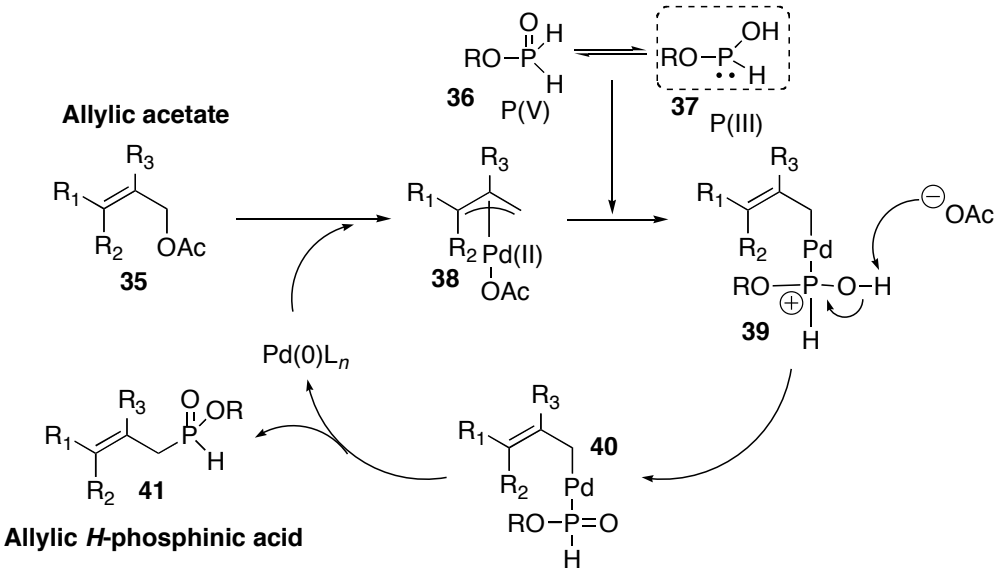
8	$PhNH_3$ (3)			DMF	86[d]		
9a 9b	Et_3NH (2.5) $PhNH_3$ (3)			DMF CH_3CN		BuOH $(BuO)_4Si$	60 91
10a 10b 10c	Et_3NH (2.5) Et_3NH (2.5) $PhNH_3$ (3)			DMF DMF CH_3CN	93	 BuOH $(BuO)_4Si$	 68 45
11a 11b 11c	Et_3NH (2.5) Et_3NH (2.5) Et_3NH (2.5)			DMF DMF DMF	69	 BnOH BuOH	 51 57
12a 12b 12c	Et_3NH (3) Et_3NH (3) $PhNH_3$ (3)[i]			DMF DMF DMF	63	 $(BuO)_4Si$ $(BuO)_4Si$	 48 58
13	Et_3NH (2.5)			DMF	0 - 5		
14a 14b	Et_3NH (2.5) H			DMF CH_3CN	0 20		
15a 15b	Et_3NH (2.5) H (2)			DMF CH_3CN	10 0		
16	$PhNH_3$ (3)			DMF	0		

[a] See Experimental Section for details of the procedures. [b] Aniline remains as impurity. [c] 1 eq Et_3N were added. [d] NMR yield. [e] Isolated as the allylic-*H*-phosphinic acid with the reduced double bonds at the positions 6 and 10. [f] 0.1 eq Et_3N were added. [g] 16% of farnesyl acetate remained as impurity. [h] 82-92% purity according to ^{31}P NMR spectra. [i] 3 eq Et_3N were added.

Furthermore, in the cross-coupling of D_3PO_2 with cinnamyl acetate, no incorporation of deuterium along the double bond was observed, which confirms, along with our GC studies, that the reaction occurs via a direct-coupling pathway. In view of these results, our rationale for the mechanism of this reaction is illustrated in Scheme 4.4.[164a] Allylic acetate **35** reacts with Pd(0) species, which are generated *in situ* by reduction of the Pd(II) to Pd(0), affording the π-allylpalladium intermediate **38**. Intermolecular nucleophilic substitution of the P(III) form of the hypophosphorous compound **37** takes place at the π-allyl system to give intermediate **39**, which

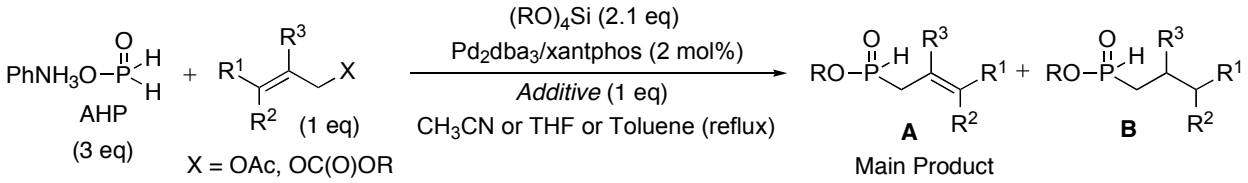
undergoes rearrangement yielding intermediate **40** that reductively eliminates Pd(0) to produce the allylic-*H*-phosphinic acid **41**.

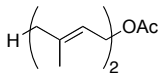
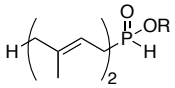
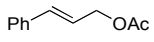
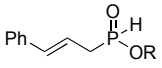
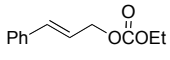
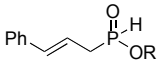
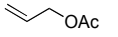
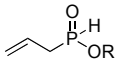
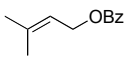
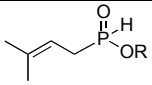
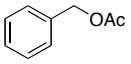
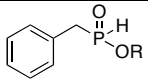
Scheme 4.4 Postulated mechanism for the cross-coupling of allylic electrophiles with hypophosphorous acid derivatives



At the same time, some efforts were devoted towards the design of a one-step preparation of allylic-*H*-phosphinate esters with aryl and alkenyl halides as previously described (Chapter 3).[62,63] The results collected in Table 4.3 show that in some cases the one-pot transformation worked, particularly when adding HCO_2NH_4 (1 eq). However, there is a marked tendency for the formation of significant amounts of products bearing a reduced double bond, which makes the isolation of the pure allylic *H*-phosphinates problematic. Furthermore, the esterification was not complete, which reduced the yields considerably. The reactivity of benzyl acetate was also examined, but we did not detect C-P bond formation. In addition, we analyzed the effect of various additives on the outcome of the reaction, but we did not improve our previous results. Finally, we tried the reaction on preformed alkyl phosphinates (prepared with alkoxysilanes),[18] but we observed the same tendency for the formation of reduced products, and there is also a big difference whether the alkyl phosphinates are prepared from AHP or from H_3PO_2 (Table 4.4).

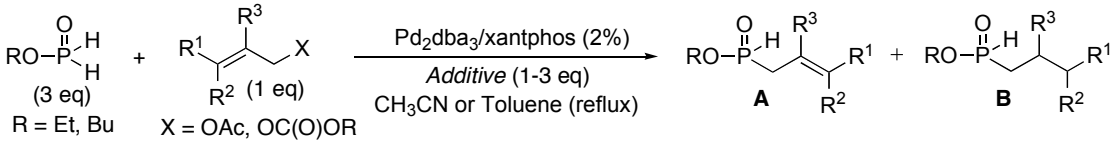
Table 4.3 Scope for the direct one-pot cross-coupling of alkyl phosphinates with allylic electrophiles[a]

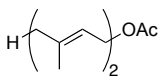
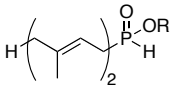
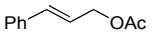
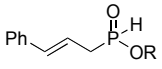
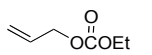
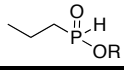


Entry	AHP (eq)	$(RO)_4Si$ R= (eq)	Substrate	Solvent	Additive	Product or Main Product	^{31}P NMR Result (%) A	^{31}P NMR Result (%) B	Isolated Yield, %
1a				Toluene	-		48	9	
1b	(3)	Bu (2.1)		Toluene	HCO_2NH_4		80	0	52
1c				CH_3CN	HCO_2NH_4		89	11	
2a				CH_3CN	HCO_2NH_4		78	7	
2b	(3)	Bu (2.1)		THF	HCO_2NH_4		32	2	
2c				CH_3CN	Zn powder		89	11	
2d				CH_3CN	Et_3N		50	0	
3a	(3)	Bu (2.1)		Toluene	HCO_2NH_4		52	0	
3b					-		81	0	68
4a	(3)	Bu (2.1)		Toluene	HCO_2NH_4		67	0	
4b					-		58	0	32
5	(3)	Bu (2.1)		Toluene	HCO_2NH_4		97	3	61
					-		93	7	54[b]
6	(3)	Bu (2.1)		Toluene	HCO_2NH_4		0	0	
					-				

[a] See Experimental Section for details of the procedures. [b] 7% of reduced product **B**.

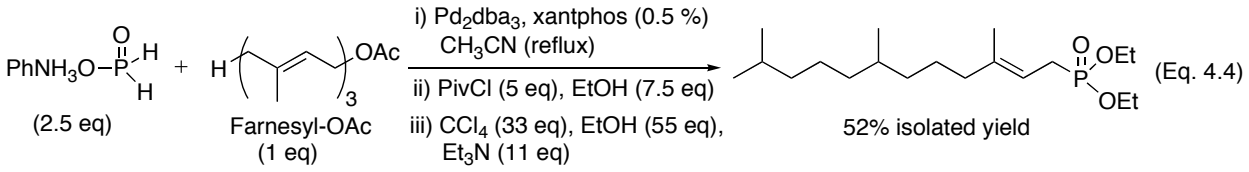
Table 4.4 Scope for the cross-coupling of alkyl phosphinates with allylic acetates and carbonates



Entry	$ROP(O)H_2$ (eq)	Substrate	Solvent	Additive	Product or Main Product	^{31}P NMR Result (%) A	^{31}P NMR Result (%) B	Isolated Yield, %
1a			Toluene	-		91	9	43[b]
1b	Bu (3)[a]		Toluene	HCO_2NH_4 (1)		87	11	
1c			CH_3CN	-		78	22	42[b]
1d	Bu (3)[c]		CH_3CN	-		36	17	
2a	Bu (3)[a]			HCO_2NH_4 (1)		72	10	
2b			CH_3CN	Et_3N (3)		48	0	
2c	Et (3)[c]			iPr_2NEt (1)		13	0	
2d				$NaOP(O)H_2$ (1)		78	22	
3	Et (3)[a]		CH_3CN	HCO_2NH_4 (1)		0	78	45

[a] Prepared from AHP and $(BuO)_4Si$. [b] Contains 7-15% of reduced product **B**. [c] Prepared from H_3PO_2 and $Me_2Si(OEt)_2$ (Ref. 18).

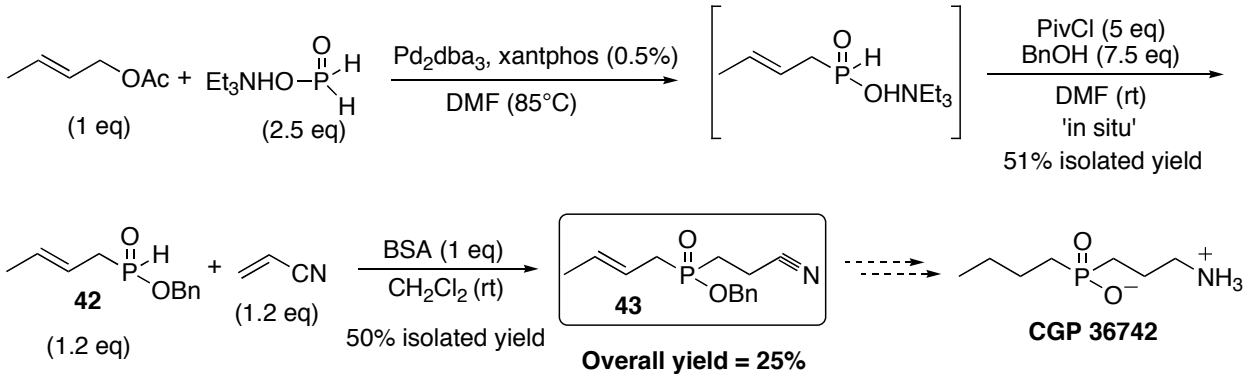
As noted in Chapter One (Section 1.3.7), the oxidative esterification of *H*-phosphinates under Atherton conditions leads to phosphonates.[113] We have demonstrated its application in tandem processes with *H*-phosphinates (Chapter 2).[35] Employing a similar approach we prepared, as a proof of concept, an allylic phosphonate (Eq. 4.4). In this particular case the product from cross-coupling followed by reduction was obtained. The reason for this behavior is somewhat unclear, as we did not observe the same behavior when the esterification was conducted with alkoxysilanes (Table 4.2, entry 4b *vs* 4c). Considering the well-established and efficient methodologies to prepare this class of compounds by C-P bond formation using allylic halides via the Arbuzov reaction with trialkylphosphites,[177] or through deprotonation-alkylation of dialkyl phosphites,[178] the present method is not very useful synthetically, however, it demonstrates the potential of *H*-phosphinates as precursors of other organophosphorus compounds.



(Eq. 4.4)

We tried to prepare a biologically active *H*-aminophosphinic acid CGP 36742 (Scheme 4.5), which is a GABA-B antagonist that is currently undergoing Phase II clinical trials.[179] However, we did not pursue this project as the yields of the intermediates were low compared to the yields reported in the literature for the synthesis of the target product. Froestl *et al.*[3b] reported the synthesis of CGP 36742 with 52% overall yield from the Ciba-Geigy reagent ethyl-(diethoxymethyl)-phosphinate **(7a,** from Chapter1**),** while more recently the Montchamp group obtained a 45% yield starting from the commercially available sodium hypophosphite salt.[104]

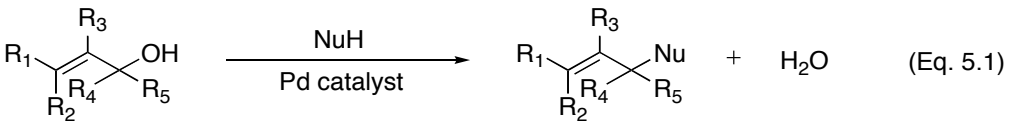
Scheme 4.5 Efforts towards the synthesis of a GABA-B antagonist



<u>Chapter Five:</u> Pd-catalyzed dehydrative allylation of hypophosphorous acid with allylic alcohols

5.1 Introduction

Given the impact of metal-catalyzed allylation reactions in organic synthesis thanks to their broad applicability and effectiveness, and considering the significant advances in developing the asymmetric potential in these reactions,[168] it has become crucial to introduce the "Green Chemistry" factor[154] into these transformations. Activated esters or halides, which are prepared form the corresponding allylic alcohols, have generally been used as substrates under basic conditions as a result of the poor reactivity of their alcohol precursors towards allylic C-O bond cleavage by metal catalysts.[180] Guided by the prospect of maximizing efficiency, palladium-catalytic allylic substitutions that use a basic feedstock, allylic alcohols, have started to emerge as viable processes for C-O, C-C, C-N, and C-S bond formation.[169,170] Though attractive, this type of allylic substitution is slow, and often requires the addition of catalytic or stoichiometric amounts of certain promoters such as PPh_3-DEAD,[181] As_2O_3,[182] B_2O_3,[183] $BF_3{\cdot}Et_2O$,[184] BEt_3,[185,169b,169i] Et_2Zn,[169b] $MgSO_4$/Pyr,[169g] BPh_3,[186] $SnCl_2$,[187] $Ti(OiPr)_4$,[188,169h] CO_2,[189] and RCO_2H,[169f] which activate and/or transform the hydroxyl group into a better leaving group. A more convenient, but highly challenging approach would be the direct reaction of allylic alcohols *in the absence of additives*, since water is the only byproduct (Eq. 5.1). This process would constitute a truly ideal reaction for forming carbon-carbon and carbon-heteroatoms bonds.



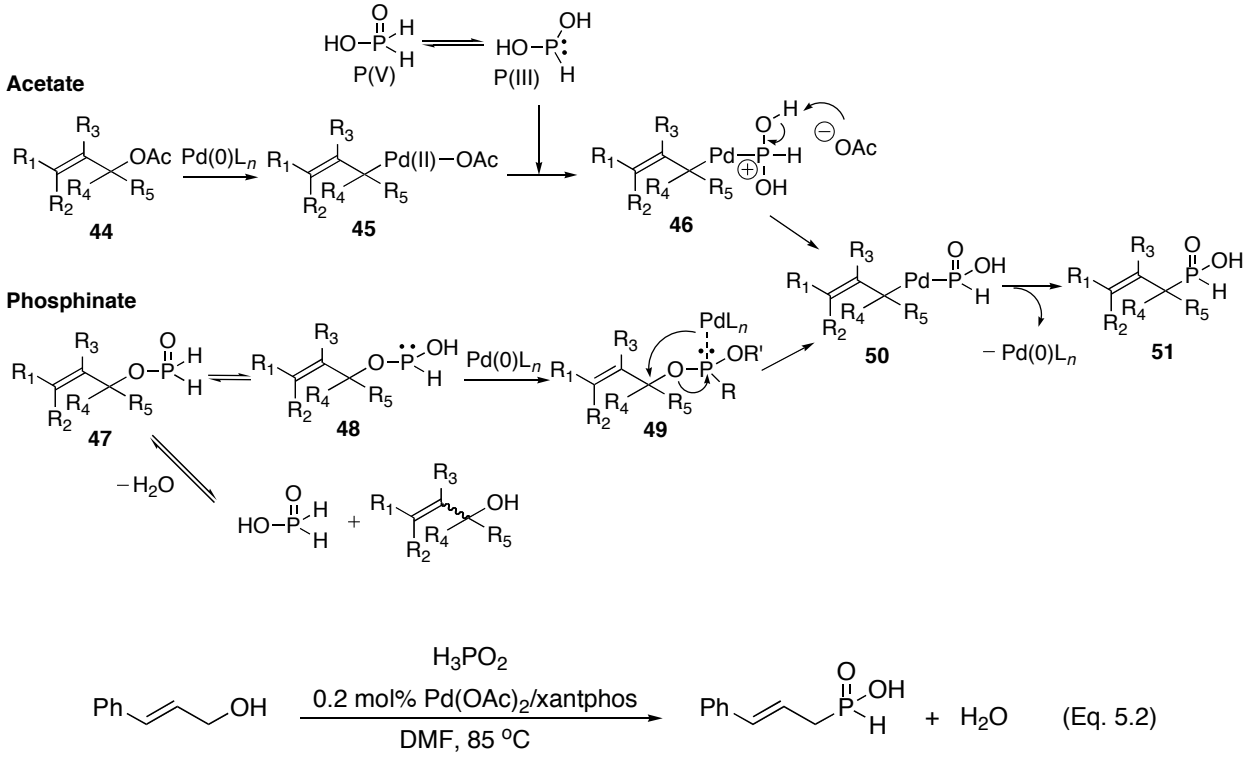
(Eq. 5.1)

As of today, just a few examples of these atom-economical and environmentally benign reactions have been reported with nitrogen, carbon and oxygen nucleophiles,[170] however, there are no precedents for this transformation with phosphorus nucleophiles. Moreover, as mentioned

in the previous chapter of this dissertation, the lack of systematic efforts towards the development of C-P bond forming methods via metal-catalyzed allylic substitution reactions is surprising.[65,171] Recently, Montchamp has demonstrated that hypophosphorous compounds ($ROP(O)H_2$) can participate effectively in metal-catalyzed reactions involving C-P bond formation, and that the competitive transfer hydrogenation (see Scheme 1.10, Chapter I) can be substantially minimized or even suppressed with an adequate catalytic system.[17,52] The challenge to overcome the reductive pathway in palladium-catalyzed allylation reactions was initially addressed by developing cross-coupling reactions between allylic halides, acetates, benzoates and carbonates with amine salts and esters of hypophosphorous acid (Chapter Four).[63,164a] Even though the cross-coupling with activated allylic electrophiles was successful, it was still highly desirable to achieve this process directly with allylic alcohols. Considering the analogy between allylic acetate **44** and allylic phosphinate **47**/**48**, we envisioned the possibility to develop a catalytic dehydrative allylation process (Scheme 5.1). Since the pK_a of H_3PO_2 (1.3) is significantly lower than the pK_a of HOAc (4.76), a phosphinate must be better leaving group than an acetate and should potentially be capable of oxidatively adding Pd into the C-O bond upon coordination of the metal with the free electron pair from the phosphorus atom in **49** producing a common intermediate **50**, which after reductive elimination generates an allylic-*H*-phosphinic acid **51**. This process would be direct if Fischer-like esterification generates the allyl phosphinate *in situ*.

Gratifyingly, our hypothesis turned out to be correct and we developed a highly regio- and *E*-selective palladium-catalyzed dehydrative allylation of hypophosphorous acid (H_3PO_2) with allylic alcohols *in the absence of any additives*, which was published as a communication in 2006 (Eq. 1.28).[66] More recently, we were invited to submit a preparative synthesis of cinnamyl-*H*-phosphinic acid (27 g) to Organic Syntheses (Eq. 5.2).[190]

Scheme 5.1 Analogy allylic acetate *versus* allylic phosphinate



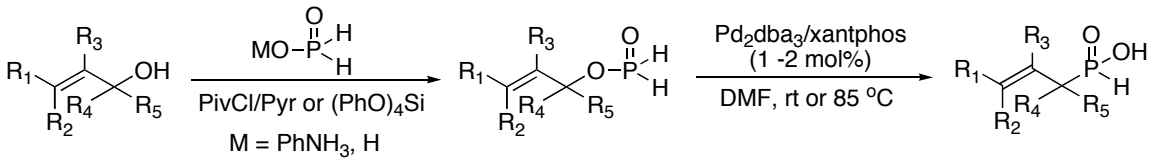
After our initial report, we have further investigated the scope and mechanism of the reaction and we employed this approach in the preparation of allylic-*H*-phosphinate esters via tandem processes and in the synthesis of phosphorous heterocycles. In the following sections of this chapter we will analyze the overall results and applications of this unique allylic substitution.

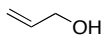
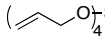
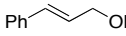
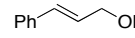
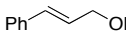
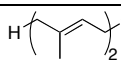
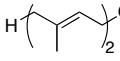
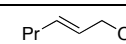
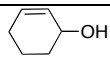
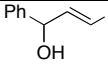
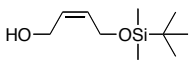
5.2 Results and discussion

Our initial approach to this project consisted of testing the hypothesized Pd-catalyzed rearrangement of preformed allylic phosphinates (Table 5.1). Various methods to prepare these compounds were investigated. Although a Dean-Stark esterification did not provide the expected products, our transesterification with phenyl phosphinate (itself prepared by the alkoxysilane method),[17,52] as well as our pivaloyl chloride methodology,[16,17] furnished the expected compounds (entries 2a *vs* 2b & 2d), which upon addition of Pd-catalysts did undergo the rearrangement to allylic-*H*-phosphinic acids in moderate to good yields. The solvent of the

reaction appeared to be critical and DMF was required for the success of the reaction, while Pd_2dba_3 and xantphos showed the best catalyst performance. This provided the proof of concept experiment for subsequent investigations.

Table 5.1 Palladium-catalyzed rearrangement of allylic phosphinates



Entry	Allylic alcohol (eq)	Method to prepare AllylOP(O)H_2	Solvent	AllylOP(O)H_2 δ, ppm (%)	Cat, %	Temp, °C	Additive (eq)	NMR yield, % (Isolated yield, %)
1a	 (2)	$(PhO)_4Si$ (1), H_3PO_2 (1), 85°C	DMF	16.9 (91)	1	85	H_3PO_2 (1)	2
1b			DMF	16.9 (91)	1	85	-	11
1c	-	 (1), H_3PO_s (1), 85°C	DMF	16.9 (100)	2	85	-	0
1d	-		DMF	16.9 (100)	2	85	H_3PO_2 (2) Et_3N (1)	54
1e	-		DMF	16.9 (100)	2	85	Et_3N (0.25)	52[2]
2a	 (1.5)	H_3PO_2 (1), reflux	Cyclo-hexanes[3]	(0)	-	-	-	-
2b	 (2)	H_3PO_2 (1), $(PhO)_4Si$ (1), 85°C	DMF	14.3 (76)	1	85	-	67[2]
2c					1	85 *or* rt	H_3PO_2 (1)	100 (60)[4]
2d	 (1.5)	AHP (1), PivCl (1.1), Pyr (1.25), rt	DMF	17.2 (100)	1	85	H_3PO_2(1)	98
3a	 (1)	H_3PO_2 (1), $(PhO)_4Si$ (1), 85°C	DMF	15.1 (83)	2	85	-	78 (57)[4]
3b	 (2)	H_3PO_2 (1), $(PhO)_4Si$ (1), 85°C	DMF	15.1 (77)	2	85	-	79[2]
3c						rt	-	78
4	 (3)	H_3PO_2 (1), $(PhO)_4Si$ (2), 85°C	DMF	15.9 (94)	1	85	-	56 (30)[5]
5	 (1.5)	AHP (1), PivCl (1.1), Pyr (1.25), rt	DMF	14.2 (55)	1	85	H_3PO_2 (1)	0
6	 (1.5 - 2)	AHP/PivCl/Pyr, rt *or* H_3PO_2/$(PhO)_4Si$, 85°C	DMF	(0)	-	-	-	-
7	 (1.5 - 2)	H_3PO_2 (1), $(PhO)_4Si$ (1), 85°C	DMF	(0)	-	-		-
		AHP (1), PivCl (1.1), Pyr (1.25), rt		16.6 (53)	1	85	H_3PO_2 (1)	0

[1] See Experimental Section for details of the procedures. [2] NMR yields correspond to a mixture of allylic-H-phosphinic acids plus the corresponding phenyl esters, which get hydrolyzed to the acid upon acidic workup. [3] Dean-Stark esterification. [4] Isolated as the butyl esters after esterification with $(BuO)_4Si$ in toluene. [5] Isolated as the *trans*-hexen-2-yl (trans-hexen-2-yl) phosphinate ester.

As shown in entry 2, the use of an acid additive improves the yields of products. Remarkably, we found that the rearrangement occurs even at room temperature (entry 3c). Of course, no rearrangement takes place in the absence of catalyst. This finding, along with the fact

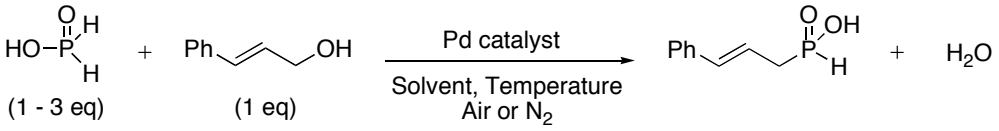
that the rearrangement of allylic phosphinates from primary alcohols provides exclusively primary *H*-phosphinic acids excludes the known thermal [2,3] sigmatropic rearrangement pathway.[191] Conversely, with allyl phosphinate, prepared from the commercially available tetraallylorthosilicate,[18] or via transesterification with phenyl phosphinate,[17] only moderate yields of rearranged products can be obtained when adding Et_3N (entries 1c *vs* 1d-e). Unfortunately, neither allylic phosphinates from secondary alcohols (entries 5-6), nor a symmetrical TBDMS (*tert*-butyldimethylsilyl) mono-protected allylic diol (entry 7) participated in the reaction under any of the conditions investigated. Surprisingly, we were unable to prepare the phosphinate ester from *trans*-1,3-diphenyl-2-propen-1-ol (entry 6), which might be due to steric hindrance and/or to an increased sensitivity towards hydrolysis at the benzylic position.

Subsequently, we focused on the development of a direct allylic substitution reaction of hypophosphorous acid with allylic alcohols. The rationale was the possible *in situ* formation of a small concentration of allylic phosphinate, which could be rearranged and drive the equilibrium forward. During our initial studies regarding the Pd-catalyzed rearrangement of allylic phosphinates, we found that Pd_2dba_3/xantphos provided the best results, with *N*,*N*-dimethylformamide (DMF) (85°C) as solvent.[66] This important precedent led us to first examine the reactivity of cinnamyl alcohol with H_3PO_2 under different experimental conditions, using various Pd sources, with xantphos as ligand in order to optimize and simplify the process, and to find out some of its limitations (Table 5.2). Indeed, the use of quite low catalyst loading (as low as 0.05 mol%, entry 4), consisting of Pd (Pd_2dba_3, $Pd(OAc)_2$ or $PdCl_2$) with xantphos as a ligand gave satisfactory results, and DMF proved to be determinant for a successful allylation reaction (entry 2). In addition, we found that the reaction proceeds in good yield even with equimolar amounts of H_3PO_2 and cinnamyl alcohol (entry 2d), and remarkably, the reaction works even at room temperature (entry 3c) and is highly water and air tolerant (entries 3 & 4). It should be

noted that aliphatic allylic alcohols did not react at room temperature. Generally, we used 0.2 M solutions of dry DMF (over 4Å molecular sieves),[66] but we found that the reaction still worked well when performed with reagent grade DMF (entry 4), even when using the commercial 50 wt%. aqueous H_3PO_2 and under very concentrated conditions (4 M) (entry 5). However, in experiments conducted under an air atmosphere, an excess of H_3PO_2 appeared to increase substantially the yields (entry 3), presumably because H_3PO_3 generated from oxidation of H_3PO_2, acts as an antioxidant and prevents the conversion of the product into the corresponding phosphonic acid. Cinnamyl *H*-phosphinic acid was isolated in good purity (>95%) by a simple acidic workup, and treatment with activated charcoal was very effective to remove traces of palladium. We also scaled up the reaction to 27 g maintaining a high yield of product cinnamyl-*H*-phosphinic acid (92%) (entry 9). This process is completely reproducible and proceeds with 0.2 mol% of catalyst (67 mg of Pd), which makes this synthesis a highly cost-effective approach to this class of compounds.[190] Moreover, 1 mol% of a polymer-supported ligand (0.18 mmol/g polystyrene-supported nixantphos)[66] also catalyzed the dehydrative allylation reaction and allowed the recovery and reuse of the ligand in several additional runs without the need to use additional Pd (entry 10). After five subsequent runs, the combined yield of 92% was achieved.

The course of the allylic substitution was monitored by gas chromatography (allylic alcohol disappearance) and ^{31}P NMR (product formation), where we observed that the reaction reached completion in less than 2 hours at 85°C or at room temperature, while no signs of reductive isomerization products (β-methylstyrene or allylbenzene, Scheme 4.2) were detected, even after long periods of heating (14 h). Consistent with this result, an isotopic labeling experiment with D_3PO_2 and cinnamyl alcohol did not show any deuterium incorporation along the allylic fragment (entry 11).

Table 5.2 Optimization of the Pd-catalyzed allylation of H_3PO_2 with cinnamyl alcohol[1]



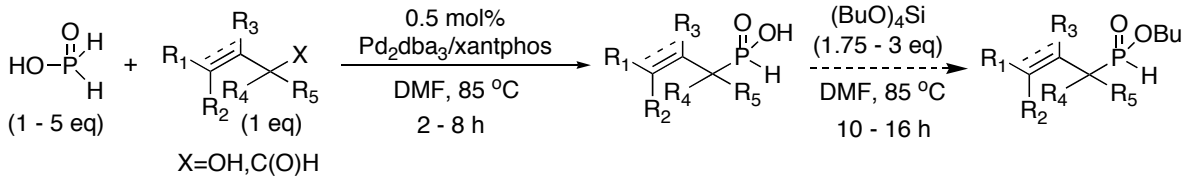
Entry	H_3PO_2 aq. *or* conc. (eq)	Catalyst Pd / Ligand (mol% Pd)	Solvent (dry *or* reagent grade, RG)	Conc. [M]	Additive (eq)	Air *or* N_2	Temp. (°C)	NMR yield, % (isolated yield, %)
1	conc. (3)	Pd_2dba_3/xantphos (2)	DMF (dry)	0.17	Et_3N (1)	N_2	85	100 (100)[2]
2a	conc. (3)	Pd_2dba_3/xantphos (2)	DMF (dry)	0.17	-	N_2	85	100 (100)
2b		(0.5)		0.17				
2c	conc. (2)	(0.5)		0.17				100 (98)
2d	conc. (1)			0.2				97 (95)
2e	conc. (2)	(0.5)	CH_3CN (RG)	0.2			82	0
3a	aq (1)	Pd_2dba_3/xantphos (0.5)	DMF (RG)	0.2	-	air	85	72
3b	aq. (2)							100 (100)
3c	aq. (2)						rt	100 (100)
4a	conc. (1.5)	Pd_2dba_3/xantphos (0.5)	DMF (RG)	0.2	-	air	85	85 (83)
4b	conc. (1.5)		DMF (dry)			air	85	83 (83)
5	aq (2)	Pd_2dba_3/xantphos (0.5)	DMF (RG)	4	-	air	85	100 (74)
6a	conc (2)	Pd_2dba_3/xantphos (0.2)	DMF (dry)	2	-	N_2	85	100
6b		(0.1)						100
6c		(0.05)						100 (99)
6d		(0.04)						20
7a	conc (2)	Pd_2dba_3 (0.5)	DMF (dry)	0.2	-	N_2	85	0
7b		No catalyst						
8a	conc. (1.5)	$Pd(OAc)_2$/xantphos (0.5)	DMF (dry)	0.2	-	N_2	85	100 (96)
8b	conc. (1.5)	$PdCl_2$/xantphos (0.5)	DMF (dry)	0.2	-	N_2	85	98 (90)
8c	conc. (1.5)	5%Pd-C/xantphos (1)	DMF (dry)	0.2	-	N_2	85	20[3]
8d	conc. (1.5)	Pd_2dba_3/dppf (0.5)	DMF (dry)	0.2	-	N_2	85	0
8e	conc. (1.5)	$Pd(OAc)_2$/dppf (1)	DMF (dry)	0.2	-	N_2	85	0
9	conc. (2)	Pd_2dba_3/xantphos (0.2)	DMF (RG)	0.5	-	N_2	85	100 (92)[4]
10	conc. (2)	Pd_2dba_3/polymer-supported nixantphos (1)	DMF (dry)	0.2	-	N_2	85	100 100 98 (92)[5] 95 90
11	D_3PO_2 (2)	Pd_2dba_3/xantphos (0.5)	DMF (dry)	0.5	-	N_2	85	100 (100)[6]

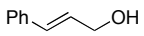
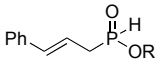
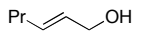
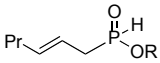
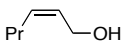
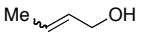
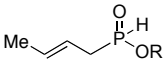
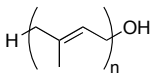
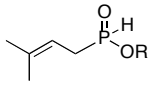
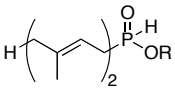
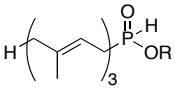
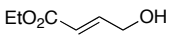
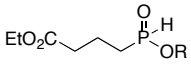
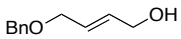
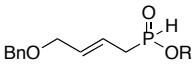
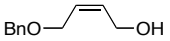
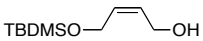
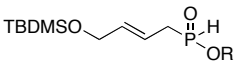
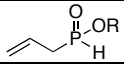
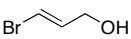
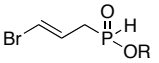
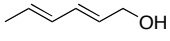
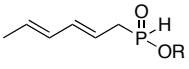
[1] See Experimental Section for details of the procedures. [2] The isolated product contains traces of Et_3N. [3] A mixture of two unidentified products was obtained. [4] The experiment was done in a 27 g scale and the yield was reproducible. The product was fully characterized and the high purity of the product was confirmed by elemental analysis and HPLC. [5] Collected isolated yield of 5 runs. [6] Cinnamyl-*H*-phosphinic acid was isolated, with no incorporation of deuterium along the allylic moiety. This supports the proposed mehanism.

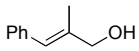
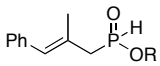
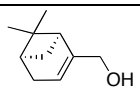
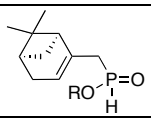
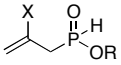
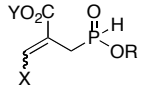
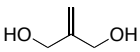
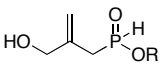
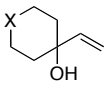
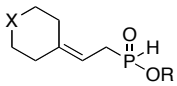
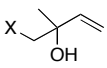
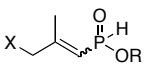
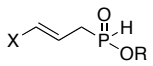
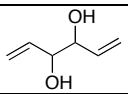
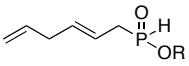
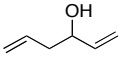
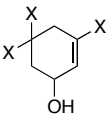
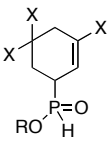
The Pd-catalyzed allylation reaction was successfully extended to other allylic alcohols possessing different substitution patterns and various functionalities.[66] We performed a very extensive study and the results are summarized in Table 5.3. The reactions were normally carried out in dry DMF at 85°C under N_2, and using 0.5 mol% of Pd_2dba_3/2xantphos. In most cases, primary *H*-phosphinic acids were isolated in moderate to good yields after extractive workup, and they could also be esterified *in situ* with alkoxysilanes to the corresponding phosphinate esters, which were purified by standard chromatographic techniques using silica gel as stationary phase. Since substrates that possess a terminal double bond and secondary or tertiary alcohols in the allylic position undergo rearrangement to form a primary C-P bond, the reaction must proceed via π-allylpalladium intermediates (entries 21-28). Interestingly, in the case of a mixture of (±) and *meso* isomers of 1,5-hexadiene-3,4-diol (entry 28), the product from mono-allylation-dehydration was obtained cleanly instead of the symmetrical 1,5-bis-*H*-phosphinate. When using low molecular weight allylic alcohols (3-4 carbons), an *in situ* esterification with alkoxysilanes to the corresponding *H*-phosphinate esters improves the yield significantly since extractive isolation of the acid is inefficient (entries 4 and 12). The reaction is highly *E*-selective (i.e. entries 2 & 3 and 4), and the *Z*- or *E*- starting materials furnish almost exclusively the *E*-isomers of the allylic-*H*-phosphinic acid products. As can be seen in entry 8, the presence of an ester functionality in the 3- position of the allylic alcohol led directly to the saturated product, whereas the allylation failed when the ester was replaced by a bromine substituent (entry 13). On the other hand, some secondary allylic alcohols react successfully in this reaction (entries 31, 32 and 35), although they require more concentrated conditions and slightly higher catalyst loading (2 mol%). Of particular relevance is the reaction of 3-penten-2-ol (entry 35), which opens up the possibility to develop an asymmetric version of this transformation since a chiral carbon is formed. We also observed that 2-substituted allylic alcohols (entry 17) did not undergo the

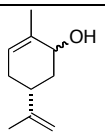
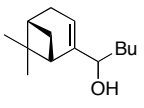
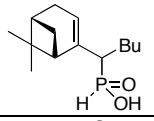
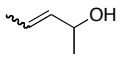
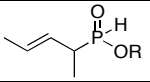
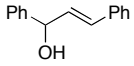
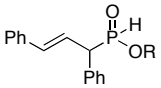
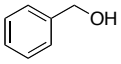
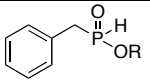
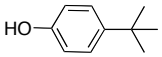
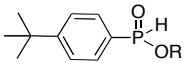
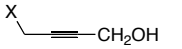
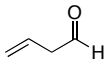
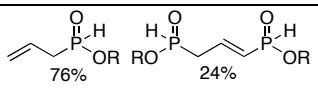
allylation reaction, either when bearing electron donating or electron withdrawing substituents. A different behavior was evidenced in the allylic acetate coupling work (Chapter Four), where electron-rich, 2-substituted allylic acetates (i.e. methallyl acetate) did participate in the reaction. The reactivity of some Baylis-Hillman adducts[192] was also investigated (entry 18), but no C-P bond formation was detected. Furthermore, in analogous experiments phenols and benzylic alcohols (entries 37 and 38) did not provide *H*-phosphinic acids, while GC-monitoring of the course of the reaction did not detect the formation of the corresponding transfer hydrogenation products, indicating the lack of oxidative addition. Additionally, various propargyl alcohols (entries 39-41) underwent C-P bond forming reactions, however no selectivity towards allylic substitution was achieved. A wide range of different products was usually formed, some of them could be a result of a [2,3] sigmatropic rearrangement.[191] Finally acrolein (entry 42) produced a mixture of allylic-*H*-phosphinate and 1,3-bis-allylic-*H*-phosphinate. Allylic *H*-phosphinic acids have been prepared previously from the reaction of an allylic halide with bis(trimethysiloxy)phosphine $(TMSO)_2PH$.[36a] However, this method requires wasteful silylation and a halide-containing electrophiles; in addition, it is difficult to minimize the formation of symmetrically disubstituted products.[193] Another synthetic approach to allylic-*H*-phosphinate esters is a base-promoted direct alkylation of alkyl phosphinates,[55,57] or a Michaelis-Becker reaction of masked hypophosphorous synthons,[58d] which requires additional protection and deprotection steps, limiting as well the number of compatible functionalized compounds.

Table 5.3 Scope of the Pd-catalyzed dehydrative allylation of H_3PO_2[1]



Entry	H_3PO_2 (eq)	Alcohol	Product *or* Outcome of the reaction	Yield, %[2] (R=H)	Yield, %[3] (R=Bu)
1a	1			95	-
1b	2			100[4]	-
1c	2			100[5]	-
1d	2.5			-	79
1e	3			-	98
2a	1			62	
2b	2.5			-	68
3a	1			92	-
3b	2.5			-	69
3c	3			-	98
4a	2			50	-
4b	2.5			-	88
5a	1	 n = 1		52	-
5b	2.5			-	52
6a	1	n = 2		100	-
6b	2			-	64
7a	1	n = 3		86	-
7b	2			94	-
7c	2.5			-	72
8a	2			68[6,7]	-
8b	2.5			-	77
9a	2.5			100[7,8]	-
9b				-	67
10	2.5			100[7,9]	-
11	2.5			0[7]	-
12	3			100[7,6,10]	43[10]
13	2.5			0[7]	-
14	2.5			0[7]	-

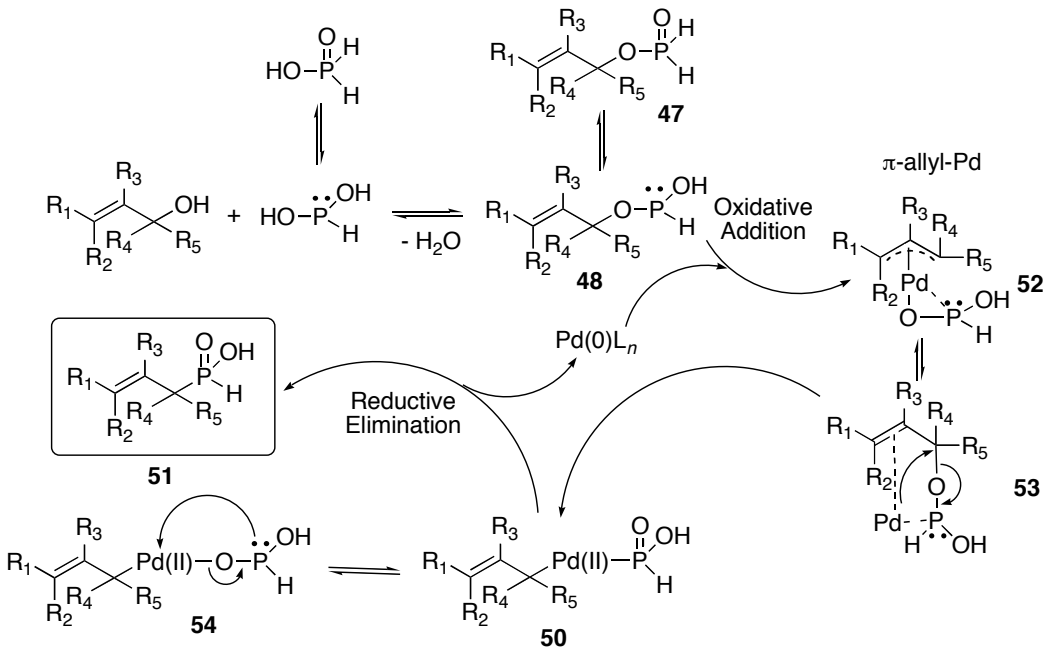
15a 15b	1 2.5				68 -	- 57
16a 16b	2 2.5				74 -	- 58
17a 17b 17c	3		X = Me X = Cl X = CN		$26^{7,11}$ 6^{7} 0^{7}	- - -
18	2.5		X = 4-ClC_6H_4 Y = Et		0^{7}	-
19	2.5		X = 3-Pyr Y = *t*-Bu		10^{7}	-
20	3				$29^{7,9}$	-
21	2		$X = CH_2$		78	-
22a 22b	2 2.5		NCO_2Et		73 -	- 61
23a 23b	1 2.5		X = H		82 -	- 68
24a 24b 24c	1 2.5 2.5		X = prenyl		93^{12} 100^{12} -	- - 50^{12}
25a 25b	1 2.5		X = geranyl		98^{12} -	- 90^{12}
26a 26b	2 2.5		X = Et		92 -	- 53
27a 27b	2 2.5		X = 4-FC_6H_4		96 -	- 59
28	3				98	-
29	2.5		Mixture of addition/allylation products		100^{7}	-
30	3		Mixture of various unidentified products		-	-
31	3		X = H		$53^{7,11}$	45^{11}
32	3		X = Me		52^{11}	-

33	2		Mixture isomers	Mixture of addition/allylation products	80[7]	-
34	3				7[7,11]	-
35	3				80[11,13]	-
36	3				15[7,11]	-
37	2				0[7]	-
38					0[7]	-
39	2		X = H	Not selective Mixtures of various unidentified products[14]	-	-
40	2		X = CH_2NEt_2		-	-
41	2		X = Pr		-	-
42	5				-	56

[1] See Experimental Section for details of the procedures. Unless otherwise noted, reactions were conducted in dry DMF (0.2M) at 85°C, with 0.5 mol% of Pd/xantphos. [2] Isolated pure (>95%) after extractive workup, unless otherwise noted. [3] Purified by chromatography on silica gel. [4] Reaction was conducted in air, 50 wt.% aq. H_3PO_2, reagent grade DMF, 85°C. [5] Reaction was conducted in air, 50 wt% aq. H_3PO_2, reagent grade DMF at rt. [6] Product is very polar and goes into the aqueous layer during workup. [7] NMR yield. [8] Product gets oxidized into the phosphonic acid during the workup. [9] Allylic-*H*-phosphinic acid is the major compound, but there is another byproduct. [10] 2 mol% Pd/xantphos. [11] [2 M] DMF, 2 mol% Pd/xantphos. [12] 1:1 mixture of isomers. [13] Contains 10% of the product with the reduced double bond. [14] Reactions were run at 85°C and at rt; substrates from entries 37 & 39 furnished mixtures of products at both temperatures, while substrate from entry 38 did not react at rt and reacted with no selectivity at 85°C.

As a result of our previous observations and corroborating our hypothesis (Scheme 5.1), we have proposed a plausible catalytic cycle for this transformation (Scheme 5.2).[66] Guided by the fact that an allylic phosphinate can form through a Fischer-like esterification of H_3PO_2 with an allylic alcohol (**47**), and considering that hypophosphorous compounds exist in a tautomeric equilibrium between the P(V) and P(III) forms due to the presence of a phosphinylidene moiety (P(O)H), compound **48** can be generated. Coordination of a Pd(0) species to the three-coordinated phosphorus atom and to the alkene in **48** might favor the oxidative addition of Pd(0), which results in the formation of species such as **52** and **53**, which in turn undergo rearrangement (**53**-**50**) followed by reductive elimination (**50**-**51**), furnishing the C-P bond formation product.

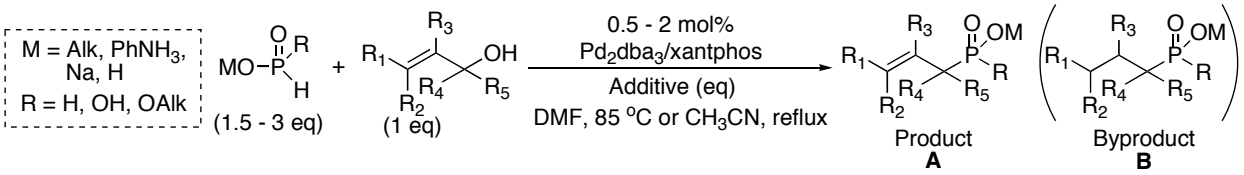
Scheme 5.2 Postulated catalytic mechanism for the Pd-catalyzed allylation of H_3PO_2 with allylic alcohols

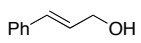
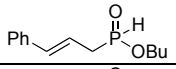
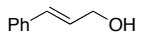
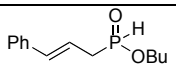
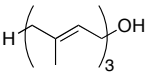
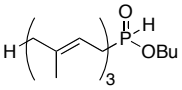
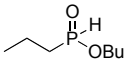
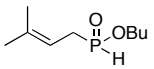
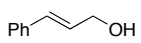
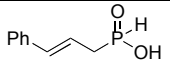
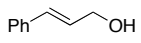


In order to accomplish the direct preparation of allylic *H*-phosphinate esters through palladium catalysis, we looked briefly into the reactivity of alkyl phosphinates with allylic alcohols in the absence of base, but we did not obtain very promising results and reduction products were often detected (Table 5.4, entries 2-5). This is not surprising according to our postulated mechanism because we suggest that the initial step is Fischer esterification of H_3PO_2 with the alcohol. In the case of the one pot-process, it appears that the competitive reductive pathway occurs faster than the esterification (entry 1). With preformed alkyl phosphinates (entries 2-5), slightly better yields of products were achieved, which is unexpected and might imply that kinetic control is governing the process by transesterification of butyl phosphinate with the electron-deficient allylic alcohol. However, this is not very probable and a different mechanism could be taking place. As for the phosphorus nucleophile, anilinium hypophosphite (entry 6) did participate in the reaction; but the highly insoluble sodium hypophosphite (entry 7) did not react under any of the conditions investigated (Table 5.4). Phosphorous acid (H_3PO_3)

(entry 8) and its esters [$(RO)_2P(O)H$] (entry 9) were also screened but no C-P bond formation was observed which further supports the importance of the equilibrium constant in the P(V) to P(III) tautomeric equilibrium (Table 5.4). For H_3PO_3, the three-coordinate form $P(OH)_3$ has proved to be thermodynamically unstable ($K \approx 1x10^{-10.5}$ in aqueous solution),[194] which has been corroborated by quantum-chemical calculations.[195] No reported values for the exact equilibrium constant of H_3PO_2 exist in the literature. However, Montchamp has performed a series of theoretical calculations with a wide range of hypophosphorous and phosphorous compounds that provide good evidence that the P(III) form in H_3PO_2 is considerably more stable than in the case of H_3PO_3.[196]

Table 5.4 Reactivity of various hypophosphorous and phosphorous compounds in the Pd-catalyzed allylation[1]

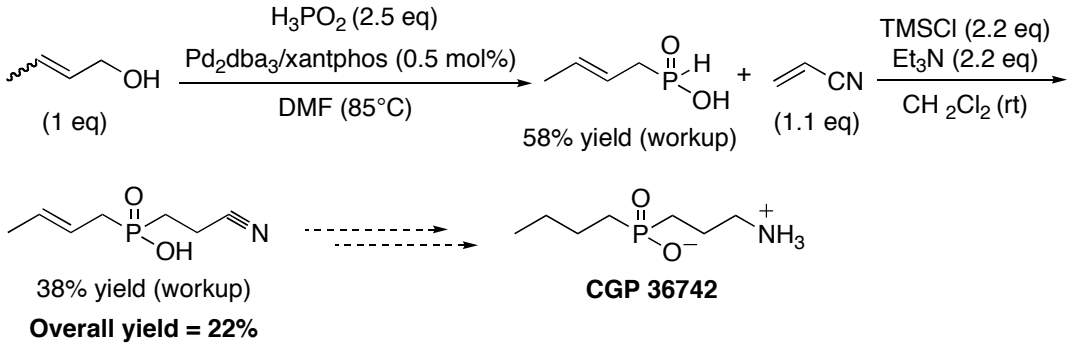


Entry	Phosphorus Compound (eq)	Allylic alcohol	Solvent	Catalyst (mol%)	Additive/ Reagent (eq)	Product or Main Product	^{31}P NMR Result (%)		Isolated Yield, %
							A	B	
1	H_3PO_2 (2)		DMF	0.5	$(BuO)_4Si$ (2)		19	0	-
2	$BuOP(O)H_2$ (2)[2]		DMF	0.5	-		73	0	60
3a	$BuOP(O)H_2$ (2)[2]		DMF	0.5	-		43	0	-
3b			CH_3CN	0.5	-		70	25	-
3c			DMF	2	-		68	18	-
3d			CH_3CN	2	-		87	13	-
4	$BuOP(O)H_2$ (3)[2]		CH_3CN	2	-		0	91	46
5	$BuOP(O)H_2$ (2)[2]		CH_3CN	2	-		100	0	80
6	$PhNH_3OP(O)H_2$ (1.5)		DMF	0.5	-		100	0	100[3]
7a	$NaOP(O)H_2$ (2)				-	No C-P bond formation	0	0	-
7b					AHP (0.05)				
8	H_3PO_3		DMF	0.5	-	No C-P bond formation	0	0	-
9	$(EtO)_2P(O)H$		DMF						

[1] See Experimental Section for details of the procedures. [2] $BuOP(O)H_2$ was prepared from H_3PO_2 and $(BuO)_4Si$. [3] Contains anliline.

Various applications of some allylic-*H*-phosphinic acid derivatives prepared via a tandem allylation-esterification process were also investigated. Initially, our efforts were focused on the preparation of GCP 36742,[179] in a similar approach to the one we described with allylic acetates in the previous chapter (Scheme 4.5). However our yields were considerably lower than what the literature describes and we did not complete the synthesis (Scheme 5.3).[3b,104]

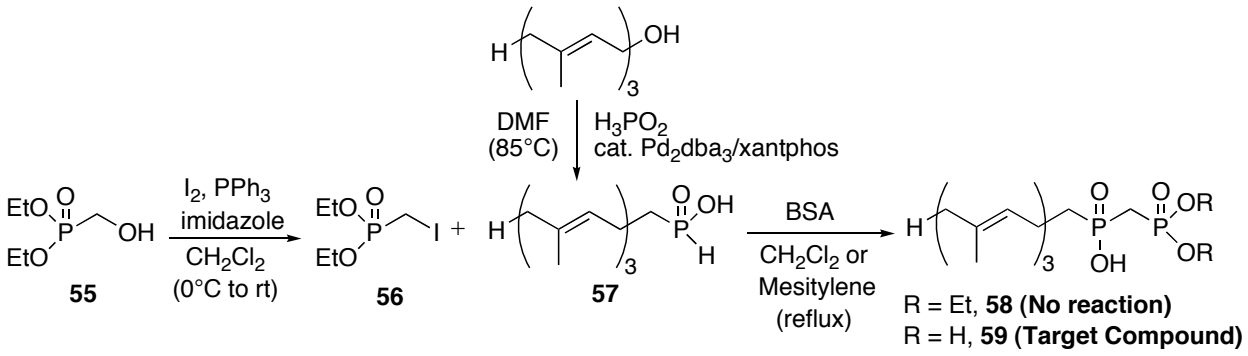
Scheme 5.3 Synthetic application of Pd-catalyzed allylation: CGP 36742, GABA-B antagonist



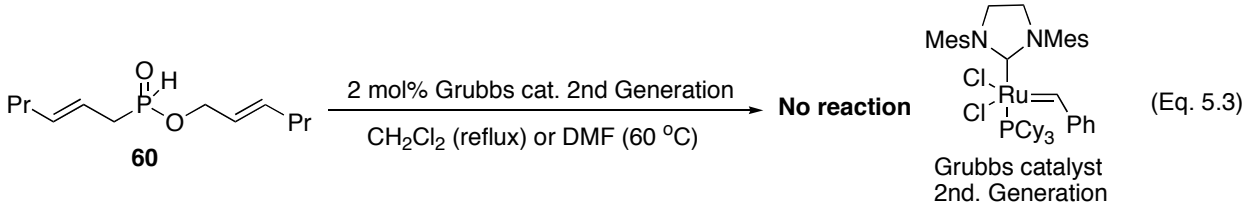
We also explored the use of our Pd-catalyzed allylation reaction in the synthesis of a farnesyl pyrophosphate analog **59** (Scheme 5.4).[197] Unfortunately, the formation of the second carbon-phosphorus bond via an Arbuzov reaction with a reactive electrophile was not accomplished (**57- 58**), neither under the conditions reported by Coward by preforming the P(III) intermediate at slightly elevated temperatures (refluxing CH_2Cl_2) prior to the addition of the alkyl halide,[151] or by using more forcing conditions as described by Frost *et al* (refluxing mesitylene).[38e] Our approach consisted in reacting farnesyl phosphinic acid **57** (Table 5.3, entry 7b)[66] with diethyl iodomethanephosphonate **56**, itself prepared from the corresponding hydroxymethylphosphonate **55**,[198] through reaction with iodine, PPh_3, and imidazole.[199] This result demonstrates that the BSA-mediated S_N2 displacement of unactivated alkyl iodides by *H*-phosphinic acids is not always efficient (Section 1.3.5, Chapter One), and that the development

of new efficient methodologies for this second carbon-phosphorus bond formation is essential for the synthesis of functionalized organophosphorus compounds.

Scheme 5.4 Efforts towards the synthesis of a farnesyl pyrophosphate analog via Pd-catalyzed allylation



Finally, we focused on the preparation of phosphorus heterocycles through ring closing metathesis (RCM) using the second generation Grubbs catalyst (Scheme 5.5).[200] The reactivity of the allylic *H*-phosphinate **60** (Table 5.1, entry 4) was briefly investigated, but we did not observe formation of the cyclic product (Eq. 5.3).

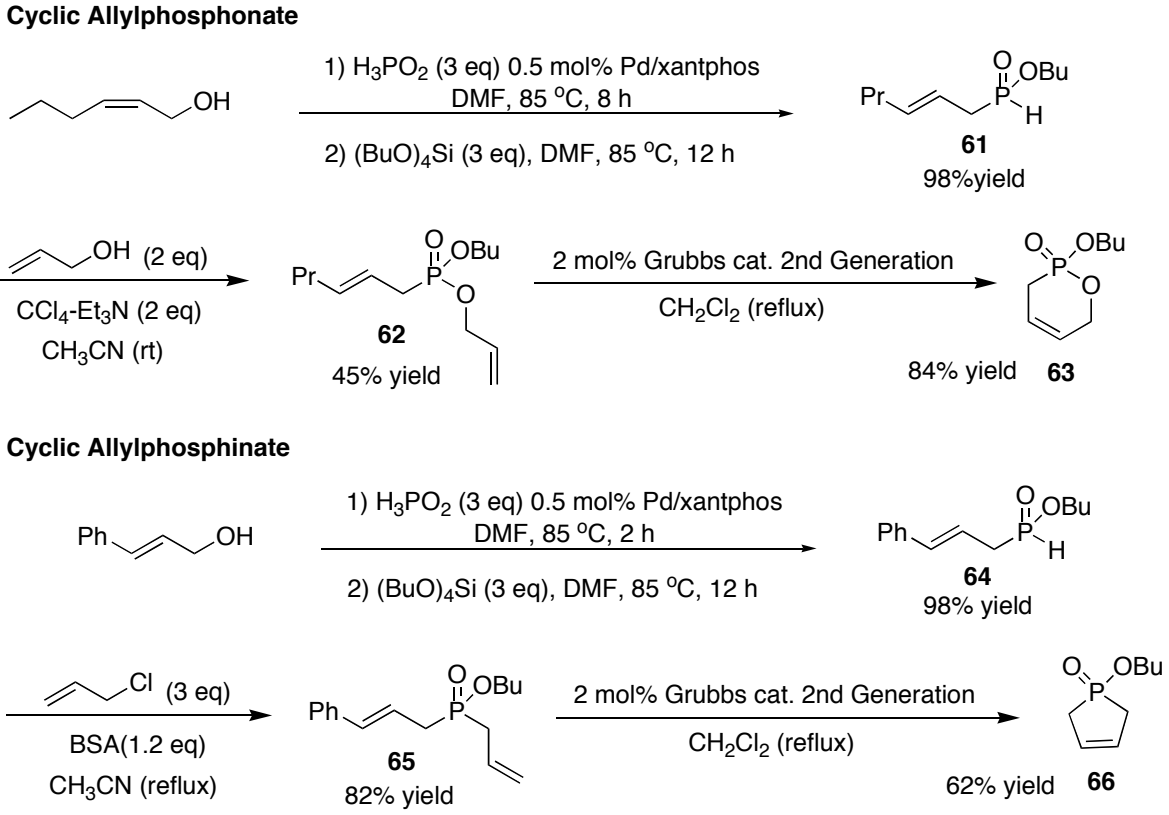


(Eq. 5.3)

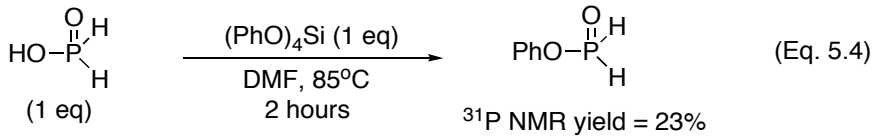
On the other hand, *H*-phosphinates **61** and **64**, prepared by tandem allylation-esterification reactions were converted into the corresponding phosphonate **62** and disubstituted phosphinate **65**, respectively, via Atherton-Todd oxidation[115] and Arbuzov-kind nucleophilic substitution.[95,36a] Compounds **62** and **65** were subjected to RCM to give *P*-heterocyclic products **63** and **66**,[201] in good yields (Scheme 5.5). The cyclic butyl allylphosphonate **63** is a new compound, however its methyl ester counterpart has been previously prepared through reaction of diphenyl phosphoryl chloride with allylmagnesium bromide, followed by selective

displacement of one of the phenoxy groups with lithium allyloxide, which is hard to achieve and the diallyl side product is always present.[193a] The overall yield in that case was 9.8% from the phosphoryl chloride, while in our present approach the yield is 37% starting from H_3PO_2. Mioskowski and coworkers previously prepared the benzyloxy and the hydroxy analogs of the butoxy phospholene oxide **66** following an RCM strategy.[193b-c] Their approach for the construction of both C-P bonds consisted of nucleophilic substitution reactions by silyl phosphonite (BTSP) of allylic halides (Section 1.2.4, Chapter One). While they report 27% overall yield for the benzyloxy adduct from ammonium hypophosphite using 2.5-3 mol% of the First Generation Grubbs Catalyst or 6-8 mol% of Schrock molybdenum catalyst,[193b] and 62% yield for the hydroxy analog using 5 mol% of the Nolan catalyst bearing an imidazol-2-ylidene ligand (IMes),[193c] we achieved 50% overall yield from hypophosphorous acid with 2 mol% of the Second Generation Grubbs Catalyst.

Scheme 5.5 Pd-catalyzed dehydrative allylation en route to *P*-heterocycles

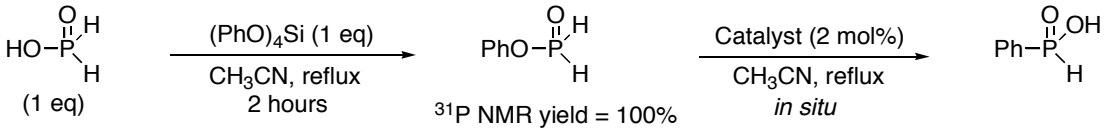


Inspired by the results obtained in the Pd-catalyzed dehydrative allylation of hypophosphorous acid with allylic alcohols, a brief study was performed in which the reactivity of various palladium and nickel catalysts for the rearrangement of phenyl phosphinate into phenyl-*H*-phosphinic acid was investigated. Since DMF had proved to be required for the rearrangement of allylic phosphinates (Table 5.1) in the absence of base, we focused initially on optimizing the preparation of phenyl phosphinate in this solvent, however we did not achieve good yields of the product (Eq. 5.4). Hence, we performed the reactions in acetonitrile (Table 5.5), but we did not observe any C-P bond formation (^{31}P NMR analysis). This is not surprising because phenyl acetates (analogs of phenyl phosphinates) do not undergo oxidative addition. Moreover, we did not observe generation of benzene (GC analysis) as a result of phenol deoxygenation. This is also an unknown transformation, which would be plausible if transfer hydrogenation takes place. Much work remains to be done in this direction, but a fundamental reactivity pattern and a potential industrial reaction weresa uncovered.



(Eq. 5.4)

Table 5.5 Reactivity of various catalysts in the rearrangement of phenyl phosphinate



Entry	Catalyst	NMR yield, %
1	$Pd(OAc)_2$/dppp	No C-P bond formation
2	$NiCl_2(dppp)_2$	
3	Pd_2dba_3/xantphos	
4	$NiCl_2(PPh_3)_2$	
5	$Pd(PPh_3)_4$	
6	$Pd(OAc)_2$/dppf	

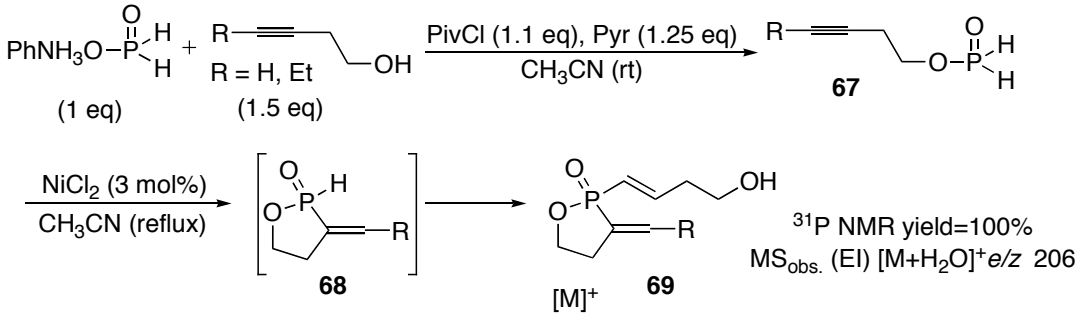
Chapter Six: P-H bond activation in *H*-phosphinic acid derivatives

6.1 Introduction

The quest for synthetic efficiency has gained particular importance over the last few years and promises to unveil novel atom-economical transformations.[154] Metal-catalyzed C-H bond functionalization processes, particularly those which lead to the formation of a C-C bond in a single step through replacement of a hydrogen atom have started to emerge and represent an important challenge, not only in target-oriented organic synthesis, but also in the design of complex molecules that contain various functionalities and C-H bonds, where selectivity issues are even more challenging.[165] Various approaches to C-H bond activation have been uncovered, such as intramolecular carbene and nitrene insertion, particularly with dirodhium catalysts, coordination-directed metallation via formation of metallacycles, and intermolecular functionalization processes where the catalysts selectively target "activated" C-H bonds (adjacent to heteroatoms or to an aromatic ring), or an isolated alkyl group (remote functionalization) relying on C-H bond strength and/or steric factors.[165] Although the main focus in this area has been associated with carbon-carbon bond formation, various reports have also addressed the generation of other linkages, such as carbon-oxygen, carbon-nitrogen, carbon-boron, and carbon-halogen.[202] Metal-catalyzed P-H bond activation stands in close analogy to C-H bond functionalization. It is indeed, an emerging field that has shown some potential in the synthesis of various phosphines (free and protected), phosphonates, phosphinates, and more recently *H*-phosphinates.[29,140] This latter transformation has been previously discussed in this dissertation (Chapter Two and Section 4.2 from Chapter Four).[33-35,63] As demonstrated by our P-H bond activation studies with hypophosphorous compounds and alkenes, alkynes, dienes, and allenes, we generally did not observe the formation of symmetrically disubstituted phosphinates, which is an indication of the higher reactivity of the P-H bond in hypophosphorous compounds

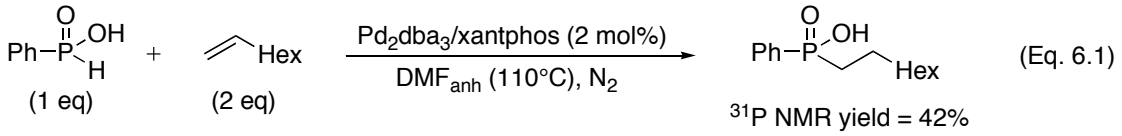
versus the one in *H*-phosphinates.[33-35,63] Notably, an exception to this behavior was detected in a nickel-catalyzed intramolecular reaction (Scheme 6.1), which may proceed through the intermediate **68**, followed by *in situ* P-H bond activation to generate **69**. The presence of a π-unsaturated cyclic precursor **68** appears to be necessary because we had not observed formation of a second C-P bond, neither under intermolecular conditions, nor with *H*-phosphinates bearing saturated alkyl chains. It is also important to point out that, even though we have proposed that our Ni-catalyzed hydrophosphinylation (**67-68**) operates via P-H bond activation (Chapter 2),[35] we cannot rule out a carbonickelation[168a] pathway at this point.

Scheme 6.1 Preparation of a disubstituted cyclic phosphinate via Ni-catalysis



As a result of our interest regarding the application of *H*-phosphinates in the synthesis of biologically active molecules, we recognized the lack of efficient and general methodologies that address the functionalization of *H*-phosphinates (Chapter I, Section 1.3). In fact, Scheme 5.4 and Eq. 5.3 from the previous chapter illustrate two representative examples of reactivity limitations of *H*-phosphinates towards Arbuzov-like and ring-closing metathesis (RCM) reactions. Another example of this fact is the base-promoted alkylation, which until recently lacked standard (Section 1.3.6) conditions.[104] P-H Bond activation processes, especially those which can fulfill the "Green Chemistry" requirements, such as atom- and step-economy, are therefore needed. As stated previously in this dissertation (Chapter One, Section 1.3.2), Tanaka and Han have disclosed the only two reports that demonstrate the ability of the P-H bond in phenyl-*H*-

phosphinates esters to undergo activation with Pd and Ni catalysts (Scheme 1.12).[73,74] However, these substrates bear a P-H bond that is especially activated towards functionalization, probably as a result of the presence of adjacent π-bonds in the aromatic ring, which can facilitate metallation. Indeed, we also observed the formation of significant amounts of a disubstituted phosphinic acid when reacting phenyl phosphinic acid with an alkene, in the presence of Pd/xantphos under anhydrous and anaerobic conditions, which probably rules out a possible free-radical pathway (Eq. 6.1).



(Eq. 6.1)

Another approach to functionalization of P-H bonds in *H*-phosphinates relies on the use of high-energy species and radical initiators (Chapter I, Section 1.3.3).[19,75] However, the syntheses of disubstituted phosphinates, which require mild radical and neutral conditions using common initiators are very limited. In fact, only the "activated" aryl-*H*-phosphinate esters react successfully with catalytic amounts of AIBN as initiator at the refluxing temperature of benzene (Eq. 1.31)[76] as well as under thermal (in the presence of air) (Eq. 1.32)[77] and microwave heating (Eq. 1.33)[78,79] using high temperatures (120-200°C).

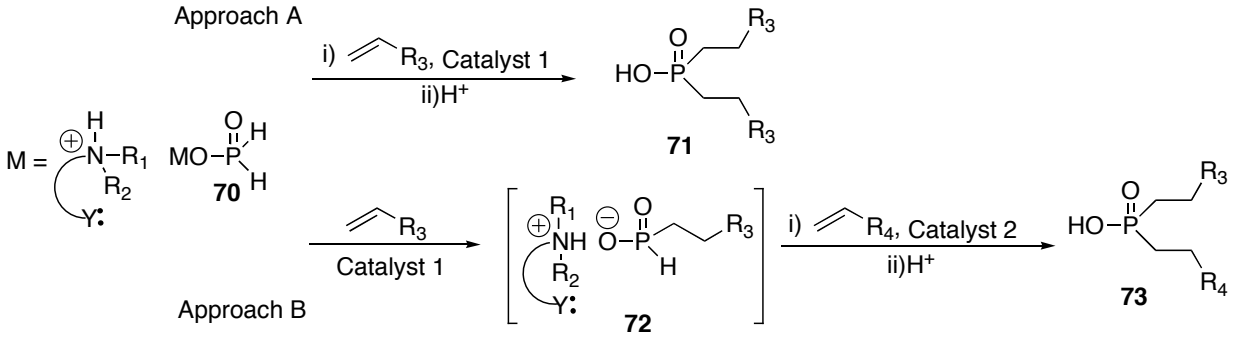
Considering that the P-H bond in *H*-phosphinates is weaker and more polarizable than a C-H bond, and that the presence of a phosphinylidene moiety (P(O)H) provides it with a particular flexibility in terms of reactivity (P-III *vs* P-V tautomers), we rationalized that its functionalization via metal-catalyzed P-H bond activation should be feasible with appropiate catalyst selection. We pursued three different approaches: chelation-assisted metallation with ionic salts of hypophosphorous acid bearing non-covalently bonded π- or n-electron donating species, a Pd-catalyzed dehydrative allylation of *H*-phosphinic acids with allylic alcohols, an

extension of our previously developed allylation of hypophosphorous acid (Chapter Five), and a highly convenient synthesis of phosphonic acids via Pd-catalyzed tandem P-C bond formation – oxidation processes. This work has not been published and most of the results are preliminary. We will discuss the outcome of our research in the following sections.

6.2 Coordination-directed metallation *en route* to disubstituted phosphinic acids

Pursuant to the design of a P-H bond functionalization process in *H*-phosphinic acids, a highly challenging, but conceivable approach to achieve this transformation would be the Pd-catalyzed simultaneous hydrophosphinylation of alkenes (Approach A, Scheme 6.2), or the sequential process (Approach B), starting with nitrogen-containing salts of hypophosphorous acid **70** (Scheme 6.2). The proposed strategy for directing the metal complex into the vicinity of the P-H bond of an *H*-phosphinate **72** (or hypophosphite, **70**) involves the use of n- or π-chelating groups in the cationic species, in order to minimize manipulation and simplify the process because *H*-phosphinate esters that contain the donor directing group covalently attached to the ester alkyl chain have proved to be very unstable.[196]

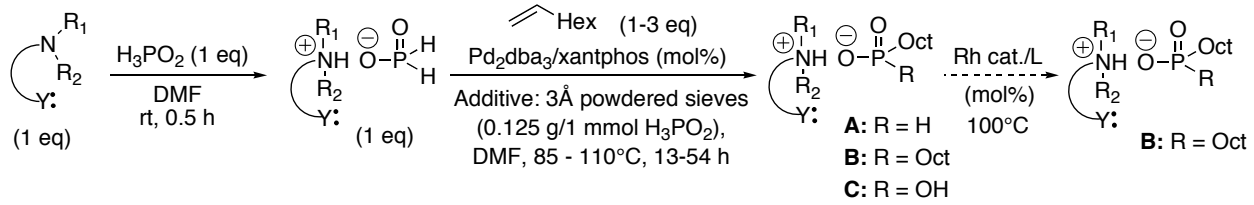
Scheme 6.2 P-H bond activation strategies towards the synthesis of disubstituted phosphinic acids

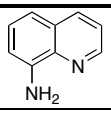
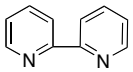
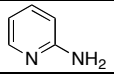
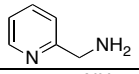
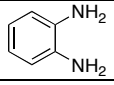
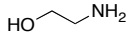
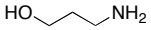
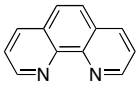


In the absence of chelating amine salts, Pd has shown to effectively insert into the P-H bond of hypophosphorous acid, producing a phosphinyl palladium intermediate, which in turn

undergoes addition into a double bond (Chapter I, Scheme 1.7); however the reaction always stops at the *H*-phosphinic acid, and no significant amounts of the disubstituted phosphinic acid have been observed under any of the conditions investigated (less than 5%).[33,203] Even though our efforts were mainly focused on the direct preparation of symmetrically disubstituted phosphinates **71** (Approach A, Scheme 6.2), it would be more interesting to attain a stepwise functionalization (Approach B, Scheme 6.2), which would lead to non-symmetrical disubstituted phosphinic acids **73**. As we can observe in Table 6.1, we did not achieve the formation of the expected disubstituted phosphinate products. Initially, we conducted the reactions in anhydrous DMF (dried over 4Å molecular sieves) at 85°C or 110°C, under nitrogen. With certain amines (entries 1a-3a), the first C-P bond formation was effective, but we observed a marked tendency towards an *in situ* transformation of the *H*-phosphinates into *H*-phosphonates, while no second C-P bond formation was detected. For example, when using 2,2'-bipyridine (entry 3a), we isolated octyl phosphonic acid in 60% yield after an acidic workup. This oxidation had not been observed previously using acetonitrile as solvent, in the absence of amines. In fact, this particular finding created precedent for the subsequent development of tandem processes for the synthesis of phosphonic acids (Section 6.4). Other hypophosphite salts reacted very inefficiently to afford either low yields of *H*-phosphinates or *H*-phosphonates, or mixtures of both products (entries 4-6 and 7a-9a). In the case of 8-aminoquinoline (entry 1), a two-step C-P bond formation process was intended using a mixture of Wilkinson's catalyst with 1,4-bis(diphenylphosphino)butane ($[(C_6H_5)_3P]_3RhCl$/dppb), however, we obtained instead the oxidized product. Considering our previous results, we then performed the reactions using anhydrous DMF (vacuum-distilled over CaH_2) with or without powdered molecular sieves as a water-scavenger (entries 2b, 3b-c, 7b-c to 9b-c). Unfortunately, we did not form our target compounds, and low yields of monosubstituted phosphinate salts or of the corresponding oxidized products were obtained.

Table 6.1 Efforts towards the synthesis of disubstituted phosphinic acids via coordination-directed metallation using ionic salts of hypophosphorous acid



Entry	Diamine *or* Amine-alcohol	Alkene, eq	Catalyst, mol%	Temp, °C	Additive *or* Rh cat/L (mol%)	DMF (4Å Sieves *or* Distilled from CaH_2)	Product (NMR yield, %)			Product (Isolated yield, %)[a]
							A	B	C	
1		2	4	85	$(Ph_3P)_3RhCl$ (1.25) / dppb[b] (5)	Sieves	(68)[b]	0	70	-
2a		2	4	85	-	Sieves	0	0	58	0[c]
2b		3	2	110	Sieves	Distilled	0	0	23	-
3a		1			-	Sieves	9	0	69	C (60)
3b		3	2	110	Sieves	Distilled	39	0	40	0[c]
3c		3			-	Distilled	8	0	0	-
4		2	4	85	-	Sieves	28	0	0	-
5		2	4	85	-	Sieves	0	0	0	-
6		2	4	85	-	Sieves	25	0	0	-
7a		1			-	Sieves	0	0	12	
7b		3	2	110	Sieves	Distilled	0	0	0	-
7c		3			-	Distilled	0	0	49	
8a		1	2	110	-	Sieves	0	0	9	-
8b		3			Sieves	Distilled	18	0	25	0[c]
9a		1			-	Sieves	9	0	14	-
9b		3	2	110	Sieves	Distilled	22	0	43[d]	-
9c		3			-	Distilled	0	0	0	-

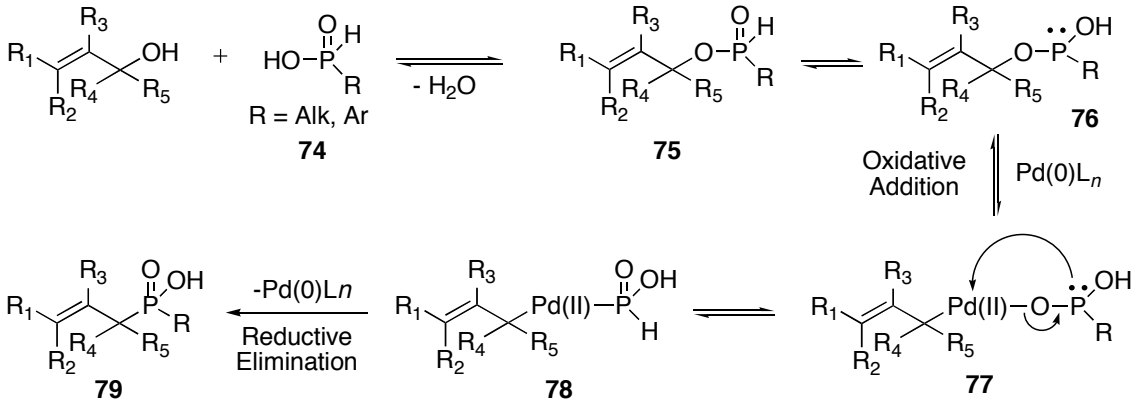
[a] Isolated as the acid after acidic workup. [b] *H*-phosphinic acid was formed before adding the Rh catalyst. [c] Isolation by acidic workup did not yield any phosphorus-containing product in the organic phase. [d] A mixture of linear and branched isomers was obtained.

6.3 Preparation of disubstituted phosphinic acids via Pd-catalyzed allylation of *H*-phosphinic acids

The Pd-catalyzed dehydrative allylation of H_3PO_2 (Chapter Five) represents a mechanistically novel platform for the development of innovative catalytic C-P bond forming reactions. Guided by the prospect of developing an efficient synthesis of disubstituted phosphinic

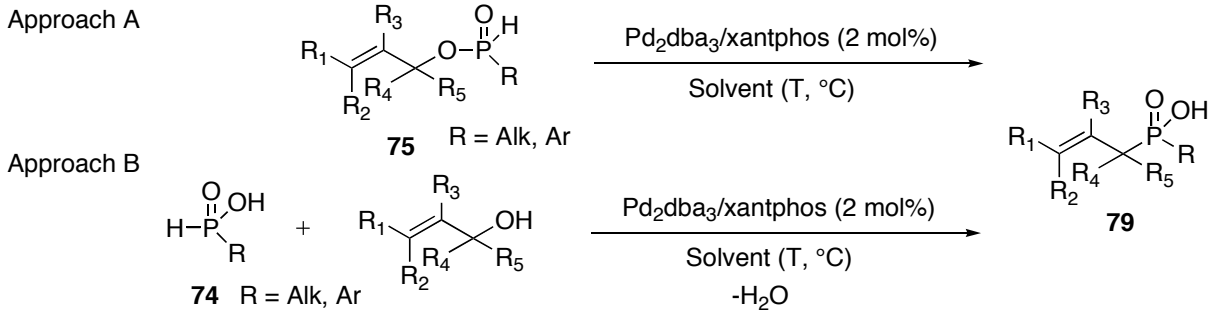
acids, the Pd-catalyzed dehydrative allylation of *H*-phosphinic acids was investigated. The hypothesized mechanism for this transformation is based on our previous studies with hypophosphorous compounds (Scheme 5.2), and it is shown on Scheme 6.3

Scheme 6.3 Postulated mechanism for the Pd-catalyzed dehydrative allylation of *H*-phosphinic acids



Our strategy for the development of this reaction involved a parallel approach (Scheme 6.4): (a) rearrangement of *H*-phosphinate allylic esters (**75 – 79**) (Approach A), similarly to the work previously developed with allylic phosphinates (See Table 5.1, Chapter Five), and (b) a direct catalytic allylic substitution of *H*-phosphinic acids with allylic alcohols (**74 – 79**) (Approach B). Even though, according to the proposed mechanism for this transformation (Scheme 6.3), these reactions might not operate via a true P-H bond activation pathway, they could fundamentally provide, not only an efficient and atom-economical approach for the synthesis of various functionalized disubstituted phosphinates, but also a better understanding of the role of the tautomeric equilibrium (P-III to P-V) in hypophosphorous and *H*-phosphinic acids derivatives in the mechanism of the reaction. Ultimately, this process could be applied to the synthesis of other phosphorus-containing compounds, such as phosphonic acids ($RP(O)(OH)_2$).

Scheme 6.4 Pd-catalyzed allylation strategies en route to disubstituted phosphinic acids



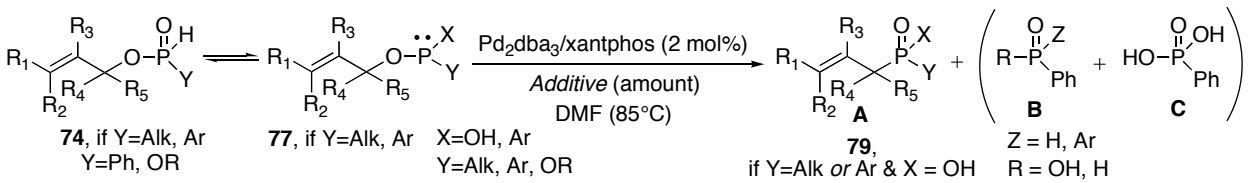
As previously described (Chapter I, Section 1.3.5), Arbuzov-like rearrangements of phosphonites $R^1P(OR^2)(OR^3)$,[92,93] stepwise silylation-alkylation of *H*-phosphinates,[95,36a] as well as the BSA/Ni(cod)$_2$ catalytic allylation reported by Lu (Eq. 1.30) are known methodologies to access disubstituted phosphinates. Nonetheless, all of them have limitations in terms of reactivity and selectivity, and they require either alkyl halides and very harsh conditions, or the use of stoichiometric amounts (or excesses) of silylating reagents and activated allylic electrophiles. The use of allylic alcohols, particularly in the absence of additives is especially attractive since the only byproduct is water.

With regard to the former strategy (Scheme 6.4, Approach A), *H*-phosphinate allylic esters **75** were reacted in the presence of a Pd catalyst (Pd_2dba_3/xantphos) in order to test the ability of these compounds to oxidatively add Pd, generating intermediates **77**, that might in turn undergo rearrangement, followed by reductive elimination, furnishing the expected products **79**. Hence, *H*-phosphinate allylic esters **75** were prepared in moderate to good yields (60-73%) using a water soluble carbodiimide activating agent (1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, hydrochloride, EDC),[164c,106e] or via Dean-Stark esterification (~50%).[204,196] As demonstrated in Table 6.2, the Pd-catalyzed rearrangement of allylic esters was very inefficient in the absence of certain acidic additives (entries 1 & 2) and, not surprisingly, ester cleavage and/or oxidation were competitive pathways, which led to *H*-phosphinic acids, phosphonate monoallyl esters and

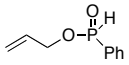
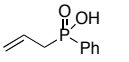
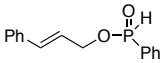
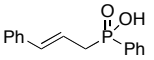
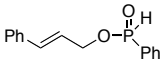
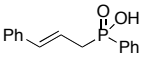
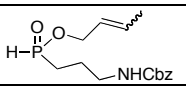
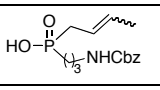
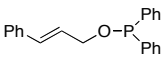
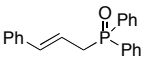
phosphonic acids. Anhydrous and anaerobic conditions were intended in order to minimize these side reactions. The role of different additives was investigated (entries 2 & 3). However, as of today, the exact role of these species still remains unclear. Acidic resins appeared to considerably increase the yields of products (entries 3c & 3g), which could be related to the fact that acidic conditions catalyze the tautomeric equilibrium of the *H*-phosphinate esters towards the P(III) form (**75 – 76**) and/or to a tandem hydrolysis-allylic substitution process. Notably, when using BSA, which was expected to form the P(III) phosphonite, we obtained the rearranged product in quantitative yield (entry 3j). Considering that a silylating agent was not necessary for the rearrangement of hypophosphite allylic esters (Table 5.1), a feasible explanation for this fact is that the three-coordinative species from hypophosphorous compounds is more readily formed than the one from *H*-phosphinic acid derivatives. These results further confirm that the P(III) tautomer is essential for the oxidative addition step, and ultimately for a successful allylic substitution. Aiming to prepare a GABA analog (GCP 36742),[179] we tried the reaction on the allylic ester from entry 4, and we obtained the target product in low yield, along with the isomer resulting from [2,3] sigmatropic rearrangement.[205] Additionally, we looked upon the reactivity of other organophosphorus compounds in this transformation. (*E*)-Cinnamic phosphinite (entry 5), did not efficiently undergo the Pd-catalyzed, or the thermal rearrangement,[205] while a cyclic allylic *H*-phosphonate (itself synthesized via dicyclohexylcarbodiimide (DCC) mediated esterification),[147] also failed to generate the desired C-P bond (entry 6). Finally, as a result of our previous failure in the direct allylation of H_3PO_3 (Table 5.4, entry 8), some efforts were directed towards synthesizing *H*-phosphonate monoallyl ester via Dean-Stark esterification,[206] or through transesterification of diphenyl-*H*-phosphonate with an allylic alcohol, followed by amminolysis,[207] however, we did not succeed in preparing the expected compounds. Even if the rearrangement of *H*-phosphinate allylic esters **75** was not successful in the absence of BSA, we

could not discard the possibility of a successful direct dehydrative allylation of *H*-phosphinic acids, since all the components in the reaction mixture can definitely play a key role in the outcome of the reaction, especially because a tiny amount of the presumably reactive species **76**, might be able to drive the equlibrium toward the C-P bond formation product **79**.

Table 6.2 Reactivity screening of allylic derivatives of *H*-phosphinates, *H*-phosphonates and phosphinites in the Pd-catalyzed rearrangement[a]



74, if Y=Alk, Ar Y=Ph, OR — **77**, if Y=Alk, Ar X=OH, Ar Y=Alk, Ar, OR — **79**, if Y=Alk *or* Ar & X = OH — **A** — **B** Z = H, Ar — **C** R = OH, H

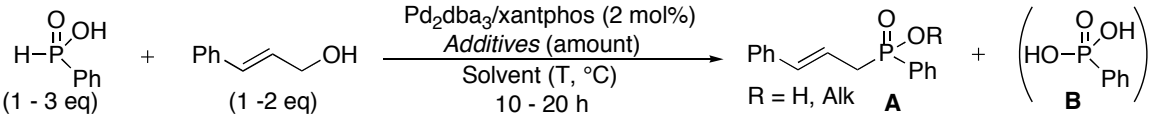
Entry	Substrate (SM)	Additive (amount)	Cat. Y/N	Expected Product (A)	DMF 4Å Sieves Distilled-CaH_2	Products NMR Yield, %[b] SM	A	B (Z, R=)	C	Isol. Yield %
1a		-	Y		Sieves	40	0	(H, OH) 0	60	-
1b			N			57	0[c]	13	16	-
2a		-	Y		Sieves	24	10	(H, OH) 13	23	-
2b		AcOH (0.2 eq)				0	8	0	80	-
3a		PhP(O)(OH)(H) (1 eq)	Y		Distilled	0	0	(H, OH) 130[d]	70[d]	-
3b		H_3PO_2 (1 eq)				82	0	76[d]	16[d]	-
3c		Amberlite (H^+) (~50 mg/1 mmol)				0	52	4	44	-
3d		Camphorsulfonic Acid (0.2 eq)				3	3	41	53	-
3e		TFA (0.2 eq)				12	6	37	25	-
3f		$TsOH·H_2O$ (1 eq)				0	23	40	35	-
3g		Dowex (H^+) (~50 mg/1 mmol)				0	69	0	31	-
3h		$BF_3·Et_2O$ (0.15 eq)				0	0	14	0	-
3i		$Yb(OTf)_3$ (0.1 eq)				0	5	0	0	-
3j		BSA (1.2 eq)				0	100	0	0	100[e]
4		BSA (1.2eq)	Y		Distilled	0	28[f]	0	14	-
5		DMAP (1 eq) + 3Å sieves (250 mg/1mmol)	Y		Distilled	21	8[g]	(Ph, H) 66	0	-
6		BSA (1 eq)	Y		Distilled	37[h]	0	0	0	-

[a] See Experimental Section for details of the procedures. [b] Phosphonate monoallyl esters (oxidation of the SM) were often present in the crude mixtures. [c] 14% of the product from thermal [2,3] sigmatropic rearrangement. [d] ^{31}P NMR based on 2 eq. of phosphorus. [e] Isolated after acidic workup. [f] 19% of the product from thermal rearrangement and 39% of the oxidized SM were also formed. [g] 5% of the products from thermal rearrangement were formed. [h] Silylated P(III) form of the *H*-phosphonate.

Indeed, when we reacted equimolar amounts of the commercially available phenyl-*H*-phosphinic acid and cinnamyl alcohol with 2 mol% of Pd_2dba_3/2xantphos as catalyst in moderately dry DMF (4Å molecular sieves) under N_2, cinnamyl phenyl phosphinic acid was obtained in 57% yield according to ^{31}P NMR, along with the oxidized starting material, phenyl phosphonic acid (43%) (entry 2a, Table 6.3). A series of control experiments were then conducted in order to better understand the process (Table 6.3). Expecting to rule out a thermal rearrangement, an experiment was carried out in the absence of catalyst to produce exclusively unreacted starting *H*-phosphinic acid (entry 1a). When pure phenyl-*H*-phosphinic acid is heated in moderately anhydrous DMF, it slowly oxidizes into the corresponding phosphonic acid (entry 1b). On the other hand, we did not look at the effect of other palladium catalysts or at the influence of the catalyst loading. Since, a detailed screening remains to be performed. The reaction proved to be highly dependent upon the dryness of the solvent (entries 2a-c) and to a lesser extent on the temperature (entries 2a/2b and 3b/3c). It proceeds more slowly (10-20 h) than the corresponding allylation of H_3PO_2 (Chapter V). As for the stoichiometry, an excess of *H*-phosphinic acid increases significantly the yield of product (entries 2d-e), however the use of these conditions is only acceptable in the case of inexpensive and easily available *H*-phosphinic acids. In addition, it complicates the isolation of pure product, making necessary, either a cumbersome ion-exchange purification, or an extra esterification step followed by a silica gel chromatography. Considering that water tends to accelerate the rate of the competitive oxidation pathway, powdered molecular sieves were added to the reactions in order to scavenge the water released (one equivalent) during the Fischer esterification step (entry 3). As a result, the yields were notably increased (entries 3a-c). When an equimolar amount of BSA was added, the yield dropped markedly (entry 3e); conversely, a mixture of BSA and powdered sieves was very effective (entry 3d). It should be noted that 2 equivalents of BSA are required to form the P(III)

form of an *H*-phosphinic acid and that the role of the silylating agent in this case is not yet well understood, but perhaps it is only operating as a drying agent.

Table 6.3 Optimization of the Pd-catalyzed allylation of phenyl phosphinic acid with cinnamyl alcohol[a]



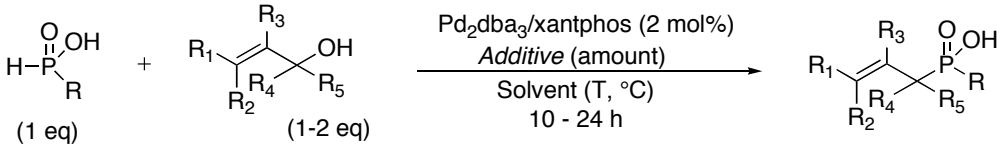
Entry	H–P(O)(OH)–Ph (eq)	Alcohol (eq)	Solvent (Grade)[b]	Additive1 (amount)	Additive2 (eq)	Cat. Y/N	Temp. (°C)	NMR Yield, %[c] A (R =)	NMR Yield, %[c] B	Isolated Yield, % (A, R=H)[d]
1a	1	1	DMF	-	-	N	85	0 (H)	0[e]	-
1b	1	-	(4Å Sieves)			Y			47[e]	
2a	1	1	DMF (4Å Sieves)	-	-	Y	85	57 (H)	43	-
2b	1	1	DMF (Reagent Grade)	-	-	Y	110	72 (H)	28	-
2c	1	1	DMF (Anhydrous)			Y	85	81[f] (H)	6[e]	56
2d	1.5	1						100 (H)	21	>100[g]
2e	2	1	DMF (4Å Sieves)	-	-	Y	85	100 (H)	40	-
2f	1	2						77 (H)	23	-
3a				3Å sieves (0.125 g/ mmol acid)	-	Y	85	92 (H)	8	58
3b	1	1	DMF (Anhydrous)	(0.25 g/ mmol acid)	-	Y	85	86 (H)	14	-
3c				(0.150 g/ mmol acid)	-	Y	110	82 (H)	19	-
3d				(0.150 g/ mmol acid)	BSA (1.2)	Y	110	95 (H)	5	69
3e				-	BSA (1.0)	Y	110	22 (H)	6[e]	-
4a			Toluene (Anhydrous)	-	-	Y	85	[h] (H)	[h]	[h]
4b			THF (Anhydrous)	-	-	Y	reflux	[h] (H)	[h]	[h]
4c	1	1	CH_3CN (Anhydrous)	-	-	Y	reflux	0 (H)	27[e]	-
4d			*tert*-Amyl-OH (Anhydrous)	-	-	Y	reflux	100 (H)	2	98
4e			NMP (4Å Sieves)	3Å sieves (0.125 g/ mmol acid)	-	Y	85[i]	96 (H)	4	95
5a				3Å sieves (0.125 g/ mmol acid)	$(PhO)_4Si$ (1)	Y	85	70 (H) 21 (Ph)	6	-
5b	1	1	DMF (Anhydrous)	-	$(EtO)_4Si$ (0.7)	Y	85	67 (H) 13(Et)	20	-
5c				-	$(iPrO)_4Si$ (1)	Y	110	73 (H) 18 (*i*Pr)	9	-

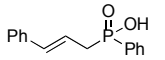
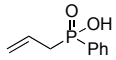
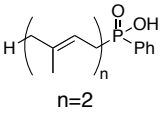
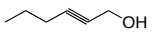
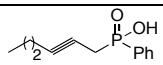
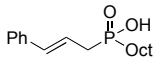
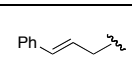
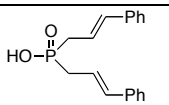
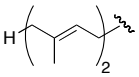
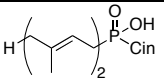
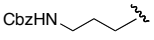
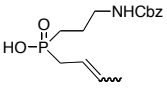
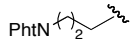
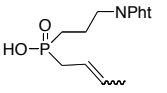
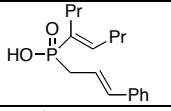
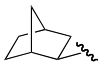
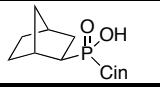
[a] See Experimental Section for details of the procedures. [b] Anhydrous solvents were distilled from Na or CaH_2, as indicated in the Experimental Section. [c] Does not include unreactive phenyl phosphinic acid and/or other byproducts. [d] Isolation consisted of an acidic workup. Unless otherwise noted, the purity of the products was ≥95% according to ^{31}P NMR spectra in $CDCl_3$, however DMSO should be used for a more accurate value, because phenyl phosphonic acid is not very soluble in $CDCl_3$. [e] The rest was unreactive phenyl phosphinic acid. [f] Similar yield was obtained when conducting the reaction with deoxygenated solvent. [g] Not pure, contains 10% of starting material and 13% of phenyl phosphonic acid. [h] NMR yield could not be determined because the reaction was not homogeneous and after acidification, an inseparable mixture of the product, unreactive alcohol and phenyl phosphonic acid was obtained. [i] 15 h at 85°C + 2 h at 110°C.

We also examined the allylation using various solvents, but the poor solubility of the acid in toluene and THF translates to an unreliable NMR yield determination (entries 4a-b), and NMR analysis of the isolated mixture further confirmed the inefficiency of these reactions. Worth noting is that *tert*-amyl alcohol proved to be the best solvent overall (entry 4d). Finally, intending to directly prepare a disubstituted phosphinate ester, addition of alkoxysilanes was explored, but the *in situ* esterification with these reagents was not effective (entry 5).

Next, we decided to evaluate the Pd-catalyzed allylic substitution with a few combinations of allylic alcohols and *H*-phosphinic acids.[33,66] A summary of the results is shown on Table 6.4. In the process of optimizing the reaction (Table 6.3), we observed a considerable increase in yields under anhydrous conditions, reason why the allylic alcohols and solvents were generally dried before use (Experimental Section). The same trend was evidenced in this study (entries 6a/6b and 7a/7b), however, we did not achieve quantitative conversions of the *H*-phosphinic acids into the corresponding disubstituted acids (except for the compound from entry 1), which did not allow the isolation of pure products by an extractive workup. Few attempts to purify the products were pursued. Initially, we failed in the purification of allyl phenyl phosphinic acid (entry 2b) by radial chromatography using a glue-bonded silica gel plate, (stable for very polar solvents). Gratifyingly, we were able to isolate its farnesyl counterpart via standard chromatography on silica gel (entry 3b), due to its lower polarity. A few other experiments were also attempted by changing the solvent, but it was observed that DMF and *tert*-amyl alcohol were superior. On the other hand, various reactions did not proceed as expected (entries 5 and 9-11) and further optimization is required to make of this transformation a useful methodology. In summary, the above presented catalytic dehydrative allylation reaction employs the least expensive and more widely available allylic precursors, and therefore, it could potentially become a highly convenient approach to disubstituted phosphinic acids.

Table 6.4 Scope of the Pd-catalyzed dehydrative allylation of *H*-phosphinic acids with allylic alcohols[a]

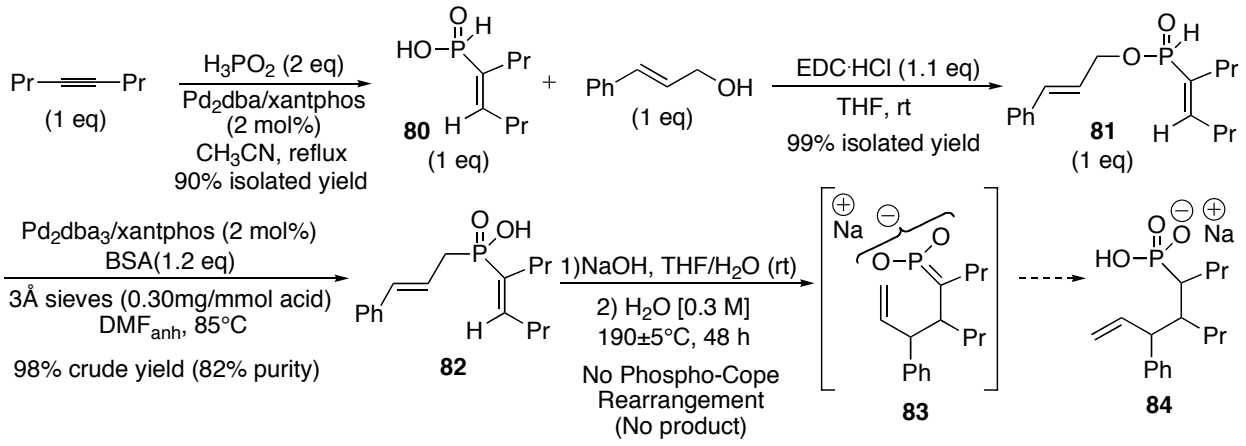


Entry	(R=)	Alcohol (eq), n=	Solvent (Grade)	Additive (amount)	Temp (°C)	Product	NMR Yield %	Isol. Yield, %[b]
1a	Ph	(1)	DMF (anh)	3Å sieves (0.150 g/mmol acid), BSA (1.2 eq)	110		95	69
1b			*tert*-amylOH (anh)	-	102		100	98
1c			NMP (4Å Sieves)	-	85		96	95
2a	Ph	(1.5 – 2)	DMF (anh)	3Å sieves (0.12 g/mmol acid)	110		45	-
2b			DMF (anh)	BSA (1 eq)	110		56	82[c]
2c			*tert*-amylOH (anh)	3Å sieves (0.12 g/mmol acid)	90		61[d]	-
3a	Ph	(1), n=2	DMF or dioxane or *n*-BuOH (anh)	-	101-110	 n=2	2-21[e]	-
3b			*tert*-amylOH (anh)		102		70[e]	62[e,f]
3c			*tert*-butanol (anh)		83		62[e]	-
4	Ph	(1), n=3	*tert*-amylOH (anh)	-	102	n=3	46	-
5	Ph		DMF (anh)	3Å sieves (0.12 g/mmol acid)	90		18	-
6a	Oct	(1)	DMF (4Å Sieves)	-	85		34	-
6b			DMF (anh)	3Å sieves (0.12 g/mmol acid)	100		78	
7a		(1)	DMF (4Å Sieves)	-	85		9	-
7b			DMF (anh)	3Å sieves (0.04 g/mmol acid)	85		60	
8		CinOH (1)	DMF (4Å Sieves)	-	85		24	-
9a		(1)	DMF (anh)	3Å sieves (0.12 g/mmol acid)	110		16	-
9b			*tert*-amylOH (anh)	-	102		29[d]	
10a		(1)	DMF (anh)	-	110		12	-
10b			*tert*-amylOH (anh)		102		2	
11		(1)	*tert*-amylOH (anh)	- BHT (0.1 eq)	102		39 25	-
12		CinOH (1)	DMF (4Å Sieves)	-	85		5	-

[a] See Experimental Section for details of the procedures. [b] Unless otherwise noted, isolation consists of an acidic workup. [c] 88% purity (12% phosphinic acid). Purification by radial chromatography on a glue-bonded silica gel plate (EtOAc/MeOH) was not successful. [d] Reaction time=64 h. [e] Mixture of isomers. [f] Purified by column chromatography on silica gel (Hex/EtOAc-EtOAc/MeOH).

Finally, a brief study on the known Phospho-Cope rearrangement of allyl-vinyl phosphinic acid salts was performed (Scheme 6.5) in order to support the presumed intermediacy of a monomeric metaphosphonate (**82**) and to rule out the possible diradical pathway.[208] An alkenyl-*H*-phosphinic acid (**80**) was prepared by means of our Pd-catalyzed hydrophosphinylation reaction[33] and subsequently esterified with cinnamyl alcohol using EDC as coupling reagent to provide **81** in excellent yield. Treatment of *H*-phosphinate ester **81** with catalytic Pd/xantphos in DMF led to rearrangement and formation of a disubstituted phosphinic acid **82**, which was used in the next reaction without further purification. Acid-base reaction of **82** with NaOH, followed by heating in water at high temperatures (190±5°C), did not furnish the expected product **84**. Instead, the phosphinate salt (starting material) was recovered, along with the oxidized alkenyl phosphonic acid sodium salt.

Scheme 6.5 Efforts towards the development of a Phospho-Cope rearrangement



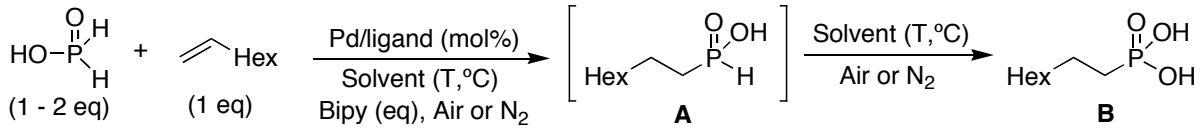
6.4 Preparation of phosphonic acids via tandem C-P bond formation – oxidation reactions

Based on our preliminary observations regarding the *in situ* oxidation of *H*-phosphinic acids into phosphonic acids during our studies on P-H bond functionalization (Sections 6.2 and 6.3), we became interested in the development of a preparatively useful methodology for the direct preparation of phosphonic acids, which not only exhibit interesting biological activities as

phosphate analogs, but are also important synthetic intermediates.[1,209] Despite the broad applications of phosphonic acids $RP(O)(OH)_2$, no efficient, step- and atom-economical methods are available for their preparation. Arbuzov[82,92,93] and Michaelis-Becker reactions,[210] as well as free radical-[19] and microwave-[77,78] mediated addition to unsaturated linkages, and the more recently developed metal-catalyzed cross-coupling,[67] and hydrophosphorylation[29] reaction of dialkyl phosphites constitute some of the present C-P bond forming methodologies for the preparation of phosphonate esters. However, all of them require an additional ester deprotection step in order to access phosphonic acids, which typically consists of treatment with trimethylsilyl bromide (TMSBr),[211] or acid hydrolysis at high temperatures.[82] This latter approach is very limited as it implies compatibility of the functionalized compounds towards strongly acidic conditions. On the other hand, as previously described in the First Chapter of this dissertation (Section 1.3.7, Eq. 1.48), the oxidation of *H*-phosphinic acids represents another viable alternative to access phosphonic acids. However the harsh and strong oxidative conditions that have been so far reported to achieve this transformation are major disadvantages.[40b,103e,105-111] In addition to the lack of mild oxidative conditions of *H*-phosphinic acids, few effective methods were available, until recently, for the synthesis of *H*-phosphinic acids (See Chapter 1, Section 1.2).[17,52] However, remarkable progress has been made mainly by the Montchamp group regarding the preparation of these compounds via radical additions and metal-catalyzed reactions.[25,33,34,41,61,66] Of particular relevance to the subject area are the Pd-catalyzed addition of hypophosphorous acid across unsaturated carbon linkages,[33-34] and the Pd-catalyzed dehydrative allylic substitution of hypophosphorous acid with allylic alcohols,[66] which are both unique and highly-atom efficient and versatile transformations. Pursuant to the design of a direct synthesis of phosphonic acids through the intermediacy of *H*-phosphinic acids, we explored and optimized reaction conditions for a target tandem C-P bond formation – oxidation process. Initially, we

explored the reaction of 1-octene with H_3PO_2 under the influence of catalytic amounts of 2,2'-bipyridine (0.1 eq), Pd_2dba_3 and xantphos (2 mol%) in DMF (110°C) under an air atmosphere, where we observed a smooth conversion of the *in situ* formed octyl phosphinic acid into its corresponding phosphonic acid (entry 1a, Table 6.5). However, we discovered later that the amine was not necessary (entry 1b, Table 6.5). In order to justify the addition of the palladium, and to investigate the influence of the solvent, temperature, air and water in the outcome of the reaction, a broad range of control experiments was performed (Table 6.5).

Table 6.5 Optimization of the tandem hydrophosphinylation – oxidation reaction of 1-octene with H_3PO_2[a]



Entry	H_3PO_2 aq/conc, (eq)	Bipy (eq)	Pd/ligand (mol%)	P-C bond formation Air/N_2, Time(h), Solvent, Temp (°C)	Oxidation Air/N_2, Time, Solvent, Temp	^{31}P NMR yield,[b] % A	B (Target)	Isolated Yield, %[c]
1a	conc. (1)	0.1	Pd_2dba_3/xantphos (2)	One step Air, 24 h, DMF, 110°C		0	82	72
1b	conc. (1)	0	Pd_2dba_3/xantphos (2)	One step Air, 24 h, DMF, 110°C		0	74	72
1c	conc. (1)		Pd_2dba_3/xantphos (2)	One step Air, 24 h, DMF, 85°C		34	53	-
1d	conc. (1)		Pd_2dba_3/xantphos (2)	One step N_2, 24 h, DMF, 85°C		62	29	-
1e	conc. (1)		Pd_2dba_3/xantphos (2)	One step Air, 24 h, DMF, rt		67	0	-
2a	conc. (1)	0	Pd_2dba_3/xantphos (2)	One pot Air, 24 h, DMF (anh.),[d] 110°C, drying trap[e]		13	77	-
2b	conc. (1)		Pd_2dba_3/xantphos (2)	One step N_2, 24 h, DMF (anh.),[d] 110°C		82	10	-
2c	conc. (1.5)		-	One step Air, 24 h, DMF, 110°C		6	0	-
2d	aq. (1.5)		-	One step Air, 30 h, DMF, 110°C		22	10	-
3a	conc. (1.5)	0	Pd_2dba_3/xantphos (2)	One step Air, 20 h, DMF, 110°C		0	100	96
3b	conc. (2)		Pd_2dba_3/xantphos (2)			0	100	100
3c	conc. (1.5)		Pd_2dba_3/xantphos (0.5)			79	26	-
3d	conc. (1.5)		Pd_2dba_3/xantphos (0.05)			100	0	-
4a	conc. (1.5)	0	Pd_2dba_3/xantphos (2)	One pot Air, 24 h, DMF, 85°C		86	34	-
4b	conc. (1.5)		Pd_2dba_3/xantphos (0.5)	One step Air, 24 h, DMF, 85°C		91	9	-
5a	conc. (1)	0	Pd_2dba_3/xantphos (2)	N_2, 12 h, DMF, 85°C	Air, 24 h, DMF, 110°C	0	89	87
5b	conc. (2)		Pd_2dba_3/xantphos (2)	N_2, 12 h, DMF, 85°C	Air, 24 h, DMF, 110°C	0	100	100

6a	aq. (1)	0	Pd_2dba_3/xantphos (2)	One step Air, 22 h, DMF, 110ºC	0	81	-
6b	aq. (1.5)		Pd_2dba_3/xantphos (2)		0	100	84
6c	aq. (2)		Pd_2dba_3/xantphos (2)		0	100	100
6d	aq. (2)		Pd_2dba_3/xantphos (1)		20	80	-
6e	aq. (2)		Pd_2dba_3/xantphos (0.5)		50	50	-
7a	conc. (1)	0	Pd_2dba_3/polymer supp. nixantphos (2)	One step Air, 24 h, DMF, 110ºC	0	71	82[f]
7b	aq. (2)		5%Pd-C/xantphos (2)		2	25	-
8a	conc. (1)	0	Pd_2dba_3/xantphos (2)	One step Air, 24 h, CH_3CN, 82ºC	46	34	-
8b	aq. (1)		Pd_2dba_3/xantphos (2)	One step N_2, 24 h, CH_3CN, 82ºC	70	11	-
9a	aq. (1)	0	Pd_2dba_3/xantphos (2)	One step N_2, 24 h, DMF, 110ºC	45	31	-
9b	aq. (1)		Pd_2dba_3/xantphos (2)	One step N_2, 24 h, No solvent, 110ºC	54	21	-
9c	aq. (1)		Pd_2dba_3/xantphos (2)	One step N_2, 24 h, DMF [10 M], 110ºC	64	0	-

[a] Unless otherwise noted, reactions were conducted in reagent grade, undried solvents [0.5 M], according to the conditions indicated in the table. [b] NMR does not consider common byproducts, such as H_3PO_3 and H_3PO_4. [c] Isolation consists of an extractive workup, and products are obtained in >95% purity. [d] DMF was distilled from CaH_2 under reduced pressure. [e] Drierite ($CaSO_4$) trap was used to avoid moisture. [f] 91% purity.

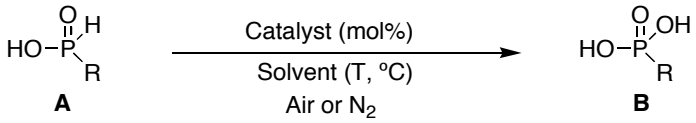
As shown in Table 6.5, we focused mainly on the development of a one-step tandem process. The reactions were initially conducted with freshly concentrated H_3PO_2 (entry 1) in the presence of 2 mol% of Pd_2dba_3/2xantphos, using undried DMF (reagent grade) as solvent, under an air atmosphere. The higher temperatures that can be attained when using this solvent proved to be necessary for an efficient oxidation step. Replacement of DMF by CH_3CN significantly decreases the yield of product, which supports the need of higher temperatures for the oxidation process (entry 8). As expected, the C-P bond-forming step proceeds very inefficiently with anhydrous H_3PO_2 in the absence of Pd catalyst (entry 2c), whereas aqueous H_3PO_2 undergoes the hydrophosphinylation in low yields (entry 2d). This suggests the mediation of free-radicals in the latter case.[77,25] On the other hand, when the reaction is performed with anhydrous DMF under a nitrogen atmosphere, *H*-phosphinic acid is the main product (entry 2b). The presence of oxygen reverses this and leads mainly to the phosphonic acid (entry 2a). A few other experiments were attempted by modifying the stoichiometry and catalyst loading (entry 3), and we found that 1.5 –

2 eq of H_3PO_2 and 2 mol% of Pd-catalyst provide excellent yields of oxidized product (entries 3a-b), however a decrease in the amount of catalyst markedly reduces the amount of phosphonic acid, while *H*-phosphinic acid becomes the dominant product. This further supports the key role of the Pd catalyst in the oxidation step. The same trend was observed when conducting the reaction at lower temperature in DMF (entry 4). We surmised that an increase in yield should be achieved by doing the process stepwise, instead of simultaneously, that is, preforming the *H*-phosphinic acid under the reported optimized conditions,[33] followed by in situ oxidation according to our above outlined results (entries 1 – 4). Entry 5 indeed confirms our hypothesis, particularly in the case of using equimolar amounts of H_3PO_2 and 1-octene (entry 5a). Next, we replaced the concentrated hypophosphorous acid with the commercially available aqueous solution (50 wt%) (entries 6-9) to further simplify the process. According to entry 6, and in agreement with our previous results, at least 2 mol% of Pd-catalyst with 2 eq of H_3PO_2 are needed for a successful synthesis of octyl phosphonic acid. It should be noted that the use of aqueous versus concentrated H_3PO_2 did not show a significant impact on the yields, contrary to the presence of air versus nitrogen in the reaction (entry 2a *vs.* 2b and 2a *vs.* 6a). Use of Pd_2dba_3 with a polymer supported ligand furnished the product in good yield, but in lower purity (entry 7a). Additionally, the concentration of the reactants also plays a key role (entry 9), and 0.5 to 1 M appears to be optimum.

One more set of control experiments was carried out, where we studied the oxidation of isolated *H*-phosphinic acids (either commercially available, or prepared form Pd-catalyzed hydrophosphinylation and allylation reactions with H_3PO_2).[33-34,66] In the absence of air, water and catalyst, no oxidation takes place, even when heating at 110°C (entries 1 and 7). However, when running the reactions with undried DMF, under air at 110°C, the oxidized phenyl and octyl phosphonic acids are formed quantitatively (entries 3a-b). Nonetheless, farnesyl- and geranyl-*H*-

phosphinic acids do not undergo the expected oxidation, even after long periods of heating; instead they decompose slowly to H_3PO_3 and H_3PO_4 (entries 3c-d). On the other hand, phenyl phosphinic acid slowly oxidizes under anhydrous and anaerobic conditions in the presence of Pd-catalysts (entry 4), in contrast to the results obtained in the absence of added catalyst (entry 1). This fact, along with the quantitative oxidation evidenced when conducting the reaction with catalytic amounts of Pd or Ni under air (entry 5) and with mild heating (85°C), corroborate the participation of the palladium in the oxidation reaction (entry 5 *vs.* entry 2).

Table 6.6 Control experiments for the oxidation of *H*-phosphinic acids[a]

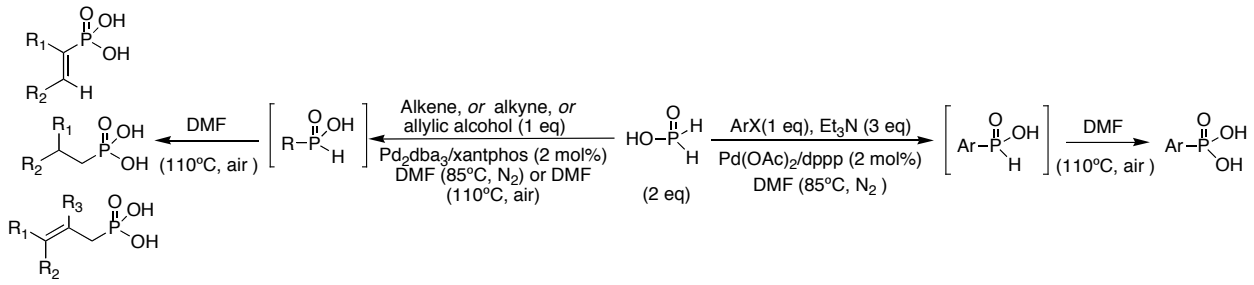


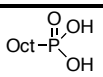
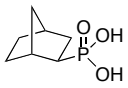
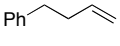
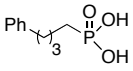
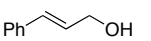
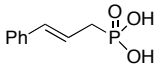
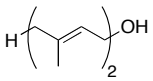
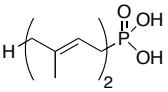
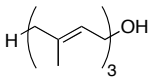
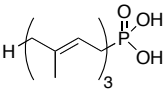
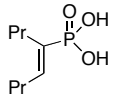
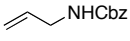
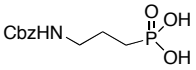
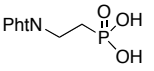
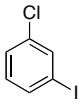
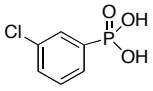
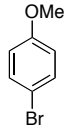
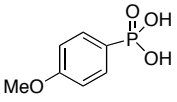
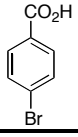
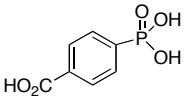
Entry	(R=)[b]	Catalyst (mol%)	Solvent, Temp (ºC)	Air/N_2	Time (h)	^{31}P NMR yield, % A	^{31}P NMR yield, % B (Target)	Isolated Yield, %[c]
1a	Oct	-	DMF/sieves (85)	N_2	14	90	0	-
1b	Ph					100	0	
2a	Oct	-	DMF/reagent grade (85)	Air	19	36	64	-
2b	Ph					75	25	-
3a	Oct	-	DMF/reagent grade (110)	Air	19	0	100	-
3b	Ph					0	100	-
3c	Ger				50	37	40	-
3d	Far					43	36	-
4	Ph	Pd_2dba_3/xantphos (2)	DMF/sieves (85)	N_2	14	53	47	-
5a	Oct	5% Pd-C (2)	DMF/reagent grade (85)	Air	14	0	100	92
5b		Ni/silica-alumina (4)						83
6	Ph	-	CH_3CN/reagent grade (82)	Air	24	90	10	-
7a	Oct	-	CH_3CN (anh.) (82)	N_2	24	100	0	-
7b	Ph		DMF (anh.) (110)					

[a] Reactions were conducted in the corresponding solvent [0.5 M]. [b] *H*-phosphinic acids were prepared by Pd-catalyzed hydrophosphinylation (Ref. 33-34), or via Pd-catalyzed dehydrative allylation from H_3PO_2 (Ref. 66). An exception is phenyl phosphinic acid, which is commercially available. [c] Isolation by extractive workup.

Next, we investigated the scope of tandem C-P bond formation – oxidation reactions with different substrates, such as alkenes, internal alkynes, allyl alcohols and aryl halides (Table 6.7). In general, the stepwise process (Method B) with concentrated H_3PO_2 provided better yields of products than the simultaneous version (Method A). In accordance with the literature,[33-34,36] Pd_2dba_3/xantphos (2 mol%) worked efficiently as a catalytic system for hydrophosphinylation and allylation reactions (entries 1-9), while $Pd(OAc)_2$/dppp (2 mol%) with Et_3N as base (3 eq) proved successful in cross-coupling (entries 10-12). The products were normally isolated in moderate to good yields by an aqueous extractive workup and, if required, recrystallization was performed. However, very polar *N*-containing phosphonic acids are soluble in water, so ion-exchange chromatography was required for their isolation (entries 8 and 9). Even though the mechanism of this transformation is not completely clear at this time, it could proceed either, via a direct P-H bond activation where the Pd inserts into the P-H bond of the *H*-phosphinic acid ('inner sphere mechanism'),[202] or, most probably, through an indirect process where the metal complex first activates molecular oxygen present in the solution forming a highly reactive species (as a radical), that in turn reacts with the *H*-phosphinic acid.[165f] Further work will be required to delineate the mechanism and to investigate the scope of the reaction. However, this transformation constitutes a promising and novel access to phosphonic acids.

Table 6.7 Synthesis of phosphonic acids via tandem C-P bond formation – oxidation reactions[a]

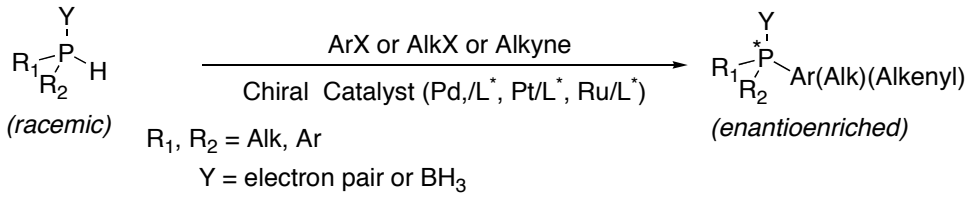


Entry	Substrate	Method[b]	Catalyst	Base (eq)	Product	1st Step Time (h)	2nd Step Time (h)	Isolated Yield, %[c] (NMR Yield,%)
1a		A	Pd_2dba_3/xantphos (2 mol%)	-		One step, 20 h		100
1b		B				12	24	100
2a		A	Pd_2dba_3/xantphos (2 mol%)	-		One step, 50 h		81
2b		B		-		12	64	97
3		A	Pd_2dba_3/xantphos (2 mol%)	-		One step, 50 h		95
4		B	Pd_2dba_3/xantphos (2 mol%)	-		12	22	89
5		B	Pd_2dba_3/xantphos (2 mol%)	-		12	45	77[d] (72)
6		B	Pd_2dba_3/xantphos (2 mol%)	-		15	55	(92)[e]
7		B	Pd_2dba_3/xantphos (2 mol%)	-		12	50	91
8		B	Pd_2dba_3/xantphos (2 mol%)	-		12	50	86[f]
9		B	Pd_2dba_3/xantphos (2 mol%)			12	20	(81)[f,g]
10		B	$Pd(OAc)_2$/dppp (2 mol%)	Et_3N (3 eq)		15	22	82[h]
11		B	$Pd(OAc)_2$/dppp (2 mol%)	Et_3N (3 eq)		15	22	55[h]
12		B	$Pd(OAc)_2$/dppp (2 mol%)	Et_3N (3 eq)		15	42	52[h]

[a] See Experimental Section for details of the procedures. [b] Method A: One step; 2 eq. 50% aqueous H_3PO_2, hydrophosphinylation-oxidation, DMF, 110ºC, air. Method B: Two steps, 2 eq. concentrated H_3PO_2. 1st Step: P-C bond formation = DMF, 85ºC, N_2; 2nd Step: Oxidation = DMF, 110ºC, air. [c] Unless otherwise noted, isolation consists of an extractive workup. [d] Isolated in 87% purity. [e] ^{31}P NMR spectrum shows an extra signal (8%) of the product from reduction of the allylic double bond. [f] Purified by ion-exchange chromatography. [g] A large amount of product stayed in the column, purification was not successful. [h] Purified by recrystallization.

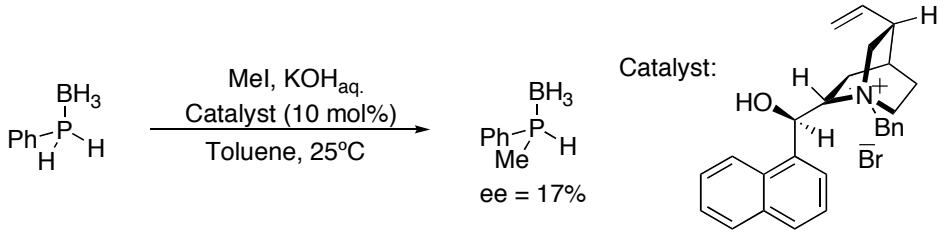
<u>Chapter Seven:</u> Preparation of *P*-chiral *H*-phosphinates via desymmetrization of alkylphosphinates

The most common methods to prepare *P*-chiral organophosphorus compounds consist of resolution of racemates or asymmetric synthesis, which require a stoichiometric amount of a chiral auxiliary.[128-133] These previous approaches leave a lot to be desired in terms of cost-effectiveness and atom-economy. Recently, a few catalytic enantioselective methodologies for the synthesis of tertiary *P*-stereogenic phosphines and phosphine-boranes have been designed, which support the feasibility of this approach (Eq. 7.1).[212] Glueck and Helmchen have prepared bulky *P*-chirogenic tertiary phosphines via asymmetric cross-coupling reactions using palladium and platinum complexes,[212a-f] while Toste *et al.* synthesized tertiary phosphine ligands via ruthenium catalysis.[212g] With secondary phosphine boranes complexes, the Gaumont group has reported its preliminary results on Pd-catalyzed cross-coupling and hydrophosphination reactions, achieving enantiomeric excesses up to 45% and 42%, respectively.[212i-g]



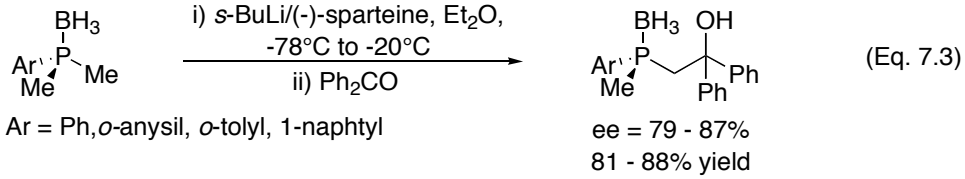
(Eq. 7.1)

On the other hand, as of today, no successful catalytic syntheses of secondary phosphines (or their complexes) have been attained. Recently, Lebel and coworkers, aiming to desymmetrize primary phosphine boranes complexes, explored an alkylation under phase-transfer catalysis, which was not successful (Eq. 7.2).[212h]



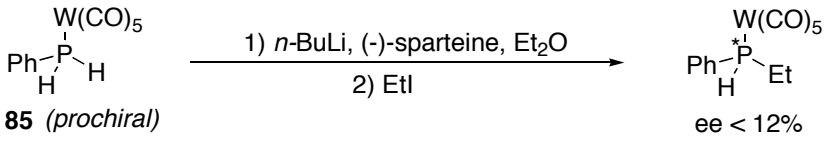
(Eq. 7.2)

In this regard, it is important to highlight that extremely few successful studies, which involve desymmetrization on tetrahedral species have been reported. An exception is the enantioselective deprotonation of prochiral dimethylphosphine boranes with (-)-sparteine alkyllithium complex that was developed by Evans (Eq. 7.3),[213] and subsequently extended by Livinghouse.[214] More recently, Kann showed that a chiral switch could be used to access the other enantiomer of the phosphine borane, by using (-)-cytisine derivatives instead of (-)-sparteine.[215]



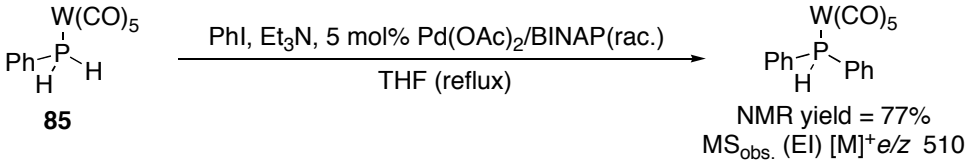
(Eq. 7.3)

In fact, the first project that was assigned to me when I started my doctoral research consisted of desymmetrizing a prochiral phosphine tungsten complex **85**, which was prepared according to the procedure described by Mathey.[216] Initial focus was on the deprotonation with stoichiometric amounts of sparteine/*n*-BuLi,[213] however we did not succeed (ee<12%) (Eq. 7.4),[203] but a similar failure was later reported by Imamoto on a phosphine borane complex.[217]



(Eq. 7.4)

At the same time, a study was performed to achieve the desymmetrization of the primary phosphine tungsten complex **85** via cross-coupling. Initially, a screening of conditions was performed in order to optimize the non-chiral reaction since the cross-coupling with this type of compounds is unknown. Even though the coupling seemed to occur as expected with aryl iodides according to ^{31}P NMR (later confirmed by mass spectra), we did not find optimum conditions to isolate the products (Eq. 7.5).



85

NMR yield = 77%
$MS_{obs.}$ (EI) $[M]^+ e/z$ 510

(Eq. 7.5)

As previously indicated in this dissertation (Chapter I, Section 1.4), *P*-stereogenic *H*-phosphinates are commonly prepared by means of classical resolution processes (involving recrystallization), where the chiral unit is incorporated in their structure.[103a,128,129] In addition, Shioji[137] and Yamagishi[138] have accomplished the enzymatic kinetic resolution (with lipases) of racemic *α*-hydroxy-*H*-phosphinates via acetylation, or through hydrolysis of their acetate precursors. However, no catalytic asymmetric approach has been reported so far to access these compounds. This fact led us to explore two different research avenues: (a) asymmetric variants of our Pd-catalyzed reactions,[33,62,63] which involves the development and validation of a novel NMR assay, and (b) a chiral auxiliary approach, which consists in the desymmetrization of chiral and prochiral alkyl phosphinates by means of various C-P bond-forming methodologies developed in the Montchamp group.[17,52,35,57,26]

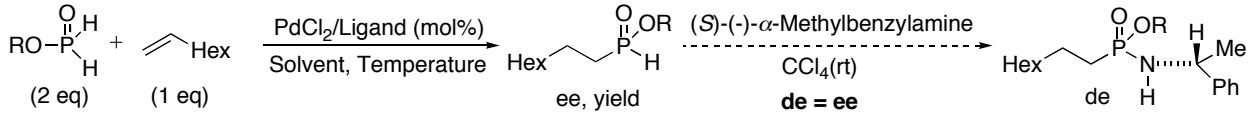
7.1 Pd-catalyzed C-P bond formation reactions using chiral catalysts

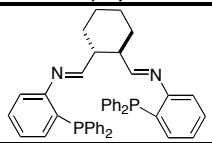
7.1.1 Pd-catalyzed hydrophosphinylation

Guided by the prospect of developing asymmetric catalytic approaches to *P*-chiral *H*-phosphinates, our Pd-catalyzed hydrophosphinylation[33] was explored using chiral ligands. Various alkyl phosphinates were prepared via esterification of hypophosphorous acid with alkoxysilanes,[18] or by transesterification of phenyl phosphinate (itself prepared by the alkoxysilane method),[17,52] and subsequently reacted with an alkene in presence of Pd-catalysts (Table 7.1). However, we faced an additional problem related to the failure of the direct measurement of the enantiomeric purity (ee) of *H*-phosphinates by HPLC. This analysis has also been reported as unsuccessful by other groups.[134] In order to overcome this difficulty; we

initially performed hydrophosphinylation reactions with hypophosphite esters possessing a chiral carbon at the ester alkyl group (racemate or enantiomerically pure) (entries 1 and 2). The best result in terms of yield and enantiomeric excess was attained with menthyl phosphinate and (*S,S*)-DIOP (52% yield, 22% de, entry 1f), however the enantioselectivity was still very low. Another more convenient approach developed by Montchamp[196] consists of a ^{31}P NMR assay by means of oxidation of *H*-phosphinates with a secondary chiral amine and carbon tetrachloride (Atherton-Todd reaction).[113] Gratifyingly, we validated this assay by HPLC resolution during our research on cross-coupling (Section 7.1.2).[203] This critical achievement opened up the possibility to perform a successful chiral catalyst screening, that could ultimately lead to the development of an asymmetric reaction. A brief screening was performed (entries 3-10). In fact, some of the experiments were carried out with non-chiral ligands in order to determine their reactivity in the reaction (entries 5-7). Much remains to be done on this topic, and the results presented here are only preliminary. So far, the best result was apparently achieved with Jacobsen's ligand (100% yield, <20% ee, entry 3a), nonetheless the control experiment with an achiral phosphine catalyst ($PdCl_2$(dppf)·MeLi) provided the product with a non-zero enantiomeric excess (7% ee, entry 9). More importantly, we discovered that $PdCl_2$ catalyzes the hydrophosphinylation of alkenes in 77% yield in toluene (entry 10). Therefore, this implies that in order to achieve a highly enantioselective process, this racemic pathway must be suppressed completely. Another important finding was discovered when comparing the reactivity of a preformed Pd-Jacobsen chiral complex (**86**),[218] (0% yield, entry 3c) to the reactivity of the presumably *in situ* formed complex (100% yield, 13% ee, when mixing $PdCl_2$ and Jacobsen's ligand, entry 3a). Thus, we cannot always rely on the *in situ* formation of the chiral complex, and the first result might be at least partially due to the intervention of a non-chiral palladium species.

Table 7.1 Screening of ligands for the Pd-catalyzed asymmetric hydrophosphinylation



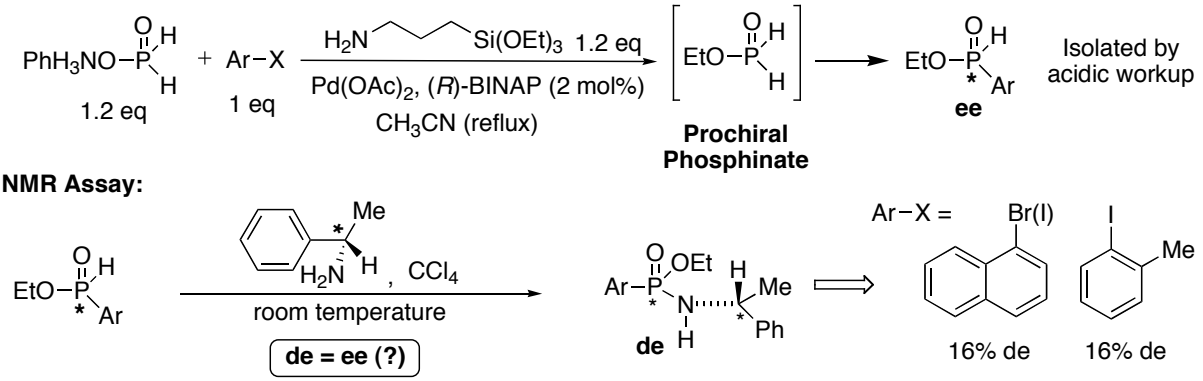
Entry	R=	Catalyst $PdCl_2$ / Ligand or Complex[a]	Catalyst, mol% Pd	Solvent	Temp (°C)	NMR yield, %	ee or de (%)[b]
1a	(-)-Menthol	xantphos	1	Toluene	85	100	18
1b		*(S,S)*-DACH- Naphtyl Trost Ligand	1		85	0	-
1c		(*R*)-BINAP	1		85	52	0
			2		110	78	8
			5		110	53	14
1d		(*S*)-BINAP	5		110	31	4
1e		(*S,S*)-BDPP	1		85	15	38
			2		110	6	4
			5		110	0	-
1f		(*S,S*)-DIOP	1		85	52	27
			2		110	62	19
			5		110	46	27
1g		*(R,R)*-Jacobsen	1		85	0	-
			2		110	58	0
			5		110	85	3
1h		SL-J001-1	1		85	0	-
		SL-J002-1				0	-
		SL-J003-1				0	-
		SL-J005-1				31	10
		SL-W001-1				0	-
2a		xantphos	2	Toluene	85	100	5
2b		(*R*)-BINAP	2		110	67	4
			5			54	3
2c		(*S*)-BINAP	2			94	5
			5			50	4
2d		(*S,S*)-BDPP	2			19	14
2e		(*S,S*)-DIOP	2			86	2
						92	1
2f		*(R,R)*-Jacobsen	5			55	2
						92	4
3a	Et	*(R,R)*-Jacobsen	3	Toluene	110	100	13[c]
3b		*(R,R)*-Jacobsen (1Pd/2Ligand)	2			28	17
3c		Pd·*(R,R)*-Jacobsen **(86)**	2	Toluene	110	0	-
				CH_3CN	82	20	9
4a	Et		2	Toluene	110	13	4
4b				CH_3CN	82	24	17
5	Et	SALEN	2	CH_3CN	82	47	-
				Toluene	110	81	-
6	Et	Phthalocyanine	2	CH_3CN	82	42	-
				Toluene	110	97	-
7	Et	Meso-tetraphenylporphine	2	CH_3CN	82	50	-
				Toluene	110	89	-
8	Et	(*R*)-BINOL	2	Toluene	110	89	9
9	Et	$PdCl_2$(dppf)·MeLi	2	Toluene	110	100	7
10	Et	$PdCl_2$ (no ligand)	2	Toluene	110	77	-
				CH_3CN	82	30	-

[a] Unless otherwise specified, the chiral catalyst was prepared *in situ* by mixing equimolar amounts of $PdCl_2$ and the corresponding ligand (1/1). [b] In entries 1 and 2, the ee(de) was measured directly by ^{31}P NMR of the crude mixture. In the other entries, the NMR assay was performed to determine the ee's. [c] HPLC resolution with a chiral (S,S)-WHELK-01 column/UV detector was not successful.

7.1.2 Pd-catalyzed cross-coupling of alkylphosphinates with aryl halides

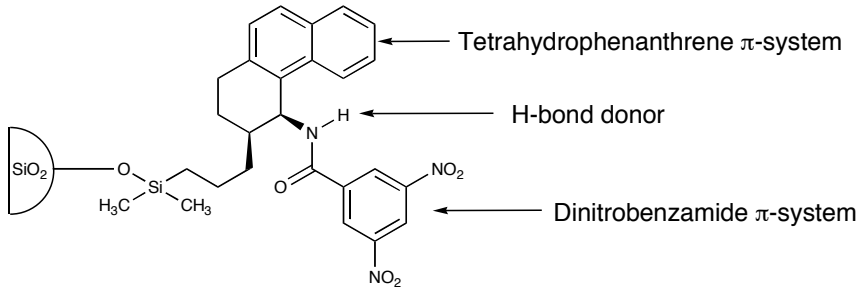
The desymmetrization of prochiral phosphinates via Pd-catalyzed cross-coupling[62,63] was also briefly investigated with various aryl iodides and bromides. It should be noted that the proposed mechanistic pathway for this reaction (Chapter Three, Scheme 3.1) questions the possibility of developing an asymmetric version with aryl electrophiles other than iodides. Presumably, aryl iodides are the only electrophiles that undergo a direct cross-coupling with alkyl phosphinates, while bromides and triflates cross-couple with salts of the base yielding an *H*-phosphinate salt, which is subsequently esterified *in situ*.[63] This suggests that all the intermediates involved in the coupling step (where the chiral catalyst should participate) are achiral salts. Nonetheless, we pursued our study using an aminosilicate, as both esterifying agent and base, in the presence of Pd-catalysts and using acetonitrile as solvent. $PdCl_2$ or $Pd(OAc)_2$ were generally used as Pd-sources, with (*R*)-BINAP as ligand. Other Joshiphos and Walphos-type ligands were also screened with no success. In general, we observed extremely low enantiomeric excesses (<16% ee), which were determined by our ^{31}P NMR assay.[193,203] The best results were achieved with 1-bromo and 1-iodonaphthalene, as well as with 2-methyliodobenzene, which furnished the product with 16% ee (Scheme 7.1).

Scheme 7.1 Preliminary results for the development of an asymmetric Pd-catalyzed cross-coupling of alkyl phosphinates



At the time there remained the question of whether the ^{31}P NMR assay was reliable, the validation of the NMR assay by HPLC resolution with a chiral column was absolutely required. Through screening of various chiral stationary phases, it was found that (*S,S*)-WHELK-01 from Regis Technologies, based on 1-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene (Scheme 7.2), acting as a π–electron acceptor/π–electron donor phase, worked successfully in the resolution of ethyl phenylphosphinate contrary to various carbohydrate-base chiral columns, such as CHIRALPAK-AD-Daicel.

Scheme 7.2 Chiral stationary phase from (*S,S*)-WHELK-01, Regis Technologies



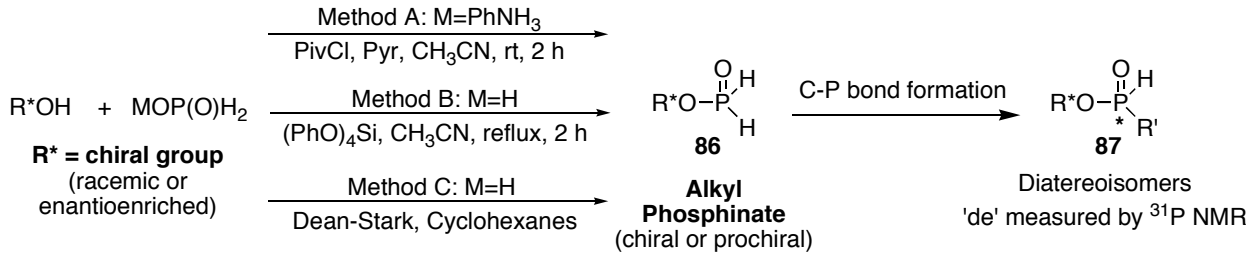
1-(3,5-Dinitrobenzamido)-1,2,3,4,-tetrahydrophenanthrene

Next, we developed an HPLC (and LC/MS) method for the resolution of ethyl (1-naphthyl) phosphinate, prepared from the cross-coupling of 1-bromonaphthalene, using both racemic and (*R*)-BINAP (Scheme 7.1). Gratifyingly, a good match was obtained between both measurements (racemic BINAP: 2.3% ee (NMR assay) *vs*. 1.9% ee (HPLC); (*R*)-BINAP: 15% ee (NMR assay) *vs.* 16% ee (HPLC)), thus validating our NMR assay (Scheme 7.1, de=ee). This represents an important step toward our ultimate goal of developing asymmetric catalytic synthesis of *H*-phosphinates. Worth noting is that, in order to achieve the desymmetrization of alkyl phosphinates [$(RO)P(O)H_2$ – P-V) and (RO)P(OH)(H) – P-III], the enantiodetermining step should involve the distinction between enantiotopic groups at the sp^3 *P*-center (P-OR *vs*. P=O – P-V tautomer or P-OR *vs.* P-OH – P-III tautomer). All popular asymmetric transition metal-catalyzed reactions involve the addition to planar systems.[168c,219]

7.2 Desymmetrization of chiral and prochiral alkyl phosphinate esters

Although the use of chiral catalysts in C-P bond forming processes is theoretically the most effective approach to *P*-stereogenic *H*-phosphinates, this field is currently in its infancy and our attempts to unravel this largely unsolved problem have not been successful (Section 7.1). Therefore, a more traditional chiral auxiliary approach was pursued, aiming at understanding the basis of transferring asymmetric information from a remote substituent in alkyl phosphinate substrates (Scheme 7.3). It should be noted that this also constitutes a novel and highly challenging approach to access *P*-chiral tetrahedral compounds as most of the chiral auxiliaries for asymmetric catalysis have been designed specifically for facial differentiation. Here, the situation is quite different because we are dealing with tetrahedral substrates, and the minimum requirement for a successful desymmetrization consists in blocking one quadrant, instead of a plane.

Scheme 7.3 Chiral auxiliary approaches towards desymmetrization of alkyl phosphinates



A study regarding the desymmetrization of chiral alkyl phosphinates via different C-P bond forming reactions was undertaken in order to access *P*-stererogenic *H*-phosphinates (Scheme 7.2). Specifically, phosphinate esters **86** were prepared by different esterification methods using chiral alcohols: (a) pivaloyl chloride-mediated esterification (Method A),[10,16-17] (b) transesterification with phenyl phosphinate (itself prepared *in situ* by reaction of tetraphenylortosilicate with hypophosphorous acid) (Method B)[10,17-18,52] and (c) Dean-Stark esterification with hypophosphorous acid.[14] After ^{31}P NMR analysis indicated the generation of

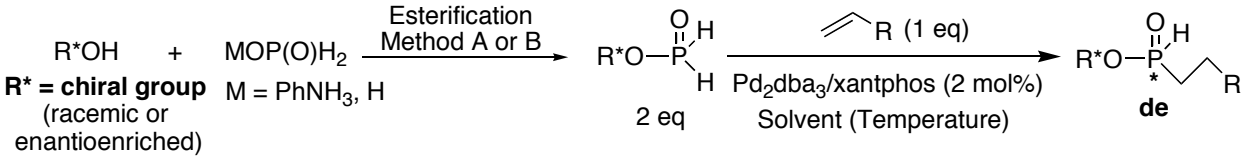
an alkyl phosphinate ester **86**, a C-P bond-forming reaction was performed *in situ* to furnish the expected *H*-phosphinate ester **87,** as a mixture of diastereoisomers.[17,52,35,57,26] Two main advantages of this process are that: (a) the diastereoisomeric excesses (de) can be determined directly by ^{31}P NMR of the crude reaction mixtures, and (b) racemic alcohols can also be used and their effectiveness can be evaluated as well by ^{31}P NMR. This is particularly important because use of stoichiometric amounts of chiral alcohols is often not cost-effective. In this way, we were able to simplify the process significantly, and evaluate a wide range of chiral alcohols. At the same time, identification of key structural features of the most successful auxiliaries guided us towards the synthesis and evaluation of several chiral alcohols. Moreover, some searches were supported by molecular-modeling (through conformational searches).[196] In general, the transesterification with $PhOP(O)H_2$ and the pivaloyl chloride methodology proved to be the most effective in terms of yields of phosphinate esters. Even more interesting, they were complementary as some substrates that react quite inefficiently with the silicate-based methodology, do react successfully using the acyl chloride-activating agent. Dean-Stark esterification was by far less convenient in terms of yields and solvents.[14] However, base-promoted alkylations[57] and free radical- mediated reactions[25,26] worked exclusively with alkyl phosphinates prepared by this process. It is important to highlight that, in addition to an efficient esterification, good yields of *H*-phosphinate products and high diasteromeric excesses (de) are required for a successful asymmetric synthesis of *H*-phosphinates. The results will be disclosed in the following sections.[203]

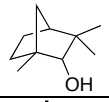
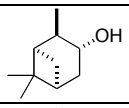
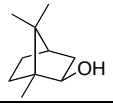
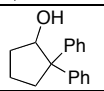
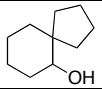
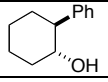
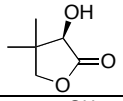
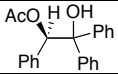
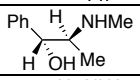
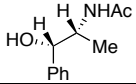
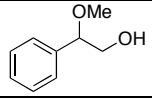
7.2.1 Pd-catalyzed hydrophosphinylation reaction

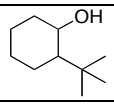
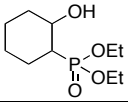
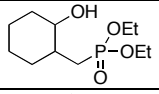
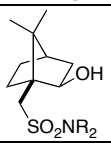
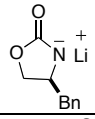
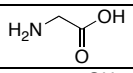
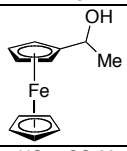
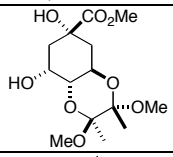
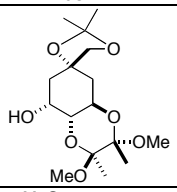
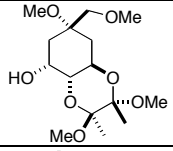
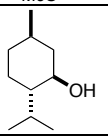
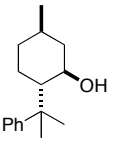
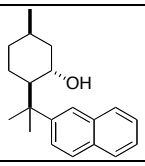
Inspired by some preliminary results from the Montchamp group regarding the desymmetrization of alkyl phosphinates,[196] we developed a preliminary study, focusing on Pd-catalyzed hydrophosphinylation[33] and cross-coupling reactions.[62,63] Our results suggest that the

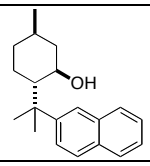
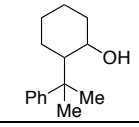
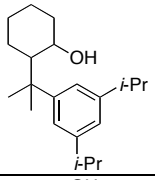
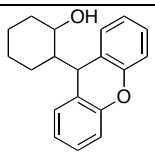
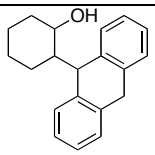
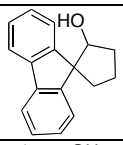
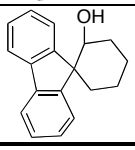
Pd-catalyzed addition to alkenes provides the best results in general (de and yields). Emphasis was placed on screening various chiral and prochiral phosphinate esters in this catalytic transformation. The chiral auxiliaries were either commercially available, or synthesized through known procedures (references are indicated on the table), and used in stoichiometric amounts for the preparation of akyl phosphinates, which in turn undergo addition to an alkene in the presence of Pd_2dba_3/2xantphos (2 mol%). The results are summarized in Table 7.2.

Table 7.2 Desymmetrization of alkyl phosphinates via Pd-catalyzed hydrophosphinylation[a]



Entry	R*OH (or R_1R_2NH)	*Synthetic Ref.*, or Commercially Available (CA)	Esterification Method or *Ref.*[b]	Yield, %	Alkene	Solvent (Temp, °C)	Isolated Yield, %[c] (NMR Yield,%)	de,[d] %
1		CA	A	77	1-octene	CH_3CN (82)	(100)	20
2		CA	A	66	1-octene	CH_3CN (82)	(100)	34
3		*220*	A	0	-	-	-	-
			B	68	1-octene	CH_3CN (82)	(18)	5
4		*221*	A	100	1-octene	CH_3CN (82)	(30)	41
5		*222*	A	93	1-octene	CH_3CN (82)	(100)	24
			B	95	2-Br-styrene	CH_3CN (rt)	(94)	26
6		CA	B	100	1-decyne	CH_3CN (82)	(100)	0
7		CA	A	61	1-decyne	CH_3CN (82)	(8)	-[e]
8		CA	A	0	-	-	-	-
9		CA	B	0	-	-	-	-
10		*223*	A	92	1-octene	CH_3CN (82)	(0)	-[f]
			B	0	-	-	-	-[f]
11		CA	A	100	1-octene	CH_3CN (82)	(10)	13

12		CA	A B	59 100	1-octene	CH_3CN (82)	(28) (100)	-[e] (36)[g]
13		*224*	A B	86 100	1-octene and 2-Br-styrene	CH_3CN (82 and rt)	(0)	-
14		*225*	B	77	1-octene	Toluene (110)	(15)	-
15		CA	A	91	1-octene	CH_3CN (82)	(0)	-
16		CA *226* (Lithiation)	B[h]	0	-	-	-	-
17		CA	*227*[i]	0	-	-	-	-
18		*228*	A and B	0	-	-	-	-
19		*229*	A and B	0 [j]	-	-	-	-
20		*196*	A and B	0 [j]	-	-	-	-
21		*229, 196*	A and B	0 [j]	-	-	-	-
22		CA	B	100	1-octene	CH_3CN (82)	(100)	18
23a		*230*	A	100	1-octene	CH_3CN (82)	100 (100)	66
23b			B	94	2-Br-styrene	CH_3CN (rt)	57 (67)	71
23c				100	styrene	CH_3CN (rt)	(100)[k]	-[e]
23d				100	2-Br-styrene	THF (66)	(0)	-
23e				100	2-Br-styrene	Toluene (110)	(0)	-
23f				85		CH_3CN (82)	71[k] (88)	46
24		*231*	B	60	1-octene	CH_3CN (82)	(traces)[k]	-

25		*231*	B	0	-	-	-	-
26a		*232*[l]	B	100	1-octene	CH_3CN (82)	93 (100)	55
26b					2-Br-styrene	CH_3CN (rt)	(43)	59
27		*232*	B	100	1-octene	CH_3CN (82)	66 (108)	48
28		*232*	B	64	1-octene	CH_3CN (82)	(90)	26
29		*232*	B	65	1-octene	CH_3CN (82)	(76)	5
30		*233*	A	67	1-octene	CH_3CN (82)	(64)	18
			B	59	1-octene	CH_3CN (82)	(59)	7
31		*233*	B	66	1-octene	CH_3CN (82)	(66)	11

[a] See Experimental Section for details of the procedures. [b] Unless otherwise indicated, the esterification methods were A (PivCl), or B ($Si(OPh)_4$) [Ref. 10, 17-18, 52]. [c] Isolation consisted in extractive workup followed by chromatography on silica gel. [d] de was determined considering the difference in heights and/or integrals in the ^{31}P NMR spectra. [e] de was undetermined. [f] The ester group gets hydrolyzed into the acid. [g] Mixture of cis and trans isomers, as in the starting material ($83_{trans}/17_{cis}$) [h] Oxazolidinone is commercially available. Lithiation was performed as specified in Ref. 226. [i] Reference 227 reports the synthesis of the corresponding phosphinamide, which we could not reproduce under any circumstance. [j] $MeOP(O)H_2$ is formed in the esterification step. [k] Mixture of various isomers. [l] Simplified non-chiral version of (-)-8-phenylmenthol (entry 23)

As we can observe in Table 7.2, from the wide range of alcohols (and amines) that was screened in this process, just a few of them have been demonstrated to promote the desymmetrization in moderate diastereomeric excesses (maximum de=70%, entries 23, 26 and 27), particulary those which possess a 2-substituted cyclohexanol in their structure. Initially, we discovered that 8-(-)-phenylmenthol[230] furnished significantly enantioenriched *H*-phosphinates (de=66%, entry 23a) when reacting with 1-octene at the reflux temperature of acetonitrile. This value was slightly increased when conducting the hydrophosphinylation at room temperature

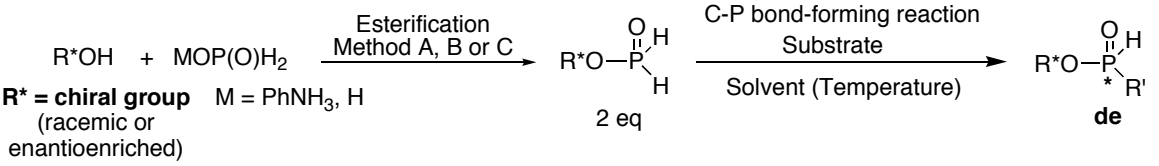
(de=71%, entry 23b). Guided by the previous discovery, we turned our attention to naphthyl analogs of 8-(-)-phenylmenthol (entries 23 and 24), which did not provide satisfactory results. In addition, these compounds were prepared by multi-step and low yielding syntheses.[231] This fact represents an important limitation and we did not pursue our original plan of screening various analogs with aryl group substituents different than phenyl and naphthyl. Of greater interest, we discovered that some racemic 2-substituted cyclohexanols gave similar results as (8)-(-)-phenylmenthol (entries 26 and 27). The major advantage of these auxiliaries is that they were prepared in good yields by a single epoxide-opening step,[232] which facilitated further screening. Of course, a real application would involve resolution or the racemates. On the other hand, we were unable to access hypophosphorous amides ($R_2NP(O)H_2$) (entries 16 and 17), which are unknown compounds. One single paper reports the synthesis of these species, however we were unable to reproduce that work.[227] Even though the 71% diastereomeric excess is still low, it supports the feasibility of desymmetrizing tetrahedral species to give access to the highly desirable *P*-chiral organophosphorus compounds.

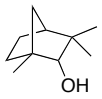
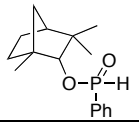
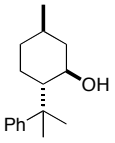
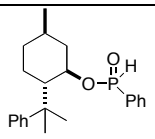
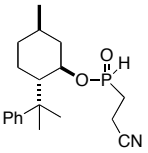
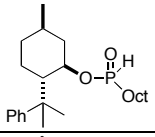
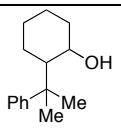
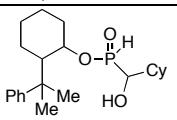
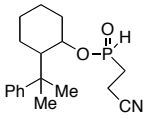
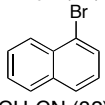
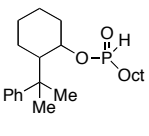
7.2.2 Other C-P bond formation methodologies

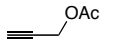
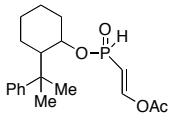
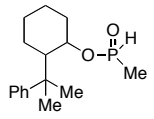
We continued our study by exploring the application of this strategy in other C-P bond-forming reactions of alkyl phosphinates that have been previously developed in our group, such as free-radical[25,26] and conjugate addition reactions,[18] base-promoted alkylation,[57] and metal-catalyzed cross-coupling.[62,63] As demonstrated in Table 7.3, the desymmetrization of tetrahedral phosphinate esters is quite general, and although additional progress is required, the results are promising. The collective data suggest that the Pd-catalyzed hydrophosphinylation reaction is probably the best model to study this process. Moreover, the use of a simplified non-chiral version of (8-(-)-phenylmenthol) (entry 4),[232] has been a key step in the development of a

complete series of experiments, thus generalizing the scope of the present desymmetrization approach.

Table 7.3 Desymmetrization of alkyl phosphinates via various C-P bond-forming reactions[a]



Entry	R*OH	Esterif. Method[b]	R*O–P(O)H Yield, %	P-C bond-forming reaction	Sustrate, Solvent (Temp, °C)	Product	Isolated Yield, %[c] (NMR Yield,%)	de,[d] %
1		A	77	Pd-cat. cross-coupling	PhI, CH_3CN (82)		(88)	11
2		A	100	Ni-cat. addition	4-octyne, CH_3CN (82)	No product	(0)	-
3a		A	100	Pd-cat. cross-coupling	PhI, CH_3CN (82)		63 (71)	11
3b				Conjugate addition	 CH_3CN (rt)		(0)	-
3c		B	100[e]	Conjugate addition	 CH_3CN (rt)		(20)	30
3d				Et_3B-mediated addition	1-octene CH_3CN (rt)		(14)	-[f]
3e		C	83	Et_3B-mediated addition	1-octene cyclohexane-CH_3CN (rt)		(38)	-[f]
4a				Addition to carbonyl	 CH_3CN (rt)		(37)	53
4b		A	100	Conjugate addition	CH_3CN (rt)		69 (74)	38
4c				Ni-cat. addition	4-octyne, CH_3C (82)	No product	(0)	-
4d				Pd-cat. cross-coupling	 CH_3CN (82)	No product	(0)	-
4e		C	90	Et_3B-mediated addition	1-octene cyclohexane-CH_3CN (rt)		46[g] (68)	33
4f				AIBN-mediated addition	1-octene cyclohexane-CH_3CN (82)		(49)	42

4g			 CH_3CN (82)		(25)	-[f]
4h	Base-promoted alkylation		MeI, THF-cyclohexane (-78-0°C)		53 (100)	21
4i			MeI, sparteine THF-cyclohexane (-78-0°C)		(72)[g]	11

[a] See Experimental Section for details of the procedures. [b] Unless otherwise indicated, the esterification methods were A (PivCl), B ($Si(OPh)_4$) or C (Dean-Stark) [Ref. 10, 14, 17-18, 52]. [c] Isolation consisted in extractive workup followed by chromatography on silica gel. [d] de was determined by the difference in heights and/or integrals in the ^{31}P NMR spectra. [e] Esterification in toluene provides also quantitative ester formation. [f] Determination of de was inaccurate. [g] Not clean conversion, reaction mixture or isolated product contains the expected products and additional unidentified compounds.

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. Stock solutions (0.5 M) of concentrated H_3PO_2 in reagent grade acetonitrile were also prepared and used for three months with out any decomposition of the acid. Triethylammonium hypophosphite was prepared according to the method described by Stawinski *et al*,[16] ammonium hypophosphite was prepared as described by Frost *et al*,[38e] anilinum hypophosphite[18,41] and alkyl phosphinates[18,33] were also prepared as previously described, from commercially available alkoxysilanes unless otherwise indicated. Stock solutions (0.5M) of alkyl phosphinates were also prepared from concentrated hypophosphorous acid and an alkoxysilane, and stored under N_2 for over a month (less than 10% decomposition).[35] Tetraphenylorthosilicate $(PhO)_4Si$ was synthesized according to the procedure described by Malatesta.[234] Unless otherwise stated, HPLC or reagent grade solvents were used. The activation of molecular sieves consisted in flaming them under vacuum (0.5 mmHg) during 20-30 min. When common anhydrous reagents and/or solvents were employed, they were prepared as follows: Et_3N, pyridine, diisopropylethylamine, diisopropylamine and *tert*-amyl alcohol were distilled under N_2 from CaH_2 and stored under N_2 over activated 4Å or 3Å (alcohol) molecular sieves. *n*-Butanol and *tert*-butanol were distilled under N_2 from sodium and either used immediately or stored under N_2 over activated 3Å molecular sieves. Anhydrous allyl alcohol was obtained by distillation from K_2CO_3 and stored under N_2 over activated 3Å molecular sieves. Other anhydrous alcohols were stored under N_2 over activated 3Å molecular sieves. Tetrahydrofuran (THF) was distilled under N_2 from sodium benzophenone ketyl, and used immediately. Anhydrous acetonitrile, toluene, benzene and dichloromethane were distilled under N_2 from

CaH_2, and used immediately. DMF and NMP were stored over activated 3Å molecular sieves, under N_2. Strictly anhydrous DMF was distilled under reduced pressure from CaH_2 (45-50°C) and stored under N_2 over activated 4Å molecular sieves. Catalysts and ligands were commonly purchased from Aldrich, Strem Chemicals or Solvias AG. Polystyrene-supported nixantphos was prepared according to the procedure described by Montchamp *et al,*[34] with a loading of 0.18 mmol/g.

Microwave Chemistry. Chemical reactions that required heating under microwave were carried out with a Biotage Initiator. Reaction mixtures were placed in Biotage® microwave vials and the reactions were heated, while stirring according to the conditions established in the computer for each run, i.e. temperature, time and power. The cooling process was accelerated with air.

Purification. Radial chromatography was carried out with a Harrison Associates Chromatotron, using 1, 2, or 4 mm layers of silica gel 60 PF_{254} containing gypsum or silica gel - glue plates. Silica gel (200-300 mesh) was used for flash chromatography. Ethyl acetate/hexanes/MeOH mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by UV, then immersed in *p*-anisaldehyde stain (by volume: 93% ethanol, 3.5% sulfuric acid, 1% acetic acid, and 2.5% anisaldehyde) followed by heating. Ion-exhange chromatography was done at low temperature (0-5°C) employing Bio-Rad AG-1-X8 anion exchange resin, and using as eluent aqueous solutions (0.05–2 M) of triethylammonium bicarbonate buffer ($Et_3NH^+HCO_3^-$ = TEAB). Fractions containing phosphorus were identified by a 'Total Phosphorus Content Assay', as described in the methods published by Avila and Ames.[235]

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 tetramethylsilane (Me_4Si, δ = 0.00 ppm) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded

at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 121 MHz and/or at 36 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid δ = 0.0 ppm). 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,[17] and a careful validation of NMR yield was verified for the hydrophosphinylation of 4-octyne with ethyl phosphinate ($EtOP(O)H_2$) using known amounts of authentic samples and then integrating the spectra (see Supporting Information from Ref. 35). Isolated yields are sometimes significantly lower because *H*-phosphinate esters are highly polar compounds and hydrolytically labile.

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

High Resolution Mass Spectrometry and Elemental Analysis. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research

Resource (Grant No. P41RR00954), or by the Mass Spectrometry Facility of the University of South Carolina. Elemental analyses were done at Atlantic Microlab, Inc., Norcross, GA.

High Performance Liquid Chromatography (HPLC) or LC/MS. Analysis by Reverse Phase Ion-Pairing HPLC was done with an Agilent Zorbax® Eclipse XDB-C8 column (4.6 x 150 mm, 5 μm) with a guard column (Agilent Zorbax® ODS, 4.6 x 12.5 mm, 5μm), using as mobile phase a Buffer (5mM hexadecyltrimethylammonium bromide, 50mM ammonium acetate, and 2% MeOH. pH 4.85, adjusted with acetic acid).[236] Chiral HPLC resolutions were done with a *(S,S)*-Whelk-01 Column (250 × 4.6 mm, 5 μm) from Regis Technologies, which was accompanied with a guard column (Agilent Zorbax® ODS, 4.6 x 12.5 mm, 5μm), using hexanes/isopropanol mixtures as the mobile phase, and the analyses and purity of the products were verified by LC/MS.

Chapter Two - Section 2.2

Representative Procedure for Table 2.2 - Method A. 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 (0.464 g, 100%).

Ethyl (1-hexyl-vinyl) phosphinate (major isomer, 94%) (Table 2.2, entry 1).[34] ^{1}H 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 (minor isomer, 6%).

Ethyl (*trans*-oct-1-enyl) phosphinate (major isomer, 88%) (Table 2.2, entry 16).[33,34] ^{1}H 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-hexyl-vinyl) phosphinate (minor isomer, 12%).

Representative Procedure for Table 2.3 - Method B. Entry 13: Pyridinium hypophosphite was first prepared by mixing equimolar amounts of 50 wt% aqueous H_3PO_2 and pyridine, followed by stirring for 1 h at rt, and evaporation and drying overnight under reduced pressure (0.1 mmHg). Then, a mixture of pyridinium hypophosphite (0.29 g, 2 mmol, 2 eq), 1-octene

(0.16 mL, 0.112 g, 1 mmol, 1 eq), Pd_2dba_3 (0.0046 g, 0.005 mmol, 1 mol% Pd) and xantphos (0.0064 g, 0.011 mmol) was heated at 85°C under N_2 for 12 h. The resulting mixture was then concentrated under high vacuum and the residue was 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 and concentration afforded the product as a light yellow solid (0.138 g, 71%).

Octyl phosphonic acid (Table 2.3, entry 13).[32] m.p. = 70-72°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.42 (bs, 2H), 1.5-1.85 (m, 4H), 1.16-1.47 (m, 10H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 31.9, 30.7, 30.5, 29.1, 25.9 (d, J_{PC} = 144 Hz), 22.7, 22.3, 14.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.81 (s); MS (EI$^+$) for $C_8H_{19}O_3P$, $[M+H]^+$ *m/z* 195.

Representative Procedure for Table 2.3 - Method E. Entry 18: To a suspension of concentrated H_3PO_2 (0.396 g, 6 mmol), $(BuO)_4Si$ (1.35 g, 4.2 mmol) and 1-octene (0.32 mL, 0.224 g, 2 mmol) in CH_3CN (12 mL) were added Pd_2dba_3 (0.0092 g, 0.01 mmol, 1 mol% Pd) and xantphos (0.0127 g, 0.022 mmol). The reaction mixture was then refluxed for 12 h. After cooling to rt, ^{31}P NMR analysis showed the product at 41.3 ppm. The mixture was diluted with EtOAc and washed with HCl (2 M) (1 x). The resulting aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aq. $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by column chromatography on silica gel (hexanes/EtOAc 3:1, v/v, EtOAc) furnished the product as a colorless oil (0.468 g, 100%).

Butyl octyl phosphinate (Table 2.3, entry 18).[25,33,104] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (dt, J_{HP} = 526 Hz, J = 2 Hz, 1H), 3.98 and 4.11 (tdd, J_{HP} = 7 Hz, J = 10 Hz, J = 8 Hz, 2H), 1.2-1.82 (m, 18 H), 0.94 (t, J = 7 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 65.9 (d, J_{POC} = 7 Hz), 32.6 (d, J_{PCC} = 6 Hz), 32.2, 31.6, 30.6 (d, J_{POC} = 16 Hz), 28.6 (d, J_{PC} = 93 Hz),

22.4, 20.6, 20.5, 18.6, 13.9, 13.4; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.29 (d, J_{PH} = 526 Hz). HRMS (EI^+) calcd. for $C_{12}H_{27}O_2P$, ($[M]^+$) 235.1827, found 235.1829.

Representative Procedure for Table 2.5. Entry 1: A mixture of a 0.5 M CH_3CN solution of H_3PO_2 (4 mL, 2 mmol, 2 eq) and 4-octyne (0.15 mL, 0.110 g, 1 mmol, 1 eq) was placed in a 2-5 mL Biotage® microwave vial and the reaction was heated for 5 min (100°C), while stirring. After cooling to rt, ^{31}P NMR analysis of the reaction mixture revealed the formation of the product at 29.9 ppm (97%). The mixture was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$. The aqueous layer was then extracted twice with EtOAc and the combined organic fractions were was washed with brine. Drying and concentration afforded the pure product as a light yellow oil (0.158 g, 90%);

(1-Propyl-pent-1-enyl) phosphinic acid (Table 2.5, Entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.1 (bs, 1 H), 7.14 (d, J_{HP} = 548 Hz, 1 H), 6.35 (dt, J = 27 Hz, J = 7 Hz, 1 H), 2.06-2.38 (m, 4 H), 1.34-1.64 (m, 4 H), 0.94 (t, J = 7 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 32.77 (dm, J = 548 Hz).

General Procedure for Tables 2.7, 2.8 and 2.9.

The unsaturated substrate (2 mmol, 1 eq) was added at room temperature to a mixture of the hypophosphorous compound (4- 6 mmol, 2-3 eq of H_3PO_2, AHP or $AlkOP(O)H_2$) in CH_3CN, or toluene, or DMF (10-12 mL). The palladium source and the ligand (2 mol% relative to the unsaturated substrate) were added and the reaction was heated to reflux (CH_3CN or Toluene) or to 85°C (DMF) under N_2 from 8-20 h. ^{31}P-NMR yields were determined on a sample of the crude reaction mixture. When the reactions were successful and unless otherwise noted, the *H*-phosphinic acids were isolated in good purity (>95%) by an acidic workup, however when using AHP an extra acidification was needed to remove the excess of aniline, which consisted in

stirring a solution of the product with amberlite resin (H^+) at room temperature, followed by filtration and concentration. On the other hand, *H*-phosphinate esters required an aqueous workup followed by purification on silica gel.

Representative Procedure for Hydrophosphinylation with H_3PO_2 - Table 2.7. Entry 1: To a solution of concentrated H_3PO_2 (0.396 g, 6 mmol) in CH_3CN (10 mL) was added 4-*tert*-butylmethylenecyclohexane (0.300 g, 2 mmol), followed by Pd_2dba_3 (0.0092 g, 0.01 mmol, 1 mol% Pd) and xantphos (0.0120 g, 0.02 mmol), at room temperature. The resulting mixture was heated at reflux under N_2 during 14 h. After cooling to room temperature, ^{31}P NMR analysis showed the products at 39.1 and 41 ppm. The mixture was then diluted with EtOAc and washed successively with 2 M aqueous HCl. The aqueous phase was extracted twice with EtOAc and the combined organic fractions were washed with brine. Drying over $MgSO_4$ and concentration afforded the mixture of isomers as an oil (0.334 g, 73%).

(4-(1,1-dimethylethyl)cyclohexyl)methyl phosphinic acid (mixture trans/cis, 7.7/1) (Table 2.7, entry 1). Major isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 10.95 (bs, 1H), 7.19 (d, J_{HP} = 541 Hz, 1H), 1.5 – 1.98 (m, 6H), 0.91 – 1.12 (m, 4H), 0.83 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 47.7, 37.1 (d, J_{PC} = 93 Hz), 37.0, 35.1 (d, J_{PCC} = 10 Hz), 32.6, 32.2, 27.7, 27.3, 22.9, 21.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.94 (dm, J_{PH} = 543 Hz); Minor isomer: ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.69 (dm, J_{PH} = 540 Hz).

Propanoic acid, 2,2-dimethyl-2-(hydroxyphosphinyl) ethyl ester (Table 2.7, entry 2). ^1H NMR ($CDCl_3$, 300 MHz) δ 10.89 (bs, 1H), 7.22 (d, J_{HP} = 561 Hz, 1H), 4.36 (dt, J = 17 Hz, J = 7 Hz, 2H), 2.17 (dtd, J = 16 Hz, J = 7 Hz, J = 2 Hz, 2H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 178.3, 58.0, 38.9, 29.7 (d, J_{PC} = 94 Hz), 27.3 (3C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.29 (d, J_{PH} = 526 Hz).

Representative Procedure for Hydrophosphinylation with (AlkO)P(O)H_2 - Table 2.7. Entry 2: To a 0.5M solution of BuOP(O)H_2 in CH_3CN (12 mL, 6 mmol, 3 eq) was added vinyl pivalate (0.30 mL, 0.256 g, 2 mmol, 1 eq), Pd_2dba_3 (0.0092 g, 0.01 mmol, 1 mol% Pd) and xantphos (0.0120 g, 0.02 mmol). The solution was heated at reflux under N_2 for 9 h. After cooling to rt, the mixture was diluted with EtOAc and washed with 2 M aqueous HCl (1 x), followed by extraction of the aqueous phase with EtOAc (2 x). Then, the organic fractions were combined and washed with saturated aqueous $NaHCO_3$ and brine. Drying and concentration furnished the crude compound, which was purified by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc). The product was obtained as a clear oil (0.500 g, 100%).

Propanoic acid, 2,2-dimethyl-2-(butoxyphosphinyl) ethyl ester (Table 2.7, entry 2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (dt, J_{HP} = 544 Hz, J = 2 Hz, 1H), 4.36 (dt, J = 17 Hz, J = 7 Hz, 2H), 4.14 and 4.05 (tdd, J_{HP} = 7 Hz, J = 8 Hz, J = 2 Hz, 2H), 2.12 – 2.26 (m, 2H), 1.70 (quint., J = 7 Hz, 2H), 1.42 (sext. J = 8 Hz, 2H), 1.21 (s, 9H), 0.95 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 178.3, 66.6 (d, J_{POC} = 7 Hz), 57.8 (d, J_{PCC} = 2 Hz), 38.8, 32.4 (d, J_{POC} = 6 Hz), 29.1 (d, J_{PC} = 94 Hz), 27.2 (3C), 18.8, 13.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.16 (dsept., J_{PH} = 544 Hz, J = 8 Hz).

Bicyclo[2.2.1]hept-2-yl-phosphinic acid (Table 2.7, entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.18 (bs, 1H), 6.90 (d, J_{HP} = 536 Hz, 1H), 2.59 (d, J = 10 Hz, 1H), 2.37 (s, 1H), 2.06 (d, J = 5 Hz, 1H), 1.40 – 1.89 (m, 5H), 1.12 – 1.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 40.8 (d, J_{PC} = 96 Hz), 37.3, 37.1, 36.4 (d, J_{PCC} = 4 Hz), 31.7 (d, J_{PCCC} = 17 Hz), 30.2 (d, J_{PCC} = 4 Hz), 28.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.54 (dm, J_{PH} = 536 Hz).

3-(Benzyloxycarbonylamino)propyl phosphinic acid (Table 2.7, entry 5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (d, J_{HP} = 548 Hz, 1H), 7.34 (m, 5H), 4.92 – 5.20 (m, 3H), 3.12 – 3.23 (m, 2H), 1.65 – 1.89 (m, 4H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.84 (dm, J_{PH} = 548 Hz).

[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-phosphinic acid (Table 2.7, entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J_{HP} = 548 Hz, 1H), 7.80 – 7.97 (m, 2H), 7.59 – 7.80 (m, 2H), 3.78 (t, J = 6 Hz, 2H), 1.88 – 2.18 (m, 2H), 1.60 – 1.88 (m, 2H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.45 (dm, J_{PH} = 548 Hz).

(*S*)-2-Benzyloxycarbonylamino-4-hydroxyphosphinoyl-butyric acid methyl ester (Table 2.7, entry 7).[151] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, J_{HP} = 555 Hz, 1H), 7.33 (m, 5H), 5.91 (bs, 1H), 5.10 (s, 2H), 4.40 (m, 1H), 3.73 (s, 3H), 2.13 (m, 1H), 1.80 – 2.0 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 172.2, 156.4, 136.4, 129.0, 128.7, 128.6, 67.6, 54.2 (d, J_{PCCC} = 16 Hz), 53.1, 25.7 (d, J_{PC} = 93 Hz), 24.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.5 (dm, J_{PH} = 555 Hz).

Representative Procedure for Tandem Hydrophosphinylation–Esterification - Table 2.7. Entry 7: To A solution of concentrated H_3PO_2 (0.356 g, 5.4 mmol, 3 eq) in CH_3CN (9 mL) were added *N*-Cbz-vinyl glycine-*O*-methyl ester (0.427 g, 1.8 mmol, 1 eq), Pd_2dba_3 (0.0165 g, 0.018 mmol, 2 mol% Pd) and xantphos (0.0231 g, 0.040 mmol). The resulting mixture was heated at reflux for 14 h. The reaction was then concentrated in vacuo and the residue was suspended in toluene (12 mL) and $(BuO)_4Si$ (1.73 g, 5.4 mmol, 3 eq) was added at room temperature. The reaction was returned to reflux temperature and heated for 20 h. After cooling to room temperature, ^{31}P NMR analysis of the reaction crude showed the product as a mixture of isomers at 37.97 and 38.33 ppm (100%). The mixture was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous layer was extracted with EtOAc (2 x). The organic layer was washed with saturated aqueous $NaHCO_3$ and then brine. Drying over $MgSO_4$, concentration and purification by column chromatography over silica gel (hexanes/EtOAc 2:1, v/v, EtOAc) to give the desired product (0.235 g, 36%).

(*S*)-2-Benzyloxycarbonylamino-4-butoxyphosphinoyl-butyric acid methyl ester (mixture of isomers, 50/50) (Table 2.7, entry 7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J_{HP} = 538 Hz, 1H),

7.36 (m, 5H), 5.61 (d, J = 2 Hz, 1H), 5.12 (s, 2H), 4.43 (m, 1H), 3.92 – 4.18 (m, 2H), 3.77 (s, 3H), 1.74 - 2.56 (m, 4 H), 1.68 (quint, J = 7 Hz, 2H), 1.39 (sext. J = 8 Hz, 2H), 0.94 (t, J = 7 Hz, 3H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.15 and 38.09 (dm, J_{PH} = 538 Hz).

Representative Procedure for Hydrophosphinylation with $PhNH_3OP(O)H_2$ - Table 2.8. Entry 1: To a solution of anilinum hypophosphite (0.955 g, 6 mmol, 3 eq) in DMF (10 mL), isoprene (0.20 mL, 0.136 g, 2 mmol, 1 eq), Pd_2dba_3 (0.0092 g, 0.01 mmol, 1 mol% Pd) and xantphos (0.0120 g, 0.02 mmol) were added in that order. The resulting mixture was heated at 85°C in an oil bath during 10 h. After this time, ^{31}P NMR analysis indicated the presence of the product at 25.8 ppm. The crude reaction mixture was concentrated by rotary evaporation (40-45°C, 0.5 mmHg) for 30 min, and then it was diluted with EtOAc and washed with 2 M aqueous HCl. The organic layer was extracted twice with EtOAc and the combined organic fractions were washed with brine, then dried over $MgSO_4$, filtered, and concentrated. The resulting oil was dissolved in CH_2Cl_2 or EtOAc and three-four tips of spatula of acidic amberlite resin were added. The suspension was stirred for 4-6 h at room temperature, followed by suction filtration on a Büchner funnel and concentration to give 0.149 g of the product as a clear oil (56%).

(3-Methyl-buten-2-yl) phosphinic acid (Table 2.8, entry 1).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.91 (bs, 1H), 6.94 (d, J_{HP} = 550 Hz, 1H), 5.13 (qq, J = 7 Hz, J = 2 Hz, 1H), 2.57 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2H), 1.77 (d, J = 6 Hz, 3H), 1.66 (d, J = 4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.4 (d, J_{PCCC} = 14 Hz), 110.6 (d, J_{PCC} = 9 Hz), 30.1 (d, J_{PC} = 92 Hz), 25.8 (d, J_{PCCCC} = 3 Hz), 18.2 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.86 (dm, J_{PH} = 550 Hz); HRMS (EI^+) calcd. for $C_5H_{11}O_2P$, ($[M]^+$) 134.0497, found 134.0494.

Geranyl phosphinic acid (*E*/*Z*, 50/50) (Table 2.8, entry 2).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.10 (bs, 1 H), 6.93 (d, J_{HP} = 552 Hz, 1 H), 5.02 – 5.21 (m, 2 H), 2.58 (dd, J_{HP} = 19 Hz, J = 8

Hz, 2 H), 2.06 (d, J = 4 Hz, 4 H), 1.76 and 1.65 [(d, J = 5 Hz) and (d, J = 4 Hz), 3 H], 1.68 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.2 (d, J_{PCCC} = 14 Hz), 142.1 (d, J_{PCCC} = 14 Hz), 132.4, 132.0, 123.9, 123.8, 111.3 (d, J_{PCC} = 9 Hz), 110.6 (d, J_{PCC} = 9 Hz), 39.9 (d, J_{PCCCC} = 3 Hz), 32.3 (d, J_{PCCCC} = 3 Hz), 30.2 (d, J_{PC} = 92 Hz), 30.1 (d, J_{PC} = 92 Hz), 26.7 (d, J_{PCCCCC} = 4 Hz), 26.5 (d, J_{PCCCCC} = 3 Hz), 25.9 (2 C), 23.7 (d, J_{PCCCC} = 3 Hz), 17.9, 17.8, 16.7 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.42 (dm, J_{PH} = 552 Hz), 36.17 (dm, J_{PH} = 552 Hz); HRMS (EI^+) calcd. for $C_{10}H_{19}O_2P$, ($[M]^+$) 202.1123, found 202.1127.

Hexen-5-yl phosphinic acid (Table 2.8, entry 3).[25] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.38 (bs, 1H), 7.10 (d, J_{HP} = 544 Hz, 1H), 5.27 – 5.86 (m, 1 H), 4.91 – 5.08 (m, 2H), 2.01 – 2.20 (m, 2H), 1.42 – 1.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.2, 115.3, 33.4, 29.7 (d, J_{PCCC} = 16 Hz), 29.1 (d, J_{PC} = 94 Hz), 20.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.96 (dm, J_{PH} = 544 Hz).

(1-Propylidene-2-methyl-propen-2-yl) phosphinic acid (Table 2.8, entry 4). Major isomer (64%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.96 (bs, 1H), 7.12 (d, J_{HP} = 565 Hz, 1H), 6.39 (dt, J_{HP} = 25 Hz, J = 7 Hz, 1H), 5.17 (s, 1H), 4.83 (s, 1H), 2.25 (qd, J = 7 Hz, J = 3 Hz, 2H), 1.92 (s, 3H), 1.04 (t, J = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 147.4 (d, J_{PCC} = 12 Hz), 138.4 (d, J_{PCC} = 10 Hz), 135.7 (d, J_{PC} = 128 Hz), 117.2 (d, J_{PCCC} = 8 Hz), 24.0, 23.0 (d, J_{PCCC} = 18 Hz), 13.6 (d, J_{PCCCC} = 5 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 27.84 (dd, J_{PH} = 515 Hz, J = 20 Hz). Minor isomer: (1-ethyl-3-methyl-butadien-1,3-yl) phosphinic acid (18%): ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.57 (dm, J_{PH} = 522 Hz) and another isomer (18%) 25.11 (dm, J_{PH} = 517 Hz).

(2-Cyclohexyl-ethen-2-yl) phosphinic acid (Table 2.9, entry 1).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.96 (bs, 1H), 6.93 (d, J_{HP} = 552 Hz, 1H), 5.07 (q, J = 7 Hz, 1H), 2.59 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2H), 2.08 – 2.21 (m, 4H), 1.47 – 1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 146.9 (d, J_{PCCC} = 14 Hz), 107.0 (d, J_{PCC} = 9 Hz), 37.4 (d, J_{PCCCC} = 3 Hz), 29.4 (d, J_{PC} = 92 Hz), 29.3 (d, J_{PCCCC} = 3 Hz), 28.7 (d, J_{PCCCCC} = 3 Hz), 28.0 (d, J_{PCCCCC} = 2 Hz), 26.8; ^{31}P NMR

($CDCl_3$, 121.47 MHz) δ 35.93 (ddd, J_{PH} = 552 Hz, J = 35 Hz, J = 2 Hz); HRMS (EI^+) calcd. for $C_8H_{15}O_2P$, ($[M]^+$) 174.0810, found 174.0807.

Cinnamyl phosphinic acid (Table 2.9, entry 2, see also **Table 5.2, entry 9).**[66,190] m.p. = 85°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.26 (bs, 1H), 7.15 – 7.43 (m, 5H), 7.01 (d, J_{HP} = 558 Hz, 1H), 6.51 (dd, J = 16 Hz, J = 5 Hz, 1H), 6.03 – 6.19 (m, 1H), 2.75 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.7 (d, J_{PCCCC} = 4 Hz), 136.2 (d, J_{PCCC} = 14 Hz), 128.8 (2C), 128.1, 126.6 (d, J_{PCCCCC} = 2 Hz, 2C), 117.0 (d, J_{PCC} = 10 Hz), 34.9 (d, J_{PC} = 90 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.32 (dm, J_{PH} = 558 Hz); HRMS (EI^+) calcd. for $C_9H_{11}O_2P$, ($[M]^+$) 182.0495, found 182.0497.

(3-Cyclohexyl-propen-2-yl) phosphinic acid (Table 2.9, entry 3). Major isomer (90%): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (bs, 1H), 6.96 (d, J_{HP} = 554 Hz, 1H), 5.51 – 5.66 (m, 1H), 5.21 – 5.37 (m, 1H), 2.55 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2H), 1.57 – 1.84 (m, 5H), 0.99 – 1.36 (m, 5H).

(2-Cyclohexyl-ethen-2-yl-vinyl) phosphinic acid (Table 2.9, entry 4). Major isomer (80%): ^1H NMR ($CDCl_3$, 300 MHz) δ 11.99 (bs, 1H), 7.08 (d, J_{HP} = 562 Hz, 1H), 6.06 (d, J = 24 Hz, 1H), 5.72 (d, J_{HP} = 6 Hz, 1H), 5.75 (d, J_{HP} = 47 Hz, 1H), 2.10 - 2.32 (m, 4H), 1.40 – 1.78 (m, 8H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 148.8 (d, J_{PCCCC} = 11 Hz), 139.5 (d, J_{PC} = 122 Hz), 128.9 (d, J_{PCCC} = 12 Hz), 114.9 (d, J_{PCC} = 11 Hz), 37.7, 29.9, 28.7, 28.3, 26.7 (2C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.34 (dm, J_{PH} = 562 Hz).

Chapter 2, Section 2.3[35]

Preparation of a Stock Solution of $AlkOP(O)H_2$. This was conducted as described in reference 18. In a typical procedure, a solution (or suspension) of concentrated H_3PO_2 (100 mmol), alkoxysilane (70 mmol for $(RO)_4Si$, or 200 mmol for $(RO)_2SiMe_2$) in the appropriate volume of solvent (CH_3CN, toluene or THF) to create a 0.5 M solution, is refluxed for 2 h under a N_2

atmosphere. After cooling to room temperature, the stock solution was kept at room temperature under N_2. Less than 10% decomposition was detected after 2 months.

Experimental Procedures for Table 2.11

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

Representative Procedure with an Alternate Work-up: Preparation of Ethyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entry 2a). To a solution of EtOP(O)H_2 (0.5 M, 10 mL, 5 mmol) in CH_3CN (prepared from $(EtO)_2SiMe_2$ as described above) was added 4-octyne (0.37 mL, 2.5 mmol) and nickel chloride (0.01 g, 0.075 mmol, 3 mol%), at room temperature (rt). The solution was refluxed under N_2 for 7 h. After cooling to rt, ^{31}P NMR analysis showed the product at 31.8 ppm. The mixture was then diluted with EtOAc and washed with dilute aqueous HCl, the resulting aqueous phase was extracted with EtOAc (3 x). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying and concentration afforded the crude compound, which was purified by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc). The product was obtained as a colorless oil (0.510 g, 100%).

General Procedure for the Hydrophosphinylation of Alkynes by Heat Activation. To the catalyst (0.05-0.075 mmol, 2-3 mol % relative to the alkyne) was added a solution of $EtOP(O)H_2$ (5 mmol) in CH_3CN (10 mL, 0.5M) at room temperature. The mixture was heated for 15min (10 min to reach reflux and 5 min at reflux) then allowed to cool back to room temperature for 15 min. This orange-red homogeneous mixture was added to the alkyne (2.5 mmol) and stirred at room temperature until completion of the reaction (NMR monitoring on a sample of the crude reaction mixture). The mixture was then concentrated in vacuo. The residue was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$, then brine. Drying on $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (hexanes, 100% v/v to EtOAc, 100% v/v).

Representative Procedure for the One-Pot Hydrophosphinylation with Anilinum Hypophosphite: Preparation of Butyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entry 1d). To a suspension of $PhNH_3OP(O)H_2$ (0.800 g, 5 mmol), $(BuO)_4Si$ (1.122 g, 3.5 mmol) and 4-octyne (0.37 mL, 2.5 mmol) in CH_3CN (10 mL) was added $NiCl_2$ (0.01 g, 0.075 mmol, 3 mol%). The reaction mixture was then refluxed for 16 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 31.2 ppm (100%). The mixture was diluted with EtOAc and washed successively with diluted HCl (1 x). The aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc) afforded the product as a colorless oil (0.521 g, 90%).

Representative Procedure with Aminosilicate/TFA: Preparation of Ethyl (*trans*-2-trimethylsilyl-vinyl) phosphinate (Table 2.11, entry 12). To a solution of concentrated H_3PO_2 (5 mmol) in HPLC grade CH_3CN (10 mL), was added 3-aminopropyltriethoxysilane (1.107 g, 5

mmol), trimethylsilylacetylene (0.35 mL, 2.5 mmol), trifluoroacetic acid (0.39 mL, 5 mmol) and nickel chloride (0.01 g, 0.075 mmol, 3 mol%), at room temperature. The solution was refluxed under N_2 for 2.5 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 25.3 ppm (98%). The mixture was then diluted with EtOAc and washed successively with diluted aqueous HCl (1 x). The aqueous phase was then extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying and concentration afforded the product as a colorless oil (0.350 g, 75%).

Methyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entry 1a). ^{1}H NMR ($CDCl_3$) δ 6.96 (d, J = 545 Hz, 1 H), 6.38 (dt, J = 26 Hz, J = 7 Hz, 1 H), 3.67 (d, J = 12 Hz, 3 H), 2.0-2.26 (m, 4 H), 1.41 (q, J = 7 Hz, 4 H), 0.87 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.4 (d, J_{PCC} = 14 Hz), 130.5 (d, J_{PC} = 123 Hz), 51.1 (d, J_{POC} = 7 Hz), 29.4 (d, J_{PCC} = 18 Hz), 27.3 (d, J_{PCCC} = 12 Hz), 20.9, 20.8, 13.1, 12.8; ^{31}P NMR ($CDCl_3$) δ 35.4 (dm, J = 545 Hz). HRMS (EI) calcd. for $C_9H_{19}O_2P$ (M^+) 190.1123, found 190.1116.

***iso*-Propyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entry 1b).** ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 540 Hz, 1 H), 6.35 (dt, J = 27 Hz, J = 6 Hz, 1 H), 4.45-4.7 (m, 1 H), 2.0-2.25 (m, 4 H), 1.34-1.53 (m, 4 H), 1.07-1.34 (m, 6 H), 0.7-1.0 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 14 Hz), 132.2 (d, J_{PC} = 125 Hz), 70.7 (d, J_{POC} = 7 Hz), 30.5 (d, J_{PCC} = 19 Hz), 28.4 (d, J_{PCCC} = 12 Hz), 24.2 (d, J_{POCC} = 4 Hz), 23.5 (d, J_{POCC} = 4 Hz), 22.5 (d, J_{PCCC} = 2 Hz), 21.9 (d, J_{PCCCC} = 1 Hz), 14.1, 13.9; ^{31}P NMR ($CDCl_3$) δ 30.0 (dm, J = 539 Hz). HRMS (EI) calcd. for $C_{11}H_{23}O_2P$ (M^+) 218.1436, found 218.1440.

Butyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entries 1c & 1d).[63] ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 542 Hz, 1 H), 6.37 (dt, J = 33 Hz, J = 7 Hz, 1 H), 3.88-4.0 (m, 2 H), 2.0-2.2 (m, 4 H), 1.55-1.63 (m, 2 H), 1.3-1.45 (m, 6 H), 0.87 (t, J = 7 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, J_{PCC} = 14 Hz), 131.19 (d, J_{PC} = 124 Hz), 65.7 (d, J_{POC} = 7 Hz), 32.6 (d, J_{POCC} = 7 Hz), 30.5 (d,

J_{PCC} = 18 Hz), 28.4 (d, J_{PCCC} = 12 Hz), 22.6, 21.9, 18.9, 14.2, 13.9, 13.7; ^{31}P NMR ($CDCl_3$) δ 33.4 (dm, J = 543 Hz). HRMS (EI) calcd. for $C_{12}H_{25}O_2P$ (M^+) 232.1592, found 232.1590.

Ethyl (1-propyl-pent-1-enyl) phosphinate (Table 2.11, entries 2a & 2b). ^{1}H NMR ($CDCl_3$) δ 6.99 (d, J = 542 Hz, 1 H), 6.36 (dt, J = 26 Hz, J = 6 Hz, 1 H), 3.89-4.1 (m, 2 H), 2.0-2.27 (m, 4 H), 1.3-1.52 (m, 4 H), 1.12-1.3 (m, 3 H), 0.72-1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.9 (d, J_{PCC} = 14 Hz), 131.6 (d, J_{PC} = 124 Hz), 61.7 (d, J_{POC} = 7 Hz), 30.3 (d, J_{PCC} = 18 Hz), 28.1 (d, J_{PCCC} = 12 Hz), 22.4, 21.7, 16.1 (d, J_{POCC} = 3 Hz), 13.9, 13.6; ^{31}P NMR ($CDCl_3$) δ 32.2 (dm, J = 543 Hz). HRMS (EI) calcd. for $C_{10}H_{21}O_2P$ (M^+) 204.1279, found 204.1275.

Ethyl (1-butyl-hex-1-enyl) phosphinate (Table 2.11, entry 3). ^{1}H NMR ($CDCl_3$) δ 7.0 (d, J_{PH} = 545 Hz), 6.36 (dt, J = 26.4 Hz, J = 7.0 Hz, 1 H), 3.95-4.1 (m, 2 H), 2.05-2.25 (m, 4 H), 1.2-1.4 (m, 11 H),0.84 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 14 Hz), 130.7 (d, J_{PC} = 124 Hz), 61.3 (d, J_{POC} = 7 Hz), 30.7 (d, J_{PCCCC} = 2 Hz), 30.0 (d, J_{PCCC} = 2 Hz), 27.4 (d, J_{PCCC} = 18 Hz), 25.3 (d, J_{PCC} = 12 Hz), 22.0, 21.7, 15.6 (d, J_{POCC} = 6Hz), 13.1, 13.1; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 33.05 (d, J_{PH} = 545 Hz). MS (EI^+): *m/z* 232 ([*M*]$^+$); HRMS (EI^+): calcd. for $C_{12}H_{25}O_2P$ 232.1592, found 232.1594.

Ethyl vinylphosphinate (Table 2.11, entry 4a).[63,237] Hydrophosphinylation of acetylene: Acetylene is produced by a slow addition of water over calcium carbide (40g, 0.62 mol) in a system previously flushed with N_2. A sulfuric acid trap followed by a drierite trap dries the resulting gas. Acetylene is bubbled gently for 2h at room temperature through a solution of pre-activated catalyst (0.01 g, 0.075 mmol, 1.5 mol%) and $ROP(O)H_2$ (0.5 M, 10 mL, 5 mmol) in CH_3CN, produced either from the appropriate alkoxysilane or the aminosilicate. The whole system is then flushed again with N_2. ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 558 Hz, 1 H), 6.1-6.4 (m, 3 H), 4.0-4.2 (m, 2 H), 1.41 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.4 (d, J_{PCC} = 4 Hz), 128.7

(d, J_{PC} = 125 Hz), 62.1 (d, J_{POC} = 7 Hz), 16.3 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.06 (d, J_{PH} = 558 Hz).

2-Ethyl-butyl vinylphosphinate (Table 2.11, entry 4b). ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 558 Hz, 1 H), 6.1-6.5 (m, 3 H), 3.9-4.1 (m, 2 H), 1.45-1.6 (m, 1 H), 1.3-1.45 (m, 4 H), 0.91 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 136.3 (d, J_{PCC} = 4 Hz), 128.8 (d, J_{PC} = 125 Hz), 67.7 (d, J_{POC} = 6 Hz), 41.7 (d, J_{POCC} = 7 Hz), 22.8, 10.9; ^{31}P NMR ($CDCl_3$) δ 25.78 (d, J_{PH} = 558 Hz).

Ethyl (1,3,3-trimethyl-but-1-enyl) phosphinate (Table 2.11, entry 5). ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J_{PH} = 546 Hz, 1 H), 6.38 (dm, J = 29.9 Hz, 1 H), 4.0-4.2 (m, 2 H), 1.92 (dd, J = 1.5 Hz, J_{PCC} = 16.1 Hz, 3 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.18 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.2 (d, J_{PCC} = 12 Hz), 125.3 (d, J_{PC} = 125 Hz), 62.0 (d, J_{POC} = 6 Hz), 34.8 (d, J_{PCCC} = 20 Hz), 30.1, 16.5 (d, J_{POCC} = 6 Hz), 11.8 (d, J_{PCC} = 13 Hz); ^{31}P NMR ($CDCl_3$) δ 35.79 (d, J_{PH} = 546 Hz). MS (EI^+): *m/z* 190 ($[M]^+$); HRMS (EI^+): calcd. for $C_9H_{19}O_2P$ 190.1123, found 190.1118.

Ethyl (*trans*-styryl) phosphinate (Table 2.11, entries 6a & 6b).[238a] ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 561 Hz, 1 H), 7.2-7.55 (m, 5 H), 6.2-6.4 (m, 2 H), 4.0-4.2 (m, 2 H), 1.33 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.9 (d, J_{PCCC} = 7 Hz), 134.6 (d, J_{PCC} = 21 Hz), 130.8, 129.1 (2 C), 128.1 (2 C), 116.5 (d, J_{PC} = 133 Hz), 62.2 (d, J_{POC} = 6 Hz), 16.6 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.7 (dm, J = 561 Hz), ^{31}P NMR ($CDCl_3$) δ 28.4. HRMS (EI) calcd. for $C_{10}H_{13}O_2P$ (M^+) 196.0653, found 196.0650.

Ethyl (1-phenyl-vinyl) phosphinate (Table 2.11, entries 6a & 6b).[238b] ^{1}H NMR ($CDCl_3$) δ 7.33-7.5 (m, 5 H), 7.32 (d, J = 564 Hz, 1 H), 6.24 (d, J = 47 Hz, 1 H), 6.18 (d, J = 24 Hz, 1 H), 4.0-4.1 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.7 (d, J_{PC} = 119 Hz), 135.4 (d, J_{PCC} = 13 Hz), 130.5 (d, J_{PCC} = 13 Hz), 129.0 (2 C), 128.6, 127.3 (d, J_{PCCC} = 6 Hz, 2 C), 62.5 (d, J_{POC} = 7 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.4 (dm, J = 564 Hz). HRMS (EI) calcd. for $C_{10}H_{13}O_2P$ (M^+) 196.0653, found 196.0650.

Ethyl (1,2-diphenyl-vinyl) phosphinate (Table 2.11, entries 7a & 7b). ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 25 Hz, 1 H), 7.29-7.44 (m, 3 H), 7.19 (d, J = 562 Hz, 1 H), 7.0-7.3 (m, 7 H), 4.1 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.4 (d, J_{PCC} = 13 Hz), 134.4 (d, J_{PCC} = 6 Hz), 134.2 (d, J_{PCCC} = 4 Hz), 132.1 (d, J_{PC} = 123 Hz), 130.6 (2 C), 129.7, 129.5, 129.4, 129.3, 129.2, 128.6 (2 C), 128.5, 62.5 (d, J_{POC} = 7 Hz), 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 29.1 (dm, J = 562 Hz). HRMS (EI) calcd. for $C_{16}H_{17}O_2P$ (M^+) 272.0966, found 272.0964.

Ethyl (1-ethylidene-but-2-ynyl) phosphinate (Table 2.11, entry 8). ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J_{PH} = 577 Hz, 1 H), 6.85 (dq, J = 19.9 Hz, J = 6.7 Hz, 1 H), 4.03 (dq, J = 9.1 Hz, J = 7.0 Hz, 2 H), 1.98 (d, J = 5.0 Hz, 3 H), 1.95 (dd, J = 7.0 Hz, J = 2.9 Hz, 3 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.2 (d, J_{PCC} = 10 Hz), 117.9 (d, J_{PC} = 134 Hz), 96.5 (d, J_{PCCC} = 8 Hz), 71.9 (d, J_{PCC} = 14 Hz), 62.1 (d, J_{POC} = 7 Hz), 17.4 (d, J_{PCCC} = 15 Hz), 16.5 (d, J_{POCC} = 6 Hz), 4.8 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 24.141 (d, J_{PH} = 577 Hz). MS (EI^+): *m/z* 172 ($[M]^+$); HRMS (EI^+): calcd. for $C_8H_{13}O_2P$ 172.0653, found 172.0651.

Ethyl (2-cyclohex-1-enyl-vinyl) phosphinate (Table 2.11, entry 9). (linear isomer): ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 555 Hz, 1 H), 7.08 (dd, J = 17.3 Hz, J = 23.5 Hz, 1 H), 6.18 (s br, 1 H), 5.64 (dd, J = 17.3 Hz, J = 21.6 Hz, 1 H), 4.05-4.2 (m, 2 H), 2.1-2.3 (m, 4 H), 1.5-1.75 (m, 4 H), 1.37 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.7 (d, J_{PCC} = 7 Hz), 139.1, 135.2 (d, J_{PCCC} = 22 Hz), 113.1 (d, J_{PC} = 137 Hz), 61.9 (d, J_{POC} = 6 Hz), 37.1 (d, J_{PCCCC} = 3 Hz), 26.6, 24.1, 22.2, 16.7 (d, J_{POCC} = 7 Hz); ^{31}P NMR ($CDCl_3$) δ 27.60 (d, J_{PH} = 555 Hz).

Ethyl (1-cyclohex-1-enyl-vinyl) phosphinates (Table 2.11, entry 9). (branched isomer): ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J_{PH} = 550 Hz, 1 H), 6.37 (s br, 1 H), 5.91 (d, J = 50.4 Hz, 1 H), 5.86 (d, J = 26.9 Hz, 1 H), 4.05-4.2 (m, 2 H), 2.1-2.25 (m, 4 H), 1.55-1.75 (m, 4 H), 1.38 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.0 (d, J_{PC} = 118 Hz), 132.2 (d, J_{PCCC} = 10 Hz), 130.8 (d, J_{PCCCC} = 7

Hz), 124.7 (d, J_{PCC} = 15 Hz), 62.4 (d, J_{POC} = 6 Hz), 26.2 (d, J_{PCCC} = 7 Hz), 26.7, 22.6, 22.0, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 32.28 (d, J_{PH} = 558 Hz).

Ethyl (1-ethoxy-vinyl) phosphinate (Table 2.11, entry 10). ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, J = 581 Hz, J = 1.2 Hz, 1 H), 5.15 (dd, J = 13.2 Hz, J = 3.2 Hz, 1 H), 4.91 (ddd, J = 35 Hz, J = 3.2 Hz, J = 1.2 Hz, 1 H), 4.1-4.2 (m, 2 H), 3.86 (q, J = 7.0 Hz, 2 H), 1.35-1.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.3 (d, J_{PC} = 160 Hz), 98.2 (d, J_{PCC} = 25 Hz), 64.4 (d, J_{POC} = 9 Hz), 62.3 (d, J_{PCOC} = 6 Hz), 16.3 (d, J_{POCC} = 6 Hz), 14.2; ^{31}P NMR ($CDCl_3$) δ 19.23 (d, J_{PH} = 581 Hz).

Ethyl (*trans*-oct-1-enyl) phosphinate (Table 2.11, entry 11). (major isomer, 68%). ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 555 Hz, 1 H), 6.7-6.9 (m, 1 H), 5.78 (m, 1 H), 4.0-4.2 (m, 2 H), 2.15-2.3 (m, 2 H), 1.2-1.55 (m, 8 H), 1.37 (t, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.1 (d, J_{PCC} = 5 Hz), 119.7 (d, J_{PC} = 131 Hz), 61.8 (d, J_{POC} = 6 Hz), 34.3 (d, J_{PCC} = 20 Hz), 31.6, 28.7, 27.7, 22.6, 16.4 (d, J_{POCC} = 6 Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 25.56 (dm, J = 547 Hz). Minor isomer: Ethyl (1-hexyl-vinyl) phosphinate (21%): ^{31}P NMR ($CDCl_3$) δ 30.3 (dm, J = 553 Hz).

Ethyl (*trans*-2-trimethylsilyl-vinyl) phosphinate (Table 2.11, entry 12). ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 558 Hz, 1 H), 7.13 (dd, J = 37 Hz, J = 21 Hz, 1 H), 6.29 (ddd, J = 32 Hz, J = 21 Hz, J = 1.5 Hz, 1 H), 4.01 (q, J = 7 Hz, 2 H), 1.24 (t, J = 7 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.0 (d, J_{PCC} = 3 Hz), 136.2 (d, J_{PC} = 119 Hz), 64.7 (d, J_{POC} = 7 Hz), 18.4 (d, J_{POCC} = 6 z), 0.0 (s, 3 C); ^{31}P NMR ($CDCl_3$) δ 27.0 (dt, J = 558 Hz, J = 32 Hz).

Ethyl (1-butyl-2-trimethylsilyl-vinyl) phosphinate (Table 2.11, entry 13a). ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 544 Hz, 1 H), 6.46 (d, J = 46 Hz, 1 H), 3.9-4.1 (m, 2 H), 2.2-2.4 (m, 2 H), 1.2-1.5 (m, 4 H), 1.22 (t, J = 7.0 Hz, 3 H), 0.80 (t, J = 7 Hz, 3 H), 0.07(s, 9 H); ^{13}C NMR ($CDCl_3$) δ 149.6 (d, J_{PC} = 95 Hz), 146.8 (d, J_{PCC} = 3 Hz), 62.3 (d, J_{POC} = 7 Hz), 32.6, 31.7 (d, J_{PCC} = 15 Hz), 23.3, 16.7 (d, J_{POCC} = 6 Hz), 14.2, 0.0; ^{31}P NMR ($CDCl_3$) δ 40.16 (d, J_{PH} = 544 Hz).

Ethyl (1-propyl-2-trimethylsilyl-vinyl) phosphinate (Table 2.11, entry 13b). ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 544 Hz, 1 H), 6.61 (d, J = 38.7 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.25-2.5 (m, 2 H), 1.5-1.65 (m, 2 H), 1.37 (t, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 150.3 (d, J_{PC} = 110 Hz), 147.3 (d, J_{PCC} = 5 Hz), 62.7 (d, J_{POC} = 7 Hz), 34.3 (d, J_{PCC} = 16 Hz), 24.1, 17.0(d, J_{POCC} = 6 Hz), 14.9, 0.4; ^{31}P NMR ($CDCl_3$) δ 33.52 (d, J_{PH} = 543 Hz).

Ethyl (3-methyl-but-2-enyl) phosphinate (Table 2.11, entry 14). ^{1}H NMR ($CDCl_3$) δ 6.95 (d, J = 538 Hz, 1H), 5.11 (q, J = 7 Hz, 1H), 4.0-4.25 (m, 2H), 2.45-2.65 (m, 2H), 1.77 (d, J = 6 Hz, 3H), 1.67 (d, J = 4Hz, 3H), 1.36 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4 (d, J_{PCCC} = 14 Hz), 110.5 (d, J_{PCC} = 9 Hz), 62.5 (d, J_{POC} = 7 Hz), 30.0 (d, J_{PC} = 92 Hz), 25.9 (d, J_{PCCCC} = 4 Hz), 18.2 (d, J_{PCCCC} = 3 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 40.2 (d, J = 538 Hz); HRMS (EI) calcd. for $C_7H_{15}O_2P$ (M^+) 162.0810, found 162.0802.

Butyl (2-pyridin-2-yl-ethyl) phosphinate (Table 2.11, entry 15). ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 4.7 Hz, 1 H), 7.62 (td, J = 7.6 Hz, J = 1.7 Hz, 1 H), 7.20 (d, J = 7.9 Hz, 1 H), 7.18 (d, J_{PH} = 538 Hz, 1 H), 7.15 (dd, J = 4.7 Hz, J = 7.6 Hz, 1 H), 3.9-4.2 (m, 2 H), 3.05-3.2 (m, 2 H),2.2-2.35 (m, 2 H), 1.6-1.75 (m, 2 H), 1.3-1.5 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.8, 149.6, 136.8, 123.1, 121.9, 66.4 (d, J_{POC} = 7 Hz), 32.6 (d, J_{PCC} = 6 Hz), 29.4 (d, J_{POCC} = 2 Hz), 28.2 (d, J_{PC} = 94 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 39.36 (d, J_{PH} = 538 Hz). HRMS (ES^+): calcd. for $C_{11}H_{19}NO_2P$ (M^+) 228.1153, found 228.1146.

Ethyl (3-cyclohexyl-propen-2-yl) phosphinate (Eq. 2.1) (linear isomer)**.** ^{1}H NMR ($CDCl_3$) δ 6.94 (dt, J_{PH} = 540 Hz, J = 2.0 Hz, 1 H), 5.50-5.65 (m, 1 H), 5.20-5.35 (m, 1 H), 4-4.25 (m, 2 H), 2.57 (ddm, J = 19.0Hz, J = 7.4 Hz, 2 H), 1.9-2.05 (m, 1 H), 1.6-1.75 (m, 5 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.0-1.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 143.9 (d, J_{PCC} = 14 Hz), 114.2 (d, J_{PCCC} = 9

Hz), 62.6 (d, J_{POC} = 7 Hz), 41.1 (d, J_{PCCCC} = 3 Hz), 33.7 (d, J_{PC} = 91 Hz), 33.0, 26.3, 26.1, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 39.10 (dm, J_{PH} = 539 Hz).

Ethyl (2-cyclohexyl-1-methyl-vinyl) phosphinate (Eq. 2.1) (branched isomer). ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J_{PH} = 544 Hz, 1 H), 6.28 (ddd, J = 26.1 Hz, J = 9.4 Hz, J = 1.5 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.3-2.45 (m, 1 H), 1.81 (dd, J = 15.0 Hz, J = 1.5 Hz, 3 H), 1.6-1.8 (m, 5 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.1-1.4 (m, 5 H); 31P NMR ($CDCl_3$, Me_4Si) δ 33.44 (dm, J_{PH} = 554 Hz).

Tandem Reactions (Table 2.13).

Diethyl (1-propyl-pent-1-enyl) phosphonate (Table 2.13, entry 1).[239] To 4-octyne (0.275 g, 2.50 mmol) and $NiCl_2$ (9.7 mg, 0.076 mmol, 3.0 mol%) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added CCl_4 (8 mL, 12.7g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9g, 29mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with EtOAc The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (299 mg, 48%) as an oil. ^{1}H NMR ($CDCl_3$) δ 6.48 (dt, J = 24 Hz, J = 7 Hz, 1 H), 3.97 (q, J = 7 Hz, 4 H), 2.05-2.18 (m, 4 H), 1.25-1.40 (m, 4 H), 1.24 (t, J = 7 Hz, 6 H), 0.86 (dt, J =3 Hz, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 147.6 (J_{PCC} = 10 Hz), 129.4 (J_{PC} = 175 Hz), 61.5 (J_{POC} = 6 Hz), 30.7 (J_{PCCC} = 19 Hz), 29.6 (J_{PCC} = 11 Hz), 22.6 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.5 (J_{POCC} = 7 Hz), 14.3, 14.0; ^{31}P NMR ($CDCl_3$) δ 23.47. MS (EI^+) m/z 248 (M^+); HRMS (EI^+) calcd. for $C_{12}H_{25}O_3P$ 248.1541, found 248.1534.

Diethyl (1,3,3-trimethyl-but-1-enyl) phosphonate (Table 2.13, entry 2). To 4,4-dimethyl-2-pentyne (0.240 g, 2.50 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred

at reflux for 24 h. To the reaction mixture was added CCl_4 (8 mL, 12.7g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9g, 29mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. The solution was quenched with 1M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (354 mg, 57%) as an oil. ^{1}H NMR ($CDCl_3$) δ 6.54 (ddd, J = 27 Hz, J = 1.47 Hz, J = 0.59 Hz, 1 H), 3.9-4.1 (m, 4 H), 1.88 (ddd, J = 15.8 Hz, J = 1.47 Hz, J = 0.59 Hz, 3 H), 1.28 (t, J = 7 Hz, 6 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.8 (d, J_{PCC} = 4 Hz), 123.2 (d, J_{POC} = 175 Hz), 61.7 (d, J_{POC} = 6 Hz), 34.5 (d, J_{PCCC} = 21 Hz), 30.2, 16.5 (d, J_{POCC} = 6Hz), 13.5 (d, J_{PCC} = 10 Hz); ^{31}P NMR ($CDCl_3$) δ 24.44. MS (EI^+): *m/z* 234 (M^+); HRMS (EI^+) calcd. for $C_{11}H_{23}O_3P$ 234.1585, found 234.1380.

(1-Propyl-pent-1-enyl)-phosphonothioic acid *O*-ethyl ester (Table 2.13, entry 3). To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.0 mg, 0.077 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture were added at room temperature sulfur (0.24g, 7.5 mmol) and triethylamine (0.762g, 7.53 mmol), and the resulting mixture was stirred at room temperature overnight. The solution was extracted with hexane, the acetonitrile layer was partitioned between 1 M HCl and EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to hexanes/EtOAc, 90/10% v/v) produced the expected compound (424 mg, 70%) as a brown oil. ^{1}H NMR ($CDCl_3$) δ 6.66 (dt, J = 27.5 Hz, J = 7.2 Hz, 1 H), 6.4-6.65 (bs, 1 H), 4.05-4.2 (m, 2H), 2.25-2.4 (m, 2 H), 2.1-2.25 (m, 2 H), 1.4-1.6 (m, 4 H), 1.33 (t, J = 7.0 Hz, 3 H), 0.95 (dt, J = 2.3 Hz, J = 7.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.6 (d, J_{PCC} = 13.8 Hz), 134.1 (d, J_{PC} = 141 Hz), 62.3 (d, J_{POC} = 6 Hz), 30.9 (d, J_{PCCC} = 20 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1, 22.2, 16.3 (d, J_{POCC} =

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

Ethyl phenyl-(1-propyl-pent-1-enyl) phosphinate (Table 2.13, entry 4). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture was added iodobenzene (1.5 g, 7.51 mmol), $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol, 1.9 mol%), and triethylamine (1.52 g, 15.1 mmol) at room temperature. The resulting mixture was stirred at reflux overnight. The solution was concentrated, partitioned between 1 M $NaHSO_4$ and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (419 mg, 58%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.64 (ddd, J = 11.7 Hz, J = 1.5 Hz, J = 0.6 Hz, 2 H), 7.29-7.45 (m, 3 H), 6.39 (dt, J = 22.28 Hz, J = 7.33 Hz, 1 H), 3.91 (ddq, J = 22.4 Hz, J = 10.1 Hz, J = 7.04 Hz, 2 H), 1.96-2.10 (m, 4 H), 1.25-1.40 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.0-1.2 (m, 2 H), 0.79 (t, J = 7.33 Hz, 3 H), 0.70 (t, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.4 (J_{PCC} = 10 Hz), 131.9 (J_{PC} = 127.5 Hz), 131.5 (J_{PCCCC} = 3 Hz), 131.3 (J_{PCC} = 10 Hz), 131.0 (J_{PC} = 131 Hz), 128.0 (J_{PCCC} = 12 Hz), 60.2 (J_{POC} = 6 Hz), 30.3 (J_{PCCC} = 17 Hz), 28.9 (J_{PCC} = 12 Hz), 22.5 (J_{PCCC} = 2 Hz), 21.6 (J_{PCCCC} = 1 Hz), 16.1 (J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$) δ 35.89. MS (EI^+): *m/z* 280 (M^+); HRMS (EI^+): calcd. for $C_{16}H_{25}O_2P$ 280.1592, found 280.1588.

Ethyl (2-cyano-ethyl)-(1-propyl-ent-1-enyl) phosphinate (Table 2.13, entry 5). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 2.9 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture was added acrylonitrile (0.403g, 7.6 mmol) and DBU (1.1g, 7.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The

solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (415 mg, 63%) as an oil. ^{1}H NMR ($CDCl_3$) δ 6.58 (dt, J = 21.40 Hz, J = 7.33 Hz, 1 H), 3.95-4.16 (m, 1 H), 3.82-3.96 (m, 1 H), 2.56-2.70 (m, 6 H), 1.35-1.60 (m, 6 H), 1.32 (t, J = 7.33 Hz, 3 H), 0.98 (t, J = 7.04 Hz, 3 H), 0.95 (t, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.8 (J_{PCC} = 9 Hz), 130.7 (J_{PC} = 118 Hz), 119.0 (J_{PCCC} = 17 Hz), 60.7 (J_{POC} = 6 Hz), 31.1 (J_{PCCC} = 16 Hz), 29.5 (J_{PCC} = 12 Hz), 24.5 (J_{PC} = 97 Hz), 23.2 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.7 (J_{POCC} = 6 Hz), 14.5, 14.1, 10.8 (J_{PCC} = 2 Hz); ^{31}P NMR ($CDCl_3$) δ 43.25. MS (EI^+): *m/z* 257 (M^+); HRMS (EI^+): calcd. for $C_{13}H_{24}NO_2P$ 257.1545, found 257.1547.

Benzyl 3-[ethoxy-(1-ethylidene-but-2-ynyl)-phosphinoyl] propionate (Table 2.13, entry 6). To 2,4-hexadiyne (0.199 g, 2.55 mmol) and $NiCl_2$ (7.0 mg, 0.054 mmol, 2.1 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added benzyl acrylate (1.22g, 7.5 mmol) and DBU (1.12g, 7.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (271 mg, 32%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.3-7.4 (br, 5 H), 6.9-7.1 (m, 1 H), 5.13 (s, 2 H), 3.85-4.2 (m, 2 H), 2.55-2.8 (m, 2 H), 2.1-2.3 (m, 2 H), 1.95-2.05 (m, 6 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2 (d, J_{PCCC} = 19 Hz), 152.1 (d, J_{PCC} = 8 Hz), 135.7, 128.6, 128.3, 128.2, 117.3 (d, J_{PC} = 128 Hz), 95.5 (d, J_{PCCC} = 8 Hz), 73.1 (d, J_{PCC} = 13 Hz), 66.6, 60.7 (d, J_{POC} = 7 Hz), 26.7 (d, J_{PCC} = 2 Hz), 22.5 (d, J_{PC} = 106 Hz), 17.3 (d, J_{PCCC}

= 14 Hz), 16.4 (d, J_{POCC} = 7 Hz), 4.7 (d, J_{PCCCC} = 2 Hz); ^{31}P NMR ($CDCl_3$) δ 41.41. MS (EI^+): *m/z* 334 (M^+); HRMS (EI^+): calcd. for $C_{18}H_{23}O_4P$ 334.1334, found 334.1340.

Ethyl allyl-(1-propyl-pent-1-enyl) phosphinate (Table 2.13, entry 7). To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.1 mg, 0.078 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture was added at room temperature BSA (1.46g, 7.2 mmol) and after 5 min of stirring allyl chloride (0.582g, 7.61 mmol) was added. The mixture was stirred at reflux for 3 h. The reaction mixture was then cooled down, quenched by saturated $NaHCO_3$, extracted with EtOAc and the combined organic phases washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (475 mg, 76%) as an oil. ^{1}H NMR ($CDCl_3$) δ 6.48 (dt, *J* = 21.1 Hz, *J* = 7.3 Hz, 1 H), 5.7-5.85 (m, 1 H), 5.1-5.22 (m, 2 H), 3.85-4.2 (m, 2 H), 2.5-2.75 (m, 2 H), 2.1-2.25 (m, 4 H), 1.35-1.55 (m, 4 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.7 (d, J_{PCC} = 9 Hz), 130.7 (d, J_{PC} = 116 Hz), 127.3 (d, J_{PCC} = 9 Hz), 119.5 (d, J_{PCCC} = 13 Hz), 59.9 (d, J_{POC} = 6 Hz), 34.0 (d, J_{PC} = 94 Hz), 30.1 (d, J_{PCCC} = 13 Hz), 29.1 (d, J_{PCC} = 12 Hz), 22.4 (d, J_{PCCCC} = 1 Hz), 21.6 (d, J_{PCCC} = 1 Hz), 16.8 (d, J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$) δ 45.18. MS (EI^+): *m/z* 244 (M^+); HRMS (EI^+): calcd. for $C_{13}H_{25}O_2P$ 244.1592, found 244.1587.

Ethyl methyl-(1-propyl-pent-1-enyl) phosphinate (Table 2.13, entry 8). To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added at room temperature BSA (1.46g, 7.2 mmol) and, after 5 min of stirring, dimethyl sulfate (0.633g, 5.02 mmol). To the mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by saturated $NaHCO_3$, extracted

with EtOAc and the combined organic phases washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (343 mg, 62%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.55 (dt, J = 21.4 Hz, J = 7.3 Hz, 1 H), 3.8-4.05 (m, 2 H), 2.1-2.25 (m, 4 H), 1.49 (d, J = 13.8 Hz, 3 H), 1.35-1.55 (m, 4 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.0 (d, J_{PCC} = 9 Hz), 132.5 (d, J_{PC} = 118 Hz), 59.9 (d, J_{POC} = 6 Hz), 30.9 (d, J_{PCCC} = 16 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.0 (d, J_{PCCCC} = 1 Hz), 22.2 (d, J_{PCCC} = 1 Hz), 14.5, 14.5 (d, J_{PC} = 99 Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 45.77. MS (EI^+): *m/z* 218 (M^+); HRMS (EI^+): calcd. for $C_{11}H_{23}O_2P$ 218.1436, found 218.1438.

Methyl-phenyl-(1-propyl-pent-1-enyl) phosphine oxide (Table 2.13, entry 9). To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. The mixture was then concentrated in high vacuo. The residue was diluted with 5 mL of dry THF. To the mixture at 0°C was added 7.5 mL (7.5 mmol) of phenylmagnesium bromide (1 M solution in THF). The mixture was warmed to room temperature and then stirred at reflux for 1.5 h. After addition of methyl iodide at 0°C (1.08 g, 7.61 mmol), the mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then quenched with 10 mL of 1 M HCl, extracted with EtOAc and the combined organic phases were washed with 1 M sodium thiosulfate, and then brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (334 mg, 53%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.65-7.8 (m, 2 H), 7.4-7.55 (m, 3 H), 6.41 (dt, J = 21.1 Hz, J = 7.3 Hz, 1 H), 2.0-2.25 (m, 4 H), 1.8 (d, J = 12.9 Hz, 3 H), 1.42-1.46 (m, 2 H), 1.20-1.35 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.5 (d, J_{PCC} = 9 Hz), 134.4 (d, J_{PC} = 94 Hz), 133.9 (d, J_{PC} = 98 Hz), 131.4 (d,

J_{PCCCC} = 3 Hz), 130.4 (d, J_{PCC} = 10 Hz), 128.5 (d, J_{PCCC} = 12 Hz), 30.8 (d, J_{PCCC} = 15 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1, 22.1, 14.9 (d, J_{PC} = 72 Hz), 14.3, 13.9; ^{31}P NMR ($CDCl_3$) δ 33.74. MS (EI^+): *m/z* 250 (M^+); HRMS (EI^+): calcd. for $C_{15}H_{23}OP$ 250.1487, found 250.1488.

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

Hydrophosphinylation with EtOP(O)D$_2$. Deuterated ethyl (1-propyl-pent-1-enyl) phosphinate (Eq. 2.2). General procedure for hydrophosphinylation is used on 4-octyne (279 mg, 2.53 mmol) using a stock solution of $(EtO)P(O)D_2$. After 3 h at reflux, the mixture is concentrated and directly purified by radial chromatography (EtOAc/Hexanes, 50/50 % v/v to EtOAc, 100% v/v) to afford the expected compound (370 mg, 71%, %D > 80%). Measurements for deuterium incorporation were conducted by integration of the ^{1}H NMR spectra. Mass spectrometric determination is problematic because the exchange of P(O)(OEt)D to P(O)(OEt)H in the product must be complete. ^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 543 Hz, 1 H), 4.0-4.2 (m, 2 H), 2.15-2.3 (m, 4 H), 1.4-1.6 (m, 4 H), 1.37 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 6 H).^{13}C NMR ($CDCl_3$) δ 147.0 (dt, J_{PCC} = 13 Hz, J_{CD} = 35 Hz), 131.9 (d, J_{PC} = 123 Hz), 61.9 (d, J_{POC} = 7 Hz),

30.6 (d, J_{PCCC} = 18 Hz), 28.5 (d, J_{PCC} = 12 Hz), 22.7 (d, J_{PCCC} = 2 Hz), 22.1 (d, J_{PCCC} = 2 Hz), 16.5 (d, J_{POCC} = 6 Hz), 14.3, 14.1. ^{31}P NMR ($CDCl_3$) δ 32.78 (d, J = 542 Hz).

Chapter Three[63]

Table 3.1, Method B.[18] Entry 1: A solution of anilinium hypophosphite (0.952 g, 6 mmol) and tetrabutoxysilane (1.933 g, 6 mmol) in CH_3CN (12 mL) was refluxed for 2 h, under N_2. After cooling to rt, iodobenzene (0.25 mL, 2 mmol), anhydrous Et_3N (0.30 mL, 2 mmol), and $Cl_2Pd(PPh_3)_2$ (0.025 g, 0.04 mmol), were added successively. The reaction mixture was then refluxed for 5 h. At that point, the black mixture was concentrated under reduced pressure, and the residue partitioned between EtOAc and aqueous $KHSO_4$. The organic layer was washed successively with saturated aqueous $NaHCO_3$ (1 x), and brine (1 x). Drying, concentration, and purification by radial chromatography (4 mm thickness, hexane, EtOAc/hexane 1:1, v/v, EtOAc) afforded butyl phenylphosphinate (0.300 g, 80%).

Table 3.1, Method B. Entry 12: To a solution of 3-bromoquinoline (0.425 g, 2 mmol), $(BuO)_4Si$ (1.923 g, 6 mmol) in DMF (12 ml), were added anilinium hypophosphite (0.955 g, 6 mmol), 1,4-diazabicyclo[2.2.2]octane (0.676 g, 6 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), 1,3-bis(diphenylphosphino)propane (0.018 g, 0.044 mmol). The resulting mixture was heated at 85°C for 2 h. The reaction mixture was concentrated in vacuo, the residue was treated with brine (15 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc 7:3, v/v, EtOAc) afforded butyl quinolin-3-yl phosphinate (0.322 g, 65% yield).

Table 3.1, Method C. Entry 8: To a suspension of anilinum hypophosphite (0.382 g, 2.4 mmol) and 3-aminopropyltriethoxysilane (0.531 g. 2.4 mmol) in CH_3CN (12 ml), was added 2-bromonaphthalene (0.414 g, 2 mmol), $Pd(OAc)_2$ (0.009 g, 0.040 mmol), and 1,3-

bis(diphenylphosphino)propane (0.0182 g, 0.044 mmol). The reaction mixture was heated at reflux for 18 h. After cooling to rt, ^{31}P NMR analysis showed the product at 25.8 ppm (90%). The mixture was then diluted with EtOAc and washed successively with aq. HCl (1 M). The aq. phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aq. $NaHCO_3$ (1 x) and brine. Drying over $MgSO_4$ and concentration afforded ethyl 2-naphthylphosphinate (0.387 g, 88%).

Table 3.2[63]

Entry 1: To a solution of benzyl chloride (0.253 g, 2 mmol), $(BuO)_4Si$ (1.923 g, 6 mmol) in CH_3CN (12 ml), were added anilinium hypophosphite (0.955 g, 6 mmol), 1,4-diazabicyclo[2.2.2]octane (0.676 g, 6 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.0266 g, 0.048 mmol). The resulting mixture was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo, the residue was treated with HCl (1 M, 15 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc 7:3, v/v, EtOAc) afforded butyl benzylphosphinate. (0.357 g, 78%)

Note: for entries 3 & 4, the difference in workup was that brine was used instead of 1 M HCl above. For entry 4, 10 mmol AHP was used instead of 6 mmol.

Table 3.3[63]

Method A. Preparation of Ethyl (vinyl-2-cyanoethyl) phosphinate (entry 1). A mixture of anilinum hypophosphite (0.955 g, 6 mmol), in CH_3CN (12 ml) was placed in a pressure tube. 3-Aminopropyltriethoxysilane (1.328 g, 6 mmol), vinyl bromide (1 M in CH_3CN, 3 mL, 3 mmol), $Pd(OAc)_2$ (0.0135 g, 0.06 mmol), and 1,1'-bis(diphenylphosphino)ferrocene (0.0400 g, 0.072 mmol) were then added in that order. The mixture was heated at 85°C for 6 h. After cooling to rt, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.90 mL, 6 mmol) and acrylonitrile (0.40 mL, 6 mmol)

were added in the same reaction tube and the reaction was stirred overnight under nitrogen. After this time, ^{31}P NMR analysis showed the product at 38.3 ppm (72%). The mixture was then diluted with EtOAc and washed successively with aq. HCl (1 M). The aq. phase was then extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aq. $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, EtOAc to MeOH) afforded the product as a dark yellow oil (0.156 g, 30%).

Preparation of Ethyl (1-bromo-oct-1-enyl) phosphinate (entry 7). To a mixture of anilinum hypophosphite (0.955 g, 6 mmol) and 3-aminopropyltriethoxysilane (1.328 g. 6 mmol) in CH_3CN (12 ml), was added 1,1-dibromo-octene (0.540 g, 2 mmol), $Pd(OAc)_2$ (0.009 g, 0.040 mmol), and 1,1'-bis(diphenylphosphino)ferrocene (0.0270 g, 0.048 mmol). The resulting mixture was heated at reflux for 7 h. The mixture was then diluted with EtOAc and washed successively with aq. HCl (1 M). The aq. phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aq. $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc) afforded the product as a light yellow oil (0.272 g, 48%).

Method B. Entry 9: A mixture of anilinum hypophosphite (0.955 g, 6 mmol) and $(BuO)_4Si$ (1.346 g, 4.2 mmol) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen and then cooled to rt. To the resulting mixture was added *tert*-butyl-1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate (0.663 g, 2.0 mmol), anhydrous Et_3N (0.28 mL, 2.0 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol) and 1,3-bis(diphenylphosphino)propane (0.0182 g, 0.044 mmol). The reaction was then refluxed under nitrogen for 8 h. After cooling to rt, ^{31}P NMR analysis showed the product at 26.0 ppm (100%). The mixture was diluted with EtOAc and washed with aq. $NaHSO_4$ (1 M). The resulting aq. phase was extracted with EtOAc (3 x) and the combined organic layers were washed with saturated aq. $NaHCO_3$ (1 x) and brine.

Drying over $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc). The product was obtained as a yellow oil (0.576 g, 95%).

Butyl phenylphosphinate (Table 3.1, entry 1). ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 7 Hz, 1 H), 7.76 (J = 7 Hz, 1 H), 7.58 (d, J = 562 Hz, 1 H), 7.55-7.6 (m, 1 H), 7.45-7.55 (m, 2 H), 3.95-4.15 (m, 2 H), 1.6-1.8 (m, 2 H), 1.35-1.5 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 132.4 (d, J_{PCCCC} = 3 Hz), 130.3 (d, J_{PCCC} = 12 Hz), 129.4 (d, J_{PC} = 132 Hz), 128.1 (d, J_{PCC} = 14 Hz), 65.1 (d, J_{POC} = 7 Hz), 31.8 (J_{POCC} = 6 Hz), 18.2, 12.9; ^{31}P NMR ($CDCl_3$) δ 25.3 (dm, $J_{P\text{-}H}$ = 563 Hz).

Ethyl phenylphosphinate (Table 3.1, entry 1). ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 14 Hz, 1 H), 7.79 (d, J = 14 Hz, 1 H), 7.60 (d, J = 563 Hz, 1 H), 7.55-7.60 (m, 1 H), 7.50-7.55 (m, 1 H), 4.15-4.20 (m, 2 H), 1.39 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 133.1 (d, J_{PCCCC} = 3 Hz), 130.9 (d, J_{PCCC} = 12 Hz), 130.0 (d, J_{PC} = 132 Hz), 128.8 (d, J_{PCC} = 14 Hz), 62.0 (d, J_{POC} = 6 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.7 (dm, $J_{P\text{-}H}$ = 562 Hz).

Butyl (*o*-tolyl) phosphinate (Table 3.1, entry 2). ^{1}H NMR ($CDCl_3$) δ 7.82 (dd, J = 16, 7 Hz, 1 H), 7.64 (d, J = 555 Hz, 1 H), 7.40-7.50 (m, 1 H), 7.25-7.35 (m, 2 H), 4.05-4.15 (m, 2 H), 2.57 (s, 3 H), 1.65-1.80 (m, 2 H), 1.35-1.50 (m, 2 H), 0.93 (t, J = 7Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.1 (d, J_{PCC} = 11 Hz), 132.9 (d, J_{PCCCC} = 7 Hz), 131.9 (d, J_{PCCC} = 13 Hz), 131.1 (d, J_{PCCC} = 12 Hz), 128.1 (d, J_{PC} = 131 Hz), 125.8 (d, J_{PCC} = 14 Hz), 65.8 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 7 Hz), 19.9 (d, J_{PCCC} = 7 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 26.9 (dm, $J_{P\text{-}H}$ = 555 Hz); HRMS (FAB) calcd. for $C_{11}H_{17}O_2P$, $(M+Li)^+$ 219.1126, found 219.1122.

Butyl (3-chlorophenyl) phosphinate (Table 3.1, entry 3). ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 14 Hz, 1 H), 7.65-7.70 (m, 1 H), 7.58 (d, J = 570 Hz, 1 H), 7.55-7.60 (m, 1 H), 7.45-7.50 (m, 1 H), 4.05-4.15 (m, 2 H), 1.70-1.75 (m, 2 H), 1.40-1.50 (m, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR

($CDCl_3$) δ 135.2 (d, J_{PCCC} = 18 Hz), 133.2 (d, J_{PCCCC} = 3 Hz), 132.2 (d, J_{PC} = 130 Hz), 130.9 (d, J_{PCC} = 13 Hz), 130.3 (d, J_{PCCC} = 15 Hz), 129.0 (d, J_{PCC} = 11 Hz), 66.7 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 23.5 (dm, J = 570 Hz); HRMS (FAB) calcd. for $C_{10}H_{14}ClO_2P$, $(M+Li)^+$ 239.0580, found 239.0586.

Butyl (4-methoxyphenyl) phosphinate (Table 3.1, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.70-7.75 (m, 2 H), 7.55 (d, J = 561 Hz, 1 H), 7.00-7.05 (m, 2 H), 4.05-4.10 (m, 2 H), 3.85 (s, 3 H), 1.65-1.75 (m, 2 H), 1.40-1.45 (m, 2 H), 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, J_{PCCCC} = 3 Hz), 133.0 (d, J_{PCC} = 13 Hz), 121.1 (d, J_{PC} = 139 Hz), 114.3 (d, J_{PCCC} = 15 Hz), 65.4 (d, J_{POC} = 7 Hz), 55.4, 32.5 (d, J_{POCC} = 6 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.9 (dm, J = 561 Hz); HRMS (FAB) calcd. for $C_{11}H_{17}O_3P$, $(M+Li)^+$ 235.1075, found 235.1084.

Butyl (4-aminophenyl) phosphinate (Table 3.1, entry 5). ^{1}H NMR ($CDCl_3$) δ 7.55 (dd, J = 13 Hz, J = 8 Hz, 2 H), 7.51 (d, J = 559 Hz, 1 H), 6.73 (dd, J = 9 Hz, J = 3 Hz, 2 H), 3.99 – 4.1 (m, 4 H), 1.67 – 1.72 (m, 2 H), 1.38 – 1.46 (m, 2 H), 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.3 (d, J_{PCCCCC} = 3 Hz), 133.1 (d, J_{PCC} = 13 Hz, 2C), 117.4 (d, J_{PC} = 142 Hz), 114.5 (d, J_{PCCC} = 15 Hz, 2C), 65.4 (d, J_{POC} = 6 Hz), 32.7 (d. J_{POCC} = 7 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 27.1 (dm, J = 559 Hz).

Butyl [(4-tert-butoxycarbonylamino)phenyl] phosphinate (Table 3.1, entry 6). ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1 H), 7.70-7.75 (m, 2 H), 7.60-7.65 (m, 2 H), 7.56 (d, J = 564 Hz), 4.05-4.10 (m, 2 H), 1.65-1.75 (m, 2 H), 1.50 (s, 9 H), 1.35-1.45 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.6, 143.6 (d, J_{PCCCC} = 3 Hz), 132.2 (d, J_{PCC} = 13 Hz), 123 (d, J_{PC} = 138 Hz), 118.0 (d, J_{PCCC} = 14 Hz), 80.9, 65.5 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 28.3, 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 26.1 (dm, J = 565 Hz); HRMS (FAB) calcd. for $C_{15}H_{24}NO_4P$, $(M+Li)^+$ 320.1603, found 320.1610.

Butyl (1-naphthyl) phosphinate (Table 3.1, entry 7). ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J = 8 Hz, 1 H), 8.11 (dd, J=7, 1Hz, 1 H), 8.05 (dd, J = 7, 4 Hz, 1 H), 7.91 (d, J = 563 Hz, 1 H), 7.90 (d, J = 8 Hz, 1 H), 7.50-7.65 (m, 3 H), 4.05-4.20 (m, 2 H), 1.60-1.75 (m, 2 H), 1.30-1.45 (m, 2 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.1 (d, J_{PCCCC} = 3 Hz), 133.6 (d, J_{PCC} = 10 Hz), 132.7 (d, J_{PCC} = 13 Hz), 132.5, 129.2 (d, J_{PCCC} = 2 Hz), 128.0, 126.9, 126.2 (d, J_{PC} = 129 Hz), 125.0 (d, J_{PCCCC} = 1 Hz), 124.8 (d, J_{PCCC} = 11 Hz); ^{31}P NMR ($CDCl_3$) δ 27.1 (dm, J = 563 Hz); HRMS (FAB) calcd. for $C_{14}H_{17}O_2P$, $(M+Li)^+$ 255.1126, found 255.1138.

Ethyl (2-naphthyl) phosphinate (Table 3.1, entry 8). ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 16 Hz, 1 H), 7.95-8.00 (m, 2 H), 7.90 (d, J = 9 Hz, 1 H), 7.72 (d, J = 564 Hz, 1 H), 7.65-7.80 (m, 1 H), 7.60-7.65 (m, 2 H); 4.15-4.25 (m, 2 H), 1.41 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.6 (d, J_{PCCCC} = 3 Hz), 133.7 (d, J_{PCCC} = 12 Hz), 132.6 (d, J_{PCC} = 15 Hz), 129.1 (d, J_{PCCC} = 3 Hz), 128.9, 128.8, 128.2, 127.1 (d, J_{PC} = 132 Hz), 127.4, 125.4 (d, J_{PCC} = 12 Hz), 62.3 (d, J_{POC} = 6 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 25.8 (dm, J = 565 Hz).

Butyl (4-cyanophenyl) phosphinate (Table 3.1, entry 9). ^{1}H NMR ($CDCl_3$) δ 7.90-8.00 (m, 2 H), 7.80-7.90 (m, 2 H), 7.65 (d, J = 574 Hz, 1 H), 4.10-4.20 (m, 2 H), 1.70-1.80 (m, 2 H), 1.40-1.50 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.0 (d, J_{PC} = 129 Hz), 132.3 (d, J_{PCCC} = 14 Hz), 131.6 (d, J_{PCC} = 12 Hz), 117.7, 116.7 (d, J_{PCCCC} = 3 Hz), 66.5 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 22.5 (dm, J = 574 Hz); HRMS (FAB) calcd. for $C_{11}H_{14}NO_2P$, $(M+Li)^+$ 230.0922, found 230.0917.

Butyl (3-pyridinyl) phosphinate (Table 3.1, entry 10). ^{1}H NMR ($CDCl_3$) δ 8.98 (dm, J = 7 Hz, 1 H), 8.85 (m, 1 H), 8.10-8.20 (m, 1 H), 7.45-7.50 (m, 1 H), 7.69 (d, J = 573 Hz, 1 H), 4.15-4.20 (m, 2 H), 1.70-1.80 (m, 2 H), 1.40-1.50 (m, 2 H), 0.96 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.7 (d, J_{PCCNC} = 2 Hz), 151.8 (d, J_{PCC} = 14 Hz), 139.0 (d, J_{PCC} = 10 Hz), 126.2 (d, J_{PC} = 131

Hz), 123.7 (d, J_{PCCC} = 10 Hz), 66.4 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 7 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 22.0 (dm, J = 573 Hz).

Butyl (2-thienyl) phosphinate (Table 3.1, entry 11). ^{1}H NMR ($CDCl_3$) δ 7.75-7.80 (m, 1 H), 7.70-7.75 (m, 1 H), 7.72 (d, J = 593 Hz, 1 H), 7.25-7.30 (m, 1 H), 4.10-4.20 (m, 2 H), 1.70-1.80 (m, 2 H), 1.40-1.50 (m, 2 H), 0.95 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.7 (d, J_{PCC} = 13 Hz), 134.5 (d, J_{PCSC} = 6 Hz), 130.2 (d, J_{PC} = 145 Hz), 128.5 (d, J_{PCCC} = 16 Hz), 65.8 (d, J_{POC} = 6 Hz), 32.4 (d, J_{POCC} = 7 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 16.3 (dm, J = 593 Hz); HRMS (FAB) calcd. for $C_8H_{13}O_2PS$, $(M+Li)^+$ 211.0534, found 211.0531.

Butyl (3-quinolinyl) phosphinate (Table 3.1, entry 12). ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, J = 5, 2 Hz, 1 H), 8.71 (d, J = 15 Hz, 1 H), 8.19 (d, J = 9 Hz, 1 H), 7.95 (d, J = 8 Hz, 1 H), 7.85-7.90 (m, 1 H), 7.82 (d, J = 573 Hz, 1 H), 7.65-7.70 (m, 1 H), 4.15-4.25 (m, 2 H), 1.75-1.85 (m, 2 H), 1.40-1.55 (m, 2 H), 0.96 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.7, 149.6, 142.1 (d, J_{PCC} = 10 Hz), 132.3, 129.6, 128.8, 127.9, 126.7 (d, J_{PCC} = 12 Hz), 123.0 (d, J_{PC} = 131 Hz), 66.4 (d, J_{POC} = 7 Hz), 32.5 (d, J_{POCC} = 6 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.9 (dm, J = 561 Hz); HRMS (FAB) calcd. for $C_{13}H_{16}NO_2P$, $(M+Li)^+$ 256.1079, found 256.1072.

Butyl (4-isoquinolinyl) phosphinate (Table 3.1, entry 13). ^{1}H NMR ($CDCl_3$) δ 9.44 (d, J = 2 Hz, 1 H), 8.98 (d, J = 11 Hz, 1 H), 8.46 (d, J = 9 Hz, 1 H), 8.09 (d, J = 8 Hz, 1 H), 7.98 (d, J = 570 Hz, 1 H), 7.85-7.90 (m, 1 H), 7.70-7.80 (m, 1 H), 4.15-4.25 (m, 2 H), 1.70-1.80 (m, 2 H), 1.40-1.50 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.7 (d, J_{PCCNC} = 9 Hz), 147.8 (d, J_{PCC} = 16 Hz), 134.8 (d, J_{PCC} = 9 Hz), 132.3, 128.8, 128.3, 128.0 (d, J_{PCCC} = 8 Hz), 124.2 (d, J_{PCCC} = 6 Hz), 119.9 (d, J_{PC} = 121 Hz), 66.3 (d, J_{POC} = 6 Hz), 32.4 (d, J_{POCC} = 6 Hz), 18.8, 13.5; ^{31}P NMR nb($CDCl_3$) δ 24.3 (dm, J = 570 Hz); HRMS (FAB) calcd. for $C_{13}H_{16}NO_2P$, $(M+Li)^+$ 256.1079, found 256.1086.

Butyl benzylphosphinate (Table 3.2, entry 1).[240] ^{1}H NMR ($CDCl_3$) δ 7.20-7.35 (m, 5 H), 7.03 (d, J = 544 Hz, 1 H), 3.90-4.10 (m, 2 H), 3.19 (d, J = 18 Hz, 2 H), 1.55-1.65 (m, 2 H), 1.25-1.40 (m, 2 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 129.9, 129.8 (d, J_{PCCC} = 7 Hz), 128.9 (d, J_{PCCCC} = 3 Hz), 127.7 (d, J_{PCCCCC} = 4 Hz), 66.4 (d, J_{POC} = 7 Hz), 37.0 (d, J_{PC} = 89 Hz), 32.3 (d, J_{POCC} = 6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 37.9 (dm, J = 545 Hz); HRMS (FAB) calcd. for $C_{11}H_{17}O_2P$, $(M+Li)^+$ 219.1126, found 219.1125.

Butyl (4-methoxybenzyl) phosphinate (Table 3.2, entry 2). ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, J = 9 Hz, J = 3 Hz, 2 H), 7.0 (d, J = 542 Hz, 1 H), 6.87 (d, J = 8 Hz, 2 H), 3.9 – 4.15 (m, 2H), 3.8 (s, 3 H), 3.14 (d, J = 18 Hz, 2 H), 1.58 – 1.68 (m, 2 H), 1.28 – 1.42 (m, 2 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.0 (d, J_{PCCCCC} = 4 Hz), 131.0 (d, J_{PCCC} = 6 Hz, 2C), 121.8 (d, J_{PCC} = 8 Hz), 114.6 (d, J_{PCCCC} = 3 Hz, 2C), 66.7 (d, J_{POC} = 7 Hz), 55.5, 36.2 (d, J_{PC} = 90 Hz), 32.6 (d, J_{POCC} = 6 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 40.2 (dm, J = 542 Hz); HRMS (EI^+) calcd. for $C_{12}H_{19}O_3P$, $(M)^+$ 242.1072, found 242.1069.

Butyl (pyridin-3-yl-methyl) phosphinate (Table 3.2, entry 3). ^{1}H NMR ($CDCl_3$) δ 8.50-8.55 (m, 2 H), 7.60-7.65 (m, 1 H), 7.25-7.35 (m, 1 H), 7.12 (d, J = 548 Hz, 1 H), 4.00-4.15 (m, 2 H), 3.20 (d, J = 18 Hz, 2 H), 1.60-1.70 (m, 2 H), 1.30-1.40 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR (CDCl3) δ 150.6 (d, J_{PCCC} = 7 Hz), 148.7 (d, J_{PCCCNC} = 4 Hz), 137.3 (d, J_{PCCC} = 6 Hz), 126.1 (d, J_{PCC} = 7 Hz), 123.7, 66.8 (d, J_{POC} = 7 Hz), 34.2 (d, J_{PC} = 89 Hz), 32.3 (d, J_{POCC} = 6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 35.1, (dm, J = 547 Hz); HRMS (FAB) calcd. for $C_{10}H_{16}NO_2P$, $(M+Li)^+$ 220.1079, found 220.1131.

Butyl (pyridin-2-yl-methyl) phosphinate (Table 3.2, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.20-7.25 (m, 2 H), 7.19 (d, J = 548 Hz, 1 H), 6.75-6.85 (m, 1 H), 6.69 (d, J = 8 Hz, 1 H), 4.05-4.20 (m, 2 H), 3.57 (dm, J = 10 Hz, 2 H), 1.65-1.75 (m, 2 H), 1.35-1.45 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, J_{PCC} = 9 Hz), 129.7, 119.2, 113.7, 113.5, 67.1 (d, J_{POC} = 7 Hz),

42.8 (d, J_{PC} = 105 Hz), 32.6 (d, J_{POCC} = 6 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 33.3 (dm, J = 548 Hz).

Ethyl (vinyl-2-cyanoethyl) phosphinate (Table 3.3, entry 1). ^{1}H NMR ($CDCl_3$) δ 6.03 – 6.5 (m, 3 H), 3.96 – 4.16 (m, 2 H), 2.6 – 2.71 (m, 2 H), 2.0 – 2.2 (m, 2 H), 1.35 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.4, 127.9 (d, J_{PC} = 121 Hz), 118.6, 61.4 (d, J_{POC} = 6 Hz), 29.9, 25.2 (d, J_{PC} = 101 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 38.3 (s); HRMS (ES^+) calcd. for $C_7H_{12}NO_2P$, $(M+H)^+$ 172.0527, found 172.0529.

Butyl (1-phenyl-vinyl) phosphinate (Table 3.3, entry 2).[33] ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 563 Hz, 1 H), 7.48 - 7.52 (m, 2 H), 7.35 – 7.38 (m, 3 H), 6.27 (d, J = 46 Hz, 1 H), 6.21 (d, J = 25 Hz, 1 H), 4.01 – 4.08 (m, 2 H), 1.6 – 1.66 (m, 2 H), 1.3 – 1.58 (m, 2 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.7 (d, J_{PC} = 119 Hz), 135.2 (d, J_{PCC} = 12 Hz), 130.1 (d, J_{PCC} = 13 Hz), 128.7 (3C), 127.0 (d, J_{PCCC} = 6 Hz, 2C), 65.9 (d, J_{POC} = 7 Hz), 32.3 (d, J_{POCC} = 6 Hz), 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 28.7 (dqt, J = 563 Hz, J = 25 Hz, J = 8 Hz); HRMS (EI^+) calcd. for $C_{12}H_{17}O_2P$, $(M)^+$ 224.0966, found 224.0967.

Butyl (*trans*-styryl) phosphinate (Table 3.3, entry 3).[241] ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 560 Hz, 1 H), 7.3 – 7.58 (m, 5 H), 6.4 (d, J = 18 Hz, 1 H), 6.37 (d, J = 22 Hz, 1 H), 4.06 – 4.15 (m, 2 H), 1.67 – 1.75 (m, 2 H), 1.4 – 1.48 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.7 (d, J_{PCCC} = 7 Hz), 134.5 (d, J_{PCC} = 21 Hz), 130.6, 129.0 (2C), 127.9 (2C), 116.3 (d, J_{PC} = 133 Hz), 65.7 (d, J_{POC} = 6 Hz), 32.5 (d, J_{POCC} = 6 Hz), 18.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 25.8 (dtt, J = 560 Hz, J = 23 Hz, J = 8 Hz); HRMS (EI^+) calcd. for $C_{12}H_{17}O_2P$, $(M)^+$ 224.0966, found 224.0963.

Butyl [1-(3-methyl-butyl)vinyl] phosphinate (Table 3.3, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.1 (d, J = 547 Hz, 1 H), 5.94 (d, J = 25 Hz, 1 H), 5.84 (d, J = 49 Hz, 1 H), 3.95 – 4.1 (m, 2 H), 2.2 – 2.35 (m, 2 H), 1.5 – 1.7 (m, 3 H), 1.35 – 1.44 (m, 4 H), 0.85 – 0.95 (m, 9 H); ^{13}C NMR ($CDCl_3$)

δ 142.5 (d, J_{PC} = 118 Hz), 128.5 (d, J_{PCC} = 14 Hz), 66.1 (d, J_{POC} = 7 Hz), 37.2 (d, J_{PCC} = 5 Hz), 32.7 (d, J_{POCC} = 6 Hz), 28.7 (d, J_{PCCC} = 12 Hz), 27.9, 22.6, 22.5, 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 31.6 (dm, J = 547 Hz).

Butyl (1-propyl-pent-1-enyl) phosphinate (Table 3.3, entry 5). ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 542 Hz, 1 H), 6.37 (dt, J = 33 Hz, J = 7 Hz, 1 H), 3.88 – 4.0 (m, 2 H), 2.0 – 2.2 (m, 4 H), 1.55 – 1.63 (m, 2 H), 1.3 – 1.45 (m, 6 H), 0.87 (t, J = 7 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 147.1 (d, J_{PCC} = 14 Hz), 131.9 (d, J_{PC} = 124 Hz), 65.7 (d, J_{POC} = 7 Hz), 32.6 (d, J_{POCC} = 7 Hz), 30.5 (d, J_{PCC} = 18 Hz), 28.4 (d, J_{PCCC} = 12 Hz), 22.6, 21.9, 18.9, 14.2, 13.9, 13.7; ^{31}P NMR ($CDCl_3$) δ 33.5 (dm, J = 542 Hz); HRMS (EI^+) calcd. for $C_{12}H_{25}O_2P$, $(M)^+$ 232.1592, found 232.1590.

Butyl (1-methyl-vinyl) phosphinate (Table 3.3, entry 6). ^{1}H NMR ($CDCl_3$) δ 7.09 (d, J = 549 Hz, 1 H), 5.79 – 6.0 (m, 2 H), 3.97 – 4.14 (m, 2 H), 1.96 (d, J = 14 Hz, 3 H), 1.62 – 1.75 (m, 2 H), 1.35 – 1.5 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 129.8 (d, J_{PCC} = 14 Hz), 66.0 (d, J_{POC} = 13 Hz), 32.7 (d, J_{POCC} = 6 Hz), 19.0, 17.1 (d, J_{POCCC} = 13 Hz), 13.8; ^{31}P NMR ($CDCl_3$) δ 30.5 (dm, J = 549 Hz).

Ethyl (1-bromo-oct-1-enyl) phosphinate (Table 3.3, entry 7). ^{1}H NMR ($CDCl_3$) δ 6.97 (d, J = 601 Hz, 1 H), 7.16 – 7.3 (m, 1 H), 4.07 – 4.2 (m, 2 H), 2.37 (qd, J = 7 Hz, J = 3 Hz, 2 H), 1.41 – 1.56 (m, 2 H), 1.39 (t, J = 7 Hz, 3 H), 1.23 – 1.35 (m, 6 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.9 (d, J_{PCC} = 13 Hz), 114.9 (d, J_{PC} = 136 Hz), 62.4 (d, J_{POC} = 7 Hz), 32.1 (d, J_{PCCC} = 11 Hz), 31.7, 29.1, 27.6, 22.7, 16.5 (d, J_{POCC} = 7 Hz), 14.3; ^{31}P NMR ($CDCl_3$) δ 20.9 (ddd, J = 602 Hz, J = 14 Hz, J = 9 Hz); HRMS (ES^+) calcd. for $C_{10}H_{20}BrO_2P$, $(M+H)^+$ 283.0463, found 283.0456.

Butyl (1-butyl-vinyl) phosphinate (Table 3.3, entry 8). ^{1}H NMR ($CDCl_3$) δ 7.13 (d, J = 547 Hz, 1 H), 5.97 (d, J = 25 Hz, 1 H), 5.86 (d, J = 44 Hz, 1 H), 4.0 – 4.16 (m, 2 H), 2.15 – 2.3 (m, 2 H), 1.1 – 2.06 (m, 8 H), 0.9 – 0.97 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 142.0 (d, J_{PC} = 118 Hz), 128.5

(d, J_{PCC} = 13 Hz), 65.8 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 30.4 (d, J_{PCC} = 12 Hz), 30.0 (d, J_{PCCC} = 5 Hz), 22.3, 18.8, 13.8, 13.6; ^{31}P NMR ($CDCl_3$) δ 30.9 (dm, J = 547 Hz); HRMS (ES^+) calcd. for $C_{10}H_{21}O_2P$, $(M+H)^+$ 205.1357, found 205.1360.

Butyl (1-carboxylic acid-*tert*-butyl ester-1,2,3,6-tetrahydro-pyridin-4-yl) phosphinate (Table 3.3, entry 9). ^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 552 Hz, 1H), 6.62 - 6.75 (m, 1 H), 4.0 – 4.13 (m, 4 H), 3.45 – 3.6 (m, 2 H), 2.2 – 2.4 (m, 2 H), 1.64 -1.74 (m, 2 H), 1.47 (s, 9 H), 1.36 – 1.48 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.7, 139.8 (d, J_{PCC} = 11 Hz), 129.8 (d, J_{PC} = 56 Hz), 80.4, 66.2 (d, J_{POC} = 7 Hz), 43.7 (br), 39.4 (br), 32.6 (d, J_{POCC} = 6 Hz), 28.6 (3C), 23.5 (d, J_{PCC} = 10 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 25.99, 26.6 (dm, J = 552 Hz); HRMS (EI^+) calcd. for $C_{14}H_{26}NO_4P$, $(M)^+$ 303.1599, found 303.1601.

Chapter 4, Section 4.2[63]

Representative Procedure for Table 4.1 - Palladium Catalysis. Entry 1b: A mixture of anilinum hypophosphite (0.955 g, 6 mmol, 3 eq) and $(BuO)_4Si$ (1.346 g, 4.2 mmol, 2.1 eq) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen. After cooling to room temperature, cinnamyl chloride (0.280 mL, 0.305 g, 2.0 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol, 2 mol% Pd), and 1,3-bis(diphenylphosphino)ferrocene (0.0244 g, 0.044 mmol) were added to the reaction flask and the mixture was heated at reflux under nitrogen for 10 h. At this time, ^{31}P NMR analysis of the reaction mixture showed the product at 39.7 ppm (95%). The mixture was then diluted with EtOAc and washed with aq. $NaHSO_4$ (1 M). The resulting aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc), afforded butyl (3-phenyl-propyl) phosphinate (0.351 g, 73%) as a light yellow oil.

Representative Procedure for Table 4.1 - Nickel Catalysis. Entry 1d: A mixture of anilinum hypophosphite (0.955 g, 6 mmol, 3 eq) and $(BuO)_4Si$ (1.346 g, 4.2 mmol, 2.1 eq) in CH_3CN (12 mL) was heated to reflux for 2 h under nitrogen. After cooling to room temperature, cinnamyl chloride (0.280 mL, 0.305 g, 2.0 mmol) and bis(triphenylphosphine)nickel (II) chloride (0.0327 g, 0.050 mmol, 2.5 mol% Ni) were added to the reaction flask and the mixture was heated at reflux under nitrogen, for 8 h. After this time, ^{31}P NMR analysis of the reaction mixture showed the product at 37.1 ppm (100%). The reaction mixture was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$. The resulting aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc) afforded the product (0.419 g, 88%) as a mixture of butyl cinnamyl phosphinate (95%) and butyl (3-phenyl-propyl) phosphinate (5%).

Ethyl (3-phenyl-propyl) phosphinate (Table 4.1, entry 1a).[63] ^1H NMR ($CDCl_3$) δ 7.06 (d, J_{HP} = 530 Hz, 1 H), 7.15 – 7.31 (m, 5 H), 3.98 – 4.23 (m, 2 H), 2.71 (t, J = 7 Hz, 2 H), 1.72 – 2.0 (m, 4 H), 1.34 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.74 (4 C), 126.5, 62.6 (d, J_{POC} = 7 Hz), 36.5 (d, J_{PCC} = 16 Hz), 28.3 (d, J_{PC} = 94 Hz), 22.6 (d, J_{PCCC} = 3 Hz), 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 39.7 (dm, J_{PH} = 530 Hz).

Butyl (3-phenyl-propyl) phosphinate (Table 4.1, entry 1b).[63] ^1H NMR ($CDCl_3$) δ 7.0 (d, J_{HP} = 528 Hz, 1 H), 7.15 – 7.31 (m, 5 H), 3.9 – 4.15 (m, 2 H), 2.72 (t, J = 7 Hz, 2 H), 1.57 – 2.0 (m, 6 H), 1.26 – 1.46 (m, 2 H), 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.7 (4 C), 126.5, 66.3 (d, J_{POC} = 7 Hz), 36.4 (d, J_{PCC} = 16 Hz), 32.5 (d, J_{POCC} = 6 Hz), 28.3 (d, J_{PC} = 94 Hz), 22.6 (d, J_{PCCC} = 3 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$) δ 39.9 (dm, J_{PH} = 528 Hz); HRMS (EI^+) calcd. for $C_{13}H_{21}O_2P$, $(M)^+$ 240.1279, found 240.1275.

Butyl cinnamyl phosphinate (Table 4.1, entries 1c-1d).[57,63,66] ^{1}H NMR ($CDCl_3$) δ 7.06 (dt, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 7.23 – 7.38 (m, 5 H), 6.55 (dd, J = 16 Hz, J = 6 Hz, 1 H), 6.06 – 6.17 (m, 1 H), 4.03 and 4.13 (tdd, J = 10 Hz, J_{HP} = 7 Hz, J = 8 Hz, 2 H), 2.82 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 1.65 – 1.74 (m, 2 H), 1.42 (sext., J = 8 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.6 (d, J_{PCCCC} = 4 Hz), 136.1 (d, J_{PCCC} = 14 Hz), 128.7 (2 C), 128.0, 126.4 (2 C), 116.9 (d, J_{PCC} = 10 Hz), 66.5 (d, J_{POC} = 7 Hz), 34.7 (d, J_{PC} = 90 Hz), 32.6 (d, J_{POCC} = 6 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$) δ 35.94 (dt, J_{PH} = 543 Hz, J = 7 Hz); HRMS (EI^+) calcd. for $C_{13}H_{19}O_2P$, $(M)^+$ 238.1123, found 238.1126.

Butyl (3,7-dimethyl-octen-6-yl) phosphinate (Table 4.1, entry 2).[63] Mixture of stereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.1 (d, J_{HP} = 528 Hz, 2 H), 5.08 (t, J = 7 Hz, 2 H), 3.94 – 4.17 (m, 4 H), 1.91 – 2.08 (m, 4 H), 1.1 – 1.84 (m, 34 H), 0.86 – 0.97 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 131.7 (2 C), 124.6 (2 C), 66.3 (d, J_{POC} = 7 Hz, 2 C), 36.6 (2 C), 33.1 (d, J_{PCC} = 16 Hz, 2 C), 32.6 (d, J_{POCC} = 6 Hz, 2 C), 27.5 (2 C), 26.5 (d, J_{PC} = 94 Hz, 2 C), 25.9 (2 C), 25.5 (2 C), 19.1, 19.0, 18.9 (2 C), 17.8 (2 C), 13.8 (2 C); ^{31}P NMR ($CDCl_3$) δ 41.35 and 41.33 (dm, J_{PH} = 528 Hz); HRMS (EI^+) calcd. for $C_{14}H_{29}O_2P$, $(M)^+$ 260.1905, found 260.1904.

Butyl (3-methyl-buten-2-yl) phosphinate (Table 4.1, entry 6).[57] Main product (75% purity). ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J_{HP} = 537 Hz, 1 H), 5.07- 5.16 (m, 1 H), 4.01 and 4.10 (tdd, J_{HP} = 7 Hz, J = 11 Hz, J = 8 Hz, 2 H), 2.55 – 2.66 (m, 2 H), 1.77 (d, J = 7 Hz, 3 H), 1.59 – 1.72 (m, 5 H), 1.40 (sext., J = 8 Hz, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.3 (d, J_{PCCC} = 14 Hz), 110.7 (d, J_{PCC} = 14 Hz), 66.4 (d, J_{POC} = 8 Hz), 32.7 (d, J_{POCC} = 6 Hz), 29.8 (d, J_{PC} = 92 Hz), 26.0 (d, J_{PCCCC} = 4 Hz), 18.7, 18.1 (d, J_{PCCCC} = 4 Hz), 13.8; ^{31}P NMR ($CDCl_3$) δ 38.24 (d, J_{PH} = 537 Hz). Minor isomers: ^{31}P NMR ($CDCl_3$) δ 39.96 (d, J_{PH} = 532 Hz, 17%), 27.17 (d, J_{PH} = 532 Hz, 8%).

Chapter 4, Section 4.3

General Procedure for the Preparation of Allylic *H*-Phosphinic Acids (Table 4.2). To a solution of the hypophosphorous compound (3 - 6 mmol, 1.5 - 3 eq) in DMF or CH_3CN (10 mL) (See Notes) was added the allylic electrophile (2 mmol, 1 eq), followed by Pd_2dba_3 (0.0046 - 0.0184 g, 0.005 - 2 mmol, 0.5 - 2 mol% Pd) and xantphos (0.0064 - 0.0256 g, 0.011 - 0.044 mmol) at room temperature. The mixture was heated at 85ºC in the case of DMF, or at reflux for CH_3CN. Although reaction times for the cross-coupling were not optimized, no significant differences in yields were observed according to ^{31}P NMR analysis when heating the reactions from 2 to 15 h (Product: δ 20 - 30 ppm, dm). Before doing the workup, DMF was evaporated from the solution by heating in vacuo (0.5 mmHg, 45ºC, 30 min) and the residue was dissolved in EtOAc; while in the case of an acetonitrile mixture, dilution with EtOAc was performed directly. The workup consisted in washing the EtOAc solution with aqueous HCl or $NaHSO_4$ (1 - 2 M). The aqueous layer was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine (1 x), dried over $MgSO_4$, and concentrated to afford the product. If using triethylammonium hypophosphite, the purity of the product could be improved by redissolving it in EtOAc or CH_2Cl_2 and stirred with acidic amberlite resin (3-4 tips of scoopula) at room temperature for 4 - 6 h to remove traces of amine. The products were obtained with more than 95% purity.

Notes: H_3PO_2 and D_3PO were purchased from Aldrich as 50 wt% solutions in H_2O and D_2O respectively, and concentrated by rotary evaporation (5 mmHg, 40°C) for 30 min and used immediately. When employing CH_3CN as solvent, a stock solution of concentrated H_3PO_2 (0.5 M) could also be used. $Et_3NHOP(O)H_2$,[16] $NH_4OP(O)H2$,[38e] $PhNH_3OP(O)H_2$ (AHP)[18,41] were prepared according to literature procedures; while ethylpiperidinium hypophosphite was purchased from Aldrich. DMF was dried and stored over 4Å molecular sieves before use.

CH_3CN (reagent grade) was used exclusively with AHP or with acids due to solubility and reactivity issues (see Table 4.2).

General Procedure for the Preparation of Allylic-*H*-Phosphinates (Table 4.2). The same procedure described above for the cross-coupling of a hypophosphorous acid derivative (4 - 6 mmol, 2 - 3 eq) with an allylic acetate (2 mmol, 1 eq) was followed, but after completion of the cross-coupling process (according to ^{31}P NMR), the reaction mixture was cooled to room temperature, and two optional esterification methods were followed: (a) *In situ* addition of $(RO)_4Si$ (2.8 - 6 mmol, 1.4 - 3 eq, 0.7 - 1.0 eq per 1 eq. $MOP(O)H_2$) and heating at reflux (CH_3CN) or at 85°C (DMF) for 16-24 h. Better yields were generally obtained when using 1 eq alkoxysilane per 1 eq $MOP(O)H_2$. (b) *In situ* addition of ROH (7.5 - 9 eq) and pivaloyl chloride (5 - 6 eq) and stirring at room temperature for 4 to 6 h. The reaction was monitored by ^{31}P NMR. Once completed, the workup was done depending upon the solvent of the reaction, as explained above. DMF required previous concentration and then dilution with EtOAc, while an CH_3CN mixture was diluted directly with EtOAc. The organic EtOAc solution was subsequently washed with 2 M aqueous HCl. The aqueous layer was extracted with EtOAc (2 x) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration and purification by radial chromatography (2 to 4 mm thickness, hexanes/EtOAc 7/1, v/v, EtOAc) or by column on silica gel afforded the pure allylic-*H*-phosphinate ester.

Representative Procedure for the Cross-Coupling with R_3PO_2 (R=H or D): Preparation of Cinnamyl phosphinic acid (Table 4.2, entries 2e and 2 g). Freshly concentrated acid (0.264 g, 4 mmol of H_3PO_2, or 0.276 g, 4 mmol of D_3PO_2) was dissolved in CH_3CN (10 mL) and cinnamyl acetate (0.352 g, 0.33 mL, 2 mmol), Pd_2dba_3 (0.0046 g, 0.005 mmol) and xantphos (0.0064 g, 0.011 mmol), were added at room temperature. The reaction was heated (85°C) under N_2 for 15 h. After this time, ^{31}P NMR revealed the formation of the product at 33.2 ppm (d)

when starting from H_3PO_2 or at 35.5 ppm (t) from D_3PO_2. The latter multiplicity results from deuterium exchange in the phosphinylidene moiety (P(=O)D). The resulting solution was diluted with EtOAc and washed once with aqueous $NaHSO_4$ (2 M). The aqueous layer was separated and extracted with EtOAc (2 x), and then the organic fractions were combined and washed with brine (1 x). Drying and concentration gave the pure product cinnamyl phosphinic acid in 100% yield (0.364 g). No product from deuterium incorporation along the double bond is observed.

Representative Procedure for the Cross-Coupling with a Hypophosphorous Acid Salt: Preparation of *E*-Geranyl phosphinic acid (Table 4.2, entry 3g). To a solution of $Et_3NHOP(O)H_2$ (1.0 g, 2 mmol, 3 eq) in DMF (10 mL, 0.2 M) was added *trans*-geranyl acetate (0.43 mL, 0.393 g, 2 mmol, 1 eq) followed by Pd_2dba_3 (0.0046 g, 0.005 mmol) and xantphos (0.0064 g, 0.011 mmol), at room temperature. The reaction mixture was heated at 85 °C under N_2 for 2 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 23.7 ppm (dm, 100%). The mixture was concentrated under high vacuum to remove the DMF and the residue was diluted with EtOAc, and washed successively with 2 M aqueous $NaHSO_4$ (1 x). The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine, dried, and concentrated. The residue was dissolved in EtOAc (10 mL) and a small amount of amberlite resin was added (4 tips of scoopula). The resulting suspension was stirred for 5 h, followed by suction filtration to furnish the pure product as a light yellow oil (0.404 g, 100%).

Representative Procedure for the One-Pot, Two-Steps Cross-Coupling-Esterification using $(RO)_4Si$: Preparation of Butyl (3-methyl-buten-2-yl) phosphinate (Table 4.2, entry 9b). To a suspension of $PhNH_3OP(O)H_2$ (0.955 g, 6 mmol) in CH_3CN (10 mL) were added 3-methyl-2-butenyl benzoate (0.38 mL, 0.385 g, 2 mmol), Pd_2dba_3 (0.0184 g, 0.02 mmol) and xantphos (0.0254 g, 0.044 mmol). The mixture was heated at reflux for 8 h. To the reaction mixture was

added $(BuO)_4Si$ (1.40 g, 4.2 mmol) at room temperature. The mixture was returned to reflux temperature for 16 h. After this time, ^{31}P NMR analysis showed the product at 38.9 ppm. The resulting mixture was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous phase was extracted with two portions of EtOAc and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine. Drying, concentration and purification by radial chromatography (4 mm thickness, hexanes/EtOAc 7/1, v/v, EtOAc) afforded the product as a clear oil (0.346 g, 91% yield).

Representative Procedure for the One-Pot, Two-Steps Cross-Coupling-Esterification using PivCl/ROH: Preparation of Butyl (*trans*-hexen-2-yl) phosphinate (Table 4.2, entry 10b). A 25 mL round bottom flask was charged with $Et_3NOP(O)H_2$ (0.835 g, 5 mol) and DMF (12.5 mL). *trans*-2-Hexenyl acetate (0.32 mL, 0.284 g, 2 mmol), Pd_2dba_3 (0.0046 g, 0.005 mmol) and xantphos (0.0064 g, 0.011 mmol) were added under nitrogen and the resulting mixture was heated at 85°C for 6 h. ^{31}P NMR analysis of the crude mixture revealed quantitative formation of the product at 25 ppm. The reaction was cooled to room temperature and then BuOH (1.4 mL, 1.11 g, 15 mmol) and pivaloyl chloride (1.3 mL, 1.206 g, 10 mmol) were added and the reaction was stirred at room temperature for 6 h. The reaction was diluted with EtOAc and then extracted from 2 M aqueous $NaHSO_4$. The aqueous layer was separated and washed with EtOAc (2 x). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford the crude product, which was purified by column chromatography on silica gel (hexanes/EtOAc 3/1, v/v, EtOAc) to give the product as a clear oil (0.277 g, 68% yield).

Allyl phosphinic acid (Table 4.2, entry 1a).[242,61] (96% purity) ^1H NMR ($CDCl_3$, 300 MHz) δ 12.41 (bs, 1 H), 6.99 (d, J_{HP} = 559 Hz, 1 H), 5.77 (dddd, J = 27 Hz, J = 13 Hz, J = 11 Hz, J = 3 Hz 1 H), 5.19 – 5.32 (m, 2 H), 2.65 (dd, J_{HP} = 20 Hz, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.45

MHz) δ 126.0 (d, J_{PCC} = 9 Hz), 121.6 (d, J_{PCCC} = 14 Hz), 35.4 (d, J_{PC} = 91 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.90 (dm, J_{PH} = 559 Hz).

Butyl allyl phosphinate (Table 4.2, entry 1b).[243,57,66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (dt, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 5.68 – 5.82 (m, 1 H), 5.20 – 5.31 (m, 2 H), 4.03 and 4.13 (dtd, J = 10 Hz, J = 9 Hz, J_{HP} = 7 Hz, 2 H), 2.66 (ddd, J_{HP} = 19 Hz, J = 8 Hz, J = 2 Hz, 2 H), 1.64 – 1.74 (m, 2 H), 1.42 (sext., J = 8 Hz, 2 H), 0.95 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 125.9 (d, J_{PCC} = 9 Hz), 121.5 (d, J_{PCCC} = 14 Hz), 66.5 (d, J_{POC} = 8 Hz), 35.0 (d, J_{PC} = 90 Hz), 32.6 (d, J_{POCC} = 6 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.79 (dm, J_{PH} = 543 Hz); HRMS (EI^+) calcd. for $C_7H_{15}O_2P$, ($[M]^+$) 163.0888, found 163.0883.

Cinnamyl phosphinic acid (Table 4.2, entries 2d-e, 2g, see also **Table 5.2, entry 9).**[66,190] m.p. = 84-85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.26 (bs, 1 H), 7.15 – 7.43 (m, 5 H), 7.01 (d, J_{HP} = 558 Hz, 1 H), 6.51 (dd, J = 16 Hz, J = 5 Hz, 1 H), 6.03 – 6.19 (m, 1 H), 2.75 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.7 (d, J_{PCCCC} = 4 Hz), 136.2 (d, J_{PCCC} = 14 Hz), 128.8 (2C), 128.1, 126.6 (d, J_{PCCCCC} = 2 Hz, 2C), 117.0 (d, J_{PCC} = 10 Hz), 34.9 (d, J_{PC} = 90 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.32 (dm, J_{PH} = 558 Hz); HRMS (EI^+) calcd. for $C_9H_{11}O_2P$, ($[M]^+$) 182.0495, found 182.0497.

Butyl cinnamyl phosphinate (Table 4.2, entries 2b-c, 2f & 7).[57,63,66] See above. **(Table 4.1, entries 1c-d).**

(*E*)-Geranyl phosphinic acid (Table 4.2, entries 3e-i).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.39 (bs, 1 H), 6.94 (dt, J_{HP} = 552 Hz, J = 2 Hz, 1 H), 5.0 – 5.21 (m, 2 H), 2.60 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 2.0 – 2.18 (m, 4 H), 1.68 (s, 3 H), 1.66 (d, J = 4 Hz, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.3 (d, J_{PCCC} = 14 Hz), 132.0, 124.0, 110.6 (d, J_{PCC} = 9 Hz), 39.9 (d, J_{PCCCC} = 3 Hz), 30.2 (d, J_{PC} = 92 Hz), 26.7 (d, J_{PCCCCC} = 4 Hz), 25.9, 17.9, 16.7 (d, J_{PCCCC} = 3

Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.10 (dm, J_{PH} = 552 Hz); HRMS (EI^+) calcd. for $C_{10}H_{19}O_2P$, ($[M]^+$) 202.1123, found 202.1122.

Butyl *(E)*-geranyl phosphinate (Table 4.2, entries 3c-d, 3k-l).[57] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (ddd, J_{HP} = 537 Hz, J = 3 Hz, J = 2 Hz, 1 H), 5.04 – 5.19 (m, 2 H), 4.0 and 4.09 (dtd, J = 10 Hz, J = 8 Hz, J_{HP} = 7 Hz, 2 H), 2.49 – 2.68 (m, 2 H), 2.08 (s, 3 H), 1.62 – 1.71 (m, 9 H), 1.60 (s, 3H), 1.41 (sext., J = 7 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.2 (d, J_{PCCC} = 14 Hz), 131.9, 123.9, 110.5 (d, J_{PCC} = 9 Hz), 66.4 (d, J_{POC} = 7 Hz), 39.8 (d, J_{PCCCC} = 3 Hz), 32.6 (d, J_{POCC} = 6 Hz), 29.6 (d, J_{PC} = 92 Hz), 26.6 (d, J_{PCCCCC} = 4 Hz), 25.9, 18.9, 17.9, 16.7 (d, J_{PCCCC} = 3 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.47 (dm, J_{PH} = 537 Hz); HRMS (EI^+) calcd. for $C_{14}H_{27}O_2P$, ($[M]^+$) 258.1749, found 258.1747.

***(E, E)*-Farnesyl phosphinic acid (Table 4.2, entries 4a and 4d).**[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.92 (bs, 1 H), 6.94 (d, J_{HP} = 548 Hz, 1 H), 5.0 – 5.22 (m, 3 H), 2.59 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 1.93 – 2.16 (m, 9 H), 1.63 – 1.73 (m, 6 H), 1.57 – 1.63 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.0 (d, J_{PCCC} = 14 Hz), 135.4, 131.3, 124.3, 123.7, 110.4 (d, J_{PCC} = 9 Hz), 39.8 (d, J_{PCCCC} = 3 Hz), 39.7, 30.2 (d, J_{PC} = 92 Hz), 26.7, 26.4 (d, J_{PCCCCC} = 4 Hz), 25.7, 17.7, 16.6 (d, J_{PCCCC} = 3 Hz), 16.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.72 (dm, J_{PH} = 548 Hz); HRMS (EI^+) calcd. for $C_{15}H_{27}O_2P$, ($[M]^+$) 270.1754, found 270.1749.

Ethyl (*(E)*-3,7,11-trimethyl-dodecen-2-yl) phosphinate (Table 4.2, entry 4b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (dt, J_{HP} = 542 Hz, J = 2 Hz, 1 H), 5.06 – 5.23 (m, 1 H), 4.01 – 4.27 (m, 2 H), 2.63 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.01 – 2.18 (m, 3 H), 1.48 – 1.82 (m, 23 H), 1.37 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 141.7 (d, J_{PCCC} = 14 Hz), 111.1 (d, J_{PCC} = 9 Hz), 74.6, 71.0, 62.6 (d, J_{POC} = 7 Hz), 46.1, 44.2, 43.6 (d, $J_{PCCCCCC}$ = 2 Hz), 39.7 (d, J_{PCCCCC} = 3 Hz), 32.6 (d, J_{PCCCC} = 9 Hz), 29.9, 29.7 (d, J_{PC} = 92 Hz), 22.8 (d, J_{POCC} = 3 Hz), 20.6, 16.6, 16.5

(d, J_{PCCCC} = 3 Hz), 16.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.31 (dm, J_{PH} = 542 Hz); MS (EI^+) for $C_{17}H_{35}O_2P$, $[M+H]^+$ *m/z* 303.

Butyl *(E, E)*-farnesyl phosphinate (Table 4.2, entry 4c).[57] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (d, J_{HP} = 539 Hz, 1 H), 5.03 – 5.19 (m, 3 H), 3.91 – 4.18 (m, 2 H), 2.52 – 2.71 (m, 2 H), 1.93 – 2.18 (m, 9 H), 1.63 – 1.75 (m, 10 H), 1.59 (s, 3 H), 1.41 (sext., J = 7 Hz, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.2 (d, J_{PCCC} = 14 Hz), 135.5, 131.4, 124.4, 123.7, 110.5 (d, J_{PCC} = 9 Hz), 66.6 (d, J_{POC} = 7 Hz), 39.9, 39.8 32.6 (d, J_{POCC} = 6 Hz), 29.6 (d, J_{PC} = 92 Hz), 26.9, 26.6 (d, J_{PCCCCC} = 4 Hz), 25.9, 18.9, 17.8, 16.7 (d, J_{PCCCC} = 3 Hz), 16.1, 13.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.39 (dm, J_{PH} = 539 Hz); HRMS (EI^+) calcd. for $C_{19}H_{35}O_2P$, ($[M]^+$) 326.2375, found 326.2374.

(3-Methyl-buten-2-yl) phosphinic acid (Table 4.2, entries 5a-c). [5a & 5b contain the product along with 20 wt.%. of aniline; 5c was isolated as the main peak in ^{31}P NMR (82%)]. Main product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.91 (bs, 1 H), 6.94 (d, J_{HP} = 550 Hz, 1 H), 5.13 (qq, J = 7 Hz, J = 2 Hz, 1 H), 2.57 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 1.77 (d, J = 6 Hz, 3 H), 1.66 (d, J = 4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.4 (d, J_{PCCC} = 14 Hz), 110.6 (d, J_{PCC} = 9 Hz), 30.1 (d, J_{PC} = 92 Hz), 25.8 (d, J_{PCCCC} = 3 Hz), 18.2 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.86 (dm, J_{PH} = 550 Hz).

Butyl (3-methyl-buten-2-yl) phosphinate (Table 4.2, entry 5d, 9a-b).[57] ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J_{HP} = 538 Hz, 1 H), 5.07- 5.16 (m, 1 H), 4.01 and 4.10 (dtd, J = 11 Hz, J = 8 Hz, J_{HP} = 7 Hz, 2 H), 2.55 – 2.66 (m, 2 H), 1.77 (d, J = 7 Hz, 3 H), 1.59 – 1.72 (m, 5 H), 1.40 (sext., J = 8 Hz, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.3 (d, J_{PCCC} = 14 Hz), 110.7 (d, J_{PCC} = 14 Hz), 66.4 (d, J_{POC} = 8 Hz), 32.7 (d, J_{POCC} = 6 Hz), 29.8 (d, J_{PC} = 92 Hz), 26.0 (d, J_{PCCCC} = 4 Hz), 18.7, 18.1 (d, J_{PCCCC} = 4 Hz), 13.8; ^{31}P NMR ($CDCl_3$) δ 38.01 (d, J_{PH} = 538 Hz). HRMS (EI^+) calcd. for $C_9H_{19}O_2P$, ($[M]^+$) 190.1123, found 190.1127.

(*trans*-Buten-2-yl) phosphinic acid (Table 4.2, entry 6a-c, 11a).[66] Purity (%): 6a (88%), 6b (90%), 6c (83%), 11a (100%). (^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.13 (bs, 1 H), 6.95 (d, J_{HP} = 553 Hz, 1 H), 5.64 (dt, J = 15 Hz, J = 6 Hz, 1 H), 5.38 (dq, J = 15 Hz, J = 6 Hz, 1 H), 2.56 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 1.72 (td, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 132.1 (d, J_{PCCC} = 14 Hz), 117.9 (d, J_{PCC} = 9 Hz), 33.1 (d, J_{PC} = 92 Hz), 18.2 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.78 (dm, J_{PH} = 553 Hz); HRMS (EI$^+$) calcd. for $C_4H_9O_2P$, ($[M]^+$) 120.0340, found 120.0339.

(*trans*-Hexen-2-yl) phosphinic acid (Table 4.2, entry 10a).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.15 (bs, 1 H), 6.94 (d, J_{HP} = 554 Hz, 1 H), 5.64 (dt, J = 22 Hz, J = 8 Hz, 1 H), 5.35 (dt, J = 22 Hz, J = 8 Hz, 1 H), 2.57 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.03 (t, J = 6 Hz, 2 H), 1.39 (sext., J = 7 Hz, 2 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.6 (d, J_{PCCC} = 14 Hz), 116.8 (d, J_{PCC} = 9 Hz), 34.7 (d, J_{PCCCC} = 3 Hz), 34.0 (d, J_{PC} = 91 Hz), 22.3 (d, J_{PCCCCC} = 4 Hz), 13.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.15 (dm, J_{PH} = 554 Hz); HRMS (EI$^+$) calcd. for $C_6H_{13}O_2P$, ($[M]^+$) 148.0653, found 148.0657.

Butyl (*trans*-hexen-2-yl) phosphinate (Table 4.2, entry 10b-c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (dt, J_{HP} = 540 Hz, J = 2 Hz, 1 H), 5.63 (dt, J = 22 Hz, J = 7 Hz, 1 H), 5.33 (dt, J = 22 Hz, J = 7 Hz, 1 H), 4.0 and 4.12 (dtd, J = 11 Hz, J = 8 Hz, J_{HP} = 7 Hz, 2 H), 2.59 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.03 (t, J = 7 Hz, 2 H), 1.68 (quint., J = 7 Hz, 2 H), 1.3 – 1.5 (m, 4 H), 0.94 (t, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.8 (d, J_{PCCC} = 14 Hz), 116.7 (d, J_{PCC} = 9 Hz), 66.4 (d, J_{POC} = 7 Hz), 34.9 (d, J_{PCCCC} = 3 Hz), 33.5 (d, J_{PC} = 91 Hz), 32.6 (d, J_{POCC} = 6 Hz), 22.4 (d, J_{PCCCCC} = 4 Hz), 18.9, 13.8, 13.7; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.14 (dt, J_{PH} = 540 Hz, J = 5 Hz); HRMS (EI$^+$) calcd. for $C_{10}H_{21}O_2P$, ($[M]^+$) 204.1279, found 204.1281.

Benzyl (*trans*-buten-2-yl) phosphinate (Table 4.2, entry 11b, Molecule 42). (92% purity); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (dt, J_{HP} = 545 Hz, J = 2 Hz, 1 H), 7.18 – 7.42 (m, 5 H), 5.62 (dt, J = 15 Hz, J = 6 Hz, 1 H), 5.33 (dt, J = 15 Hz, J = 7 Hz, 1 H), 5.02 and 5.11 (ABX*syst*, J_{AB} = 12 Hz, J_{AX} = 10 Hz, J_{BX} = 9 Hz, 2 H), 2.56 (dd, J_{HP} = 18 Hz, J = 7 Hz, 2 H), 1.69 (tq, J = 7 Hz, J = 1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 135.9 (d, J_{POCC} = 6 Hz), 132.8 (d, J_{PCCC} = 14 Hz), 128.9, 128.5, 128.3, 127.1, 117.5 (d, J_{PCC} = 9 Hz), 67.8 (d, J_{POC} = 7 Hz), 33.5 (d, J_{PC} = 91 Hz), 18.4 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.0 (dm, J_{PH} = 545 Hz). Minor compound (8%): *trans*-buten-2-yl phosphinic acid: ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.33 (dm, J_{PH} = 540 Hz).

Butyl (*trans*-buten-2-yl) phosphinate (Table 4.2, entry 11c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (dd, J_{HP} = 541 Hz, 1 H), 5.57 (dt, J = 11 Hz, J = 7 Hz, 1 H), 5.29 (dq, J = 11 Hz, J = 7 Hz, 1 H), 3.85 – 4.23 (m, 2 H), 2.50 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 1.54 – 1.72 (m, 5 H), 1.34 (sext., J = 7 Hz, 2 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.5 (d, J_{PCCC} = 14 Hz), 122.9 (d, J_{PCC} = 9 Hz), 71.4 (d, J_{POC} = 7 Hz), 38.6 (d, J_{PC} = 92 Hz), 37.6 (d, J_{POCC} = 6 Hz), 24.0, 23.4 (d, J_{PCCCC} = 3 Hz), 18.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.79 (dq, J_{PH} = 541 Hz, J = 6 Hz); HRMS (EI$^+$) calcd. for $C_8H_{17}O_2P$, ($[M]^+$) 176.0966, found 176.0967.

(2-Methyl-allyl) phosphinic acid (Table 4.2, entry 12a).[61] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.45 (bs, 1 H), 7.05 (d, J_{HP} = 559 Hz, 1 H), 5.0 (d, J = 5 Hz, 1 H), 4.88 (d, J = 5 Hz, 1 H), 5.19 – 5.32 (m, 2 H), 2.61 (d, J_{HP} = 20 Hz, 2H), 1.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.8 (d, J_{PCC} = 9 Hz), 116.4 (d, J_{PCCC} = 12 Hz), 39.3 (d, J_{PC} = 90 Hz), 24.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.68 (dm, J_{PH} = 559 Hz).

Butyl (2-methyl-allyl) phosphinate (Table 4.2, entry 12b-c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (dt, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 5.0 (dt, J = 6 Hz, J = 2 Hz, 1 H), 4.87 (d, J = 6 Hz, 1 H), 4.03 and 4.13 (dtd, J = 10 Hz, J = 8 Hz, J_{HP} = 7 Hz, 2 H), 2.63 (dd, J_{HP} = 19 Hz, J = 1 Hz, 1

H), 2.61 (ddd, J_{HP} = 20 Hz, J = 8 Hz, J = 2 Hz, J = 1 Hz, 1 H), 1.87 (dd, J = 3 Hz, J = 1 Hz, 3 H), 1.70 (quint., J = 7 Hz, 2 H), 1.42 (sext., J = 7 Hz, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 134.9 (d, J_{PCC} = 9 Hz), 116.2 (d, J_{PCCC} = 12 Hz), 66.5 (d, J_{POC} = 7 Hz), 38.7 (d, J_{PC} = 89 Hz), 32.6 (d, J_{POCC} = 6 Hz), 24.2 (d, J_{POCCC} = 3 Hz), 18.9, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.23 (dm, J_{PH} = 543 Hz).

General Procedure for the One-Pot Cross-Coupling of Alkyl Phosphinates with Allylic Electrophiles (Table 4.3). A 25 mL round bottomed flask was charged under air with $PhNH_3OP(O)H_2$ (6 mmol, 3 eq), reagent grade solvent (10-12 mL) and the alkoxysilane (4.2 mmol, 2.1 eq). The reaction flask was placed under N_2 and the allylic electrophile was added via syringe (2 mmol, 1 eq), followed by the additive (2 mmol, 1 eq) and the catalysts Pd_2dba_3/2xantphos (2 mol% with respect to the allylic substrate). The flask was then fitted with a condenser and the reactions were heated at reflux temperature of the corresponding solvent for 10 to 16 h. The reactions were monitored by ^{31}P NMR analysis of the crude reaction mixture. After cooling to room temperature, ^{31}P NMR revealed the formation of the product in the range of 30-40 ppm as a doublet. The reaction mixture was diluted with EtOAc and washed once with aqueous $NaHSO_4$ (2 M). The aqueous layer was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and then brine (1 x). Drying over $MgSO_4$, concentration and purification by column or by radial chromatography on silica gel afforded the pure products.

Representative Procedure for the One-Pot Cross-Coupling Reaction of Alkyl Phosphinates: Preparation of Butyl *(E)*-geranyl phosphinate (Table 4.3, entry 1b). To a suspension of anilinum hypophosphite (0.955 g, 6 mmol, 3 eq) and tetrabutoxysilane (1.346 g, 4.2 mmol, 2.1 eq) in toluene (12 ml) were added *trans*-geranyl acetate (0.43 mL, 0.393 g, 2 mmol, 1 eq) and ammonium formate (0.126 g, 2 mmol, 1 eq) followed by Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol%

Pd) and xantphos (0.0254 g, 0.044 mmol) at room temperature. The mixture was heated at reflux for 10 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 38.9 ppm (80%). The mixture was diluted with EtOAc and washed successively with 2 M aqueous $NaHSO_4$ (1 x). The aqueous phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine. Drying, concentration and purification by radial chromatography (4 mm thickness, hexanes/EtOAc 9/1, v/v, EtOAc) afforded the pure product as a clear yellow oil (0.269 g, 52% yield).

Butyl *(E)*-geranyl phosphinate (Table 4.3, entry 1b).[57] See above. **(Table 4.2, entries 3c-d, 3k-l).**

Butyl cinnamyl phosphinate (Table 4.3, entry 3b).[57,63,66] See above. **(Table 4.1, entries 1c-d).**

Butyl allyl phosphinate (Table 4.3, entry 4b).[243,57,66] See above. **(Table 4.2, entry 1b).**

Butyl (3-methyl-buten-2-yl) phosphinate (Table 4.3, entry 5).[57] See above **(Table 4.2, entry 5d, 9a-b).**

Representative Procedure for Table 4.4: Preparation of Ethyl propyl phosphinate (Table 4.4, entry 3).[244] An Ace Glass® pressure tube fitted with a rubber septum was charged with a suspension of anilinum hypophosphite (0.955 g, 6 mmol, 3 eq) and tetraethoxysilane (0.94 mL, 0.875 g, 4.2 mmol, 2.1 eq) in reagent grade CH_3CN (12 mL) and was heated at reflux temperature under N_2 for 2 h and then allowed to warm to room temperature. Allyl carbonate (prepared from allyl alcohol and ethyl chloroformate using Et_3N as base, 0.260 g, 2 mmol, 1 eq), ammonium formate (0.126 g, 2 mmol, 1 eq), Pd_2dba_3 (0.0184 g, 0.02 mmol, 1 mol% Pd) and xantphos (0.0254 g, 0.044 mmol) were added in that order while stirring. The tube was tightly closed/sealed with the corresponding PTFE plug and heated at reflux for 8 h. ^{31}P NMR analysis indicated 78% conversion to the product (40.9 ppm, doublet). The resulting mixture was diluted with EtOAc and washed with 2 M aqueous $NaHSO_4$ (1 x). The aqueous layer was extracted with

EtOAc (3 x) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine. Concentration and purification by column chromatography on silica gel (hexanes/EtOAc, 2/1 v/v to EtOAc, 100% v/v) gave the product in 45% yield (0.122 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (dt, J_{HP} = 527 Hz, J = 2 Hz, 1 H), 4.09 and 4.18 (dtd, J = 10 Hz, J = 9 Hz, J_{HP} = 7 Hz, 2 H), 1.58 – 1.83 (m, 4 H), 1.37 (t, J = 7 Hz, 3 H), 1.05 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.5 (d, J_{POC} = 8 Hz), 30.7 (d, J_{PC} = 94 Hz), 16.3 (d, J_{PCC} = 6 Hz), 15.1 (d, J_{PCCC} = 16 Hz), 14.5 (d, J_{POCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.06 (dt, J_{PH} = 527 Hz, J = 14 Hz).

Preparation of Diethyl (*(E)*-3,7,11-trimethyl-dodecen-2-yl) phosphonate (Eq. 4.4). To a suspension of $PhNH_3OP(O)H_2$ (1.591 g, 10 mmol, 2.5 eq) in CH_3CN (20 mL) were added *trans, trans*-farnesyl acetate (1.2 mL, 1.058 g, 4 mmol, 1 eq), Pd_2dba_3 (0.0092 g, 0.01 mmol, 0.5 mol% Pd) and xantphos (0.0127 g, 0.022 mmol) at room temperature. The solution was heated at reflux with good stirring for 6 h. After cooling to room temperature, pivaloyl chloride (2.5 mL, 2.412 g, 20 mmol) and ethanol (200 proof) (1.8 mL, 1.38 g, 30 mmol) were added at room temperature and the reaction was stirred for 6 h under N_2. After this time, anhydrous CCl_4 (12.7 mL, 20.7 g, 132 mmol), ethanol (200 proof) (12.8 mL, 10.135 g, 220 mmol), and triethylamine (6.1 mL, 4.452 g, 44 mmol) were added at rt and the resulting mixture was stirred under N_2 for 6 more hours. The reaction was quenched with 1 M $NaHSO_4$ and extracted with EtOAc. The aqueous phase was separated and extracted with two additional portions of EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) furnished the pure phosphonate as an oil (0.720 g, 52% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.15 – 5.27 (m, 1 H), 4.10 (quint., J = 6 Hz, 4 H), 2.58 (dd, J_{HP} = 22 Hz, J = 8 Hz, 2 H), 2.01 – 2.13 (m, 3 H), 1.48 – 1.82 (m, 23 H), 1.32 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.9 (d, J_{PCCC} = 15

Hz), 113.2 (d, J_{PCC} = 11 Hz), 74.7, 71.1, 62.0 (d, J_{POC} = 7 Hz, 2 C), 46.2, 44.2, 43.7, 39.7 (d, J_{PCCCCC} = 3 Hz), 32.7 (d, J_{PCCCC} = 9 Hz), 29.9, 26.5 (d, J_{PC} = 140 Hz), 22.8 (d, J_{POCC} = 3 Hz, 2 C), 20.7, 16.7, 16.3 (d, J_{PCCCC} = 3 Hz), 16.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 29.71.

Preparation of Benzyl (2-cyanoethyl)buten-2-yl phosphinate (Scheme 4.4, Molecule 43). Note: Details for the preparation and characterization of the starting material benzyl (*trans*-buten-2-yl) phosphinate (Table 4.2, entry 11b, Molecule **42**) are mentioned above. Procedure: An oven-dried 50 mL round bottomed flask was placed under nitrogen atmosphere and was subsequently charged with a solution of **42** (0.504 g, 2.4 mmol, 1.2 eq) in anhydrous CH_2Cl_2 (10 mL) at room temperature. BSA (0.407 g, 0.49 mL, 2 mmol, 1 eq) and acrylonitrile (0.127 g, 0.16 mL, 2.4 mmol, 1.2 eq) were added via syringe and the solution was stirred at room temperature overnight. The reaction was quenched by stirring vigorously with 2 M HCl (5 mL) for 15 min. The resulting mixture was diluted with CH_2Cl_2 and washed with 2 M HCl (2 x) and H_2O (1 x). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography on silica gel (hexanes/EtOAc 1/1, v/v to EtOAc/MeOH 95/5 v/v) to give 0.526 g of **43** (50% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 – 7.48 (m, 5 H), 5.53 – 5.7 (m, 1 H), 5.25 – 5.43 (m, 1 H), 5.07 (d, J = 9 Hz, 1 H), 5.06 (d, J = 9 Hz, 1 H), 2.43 – 2.73 (m, 4 H), 2.05 (dt, J_{HP} = 11 Hz, J = 8 Hz, 2 H), 1.70 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.2 (d, J_{POCC} = 5 Hz), 132.5 (d, J_{PCCC} = 13 Hz), 129.0 (2 C), 128.4 (2 C), 118.9 (d, J_{PCC} = 9 Hz), 66.8 (d, J_{POC} = 6 Hz), 33.8 (d, J_{PC} = 90 Hz), 23.6 (d, J_{PC} = 91 Hz), 18.4, 10.6 (d, J_{PCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 52.23.

Chapter 5, Section 5.2

General Procedure for the Pd-catalyzed Rearrangement of Allylic Phosphinates (Table 5.1). To a DMF (dried over 4Å molecular sieves) solution of an allylic phosphinate (0.2 M, 1

eq), itself prepared by esterification with (Allyl-O)$_4$Si,[18] or via transesterification with phenyl phosphinate ((PhO)$_4$Si/ROH), or using an activating agent (PivCl/ROH), was added an additive (0 - 2 eq), followed by Pd_2dba_3 (1 – 2 mol% Pd) and xantphos (1.1 eq with respect to Pd) at room temperature. The reaction mixture was either heated at 85°C, or stirred at room temperature for 4 to 12 h under nitrogen. For low boiling point allylic alcohols the reaction was run in a pressure tube. At this time, ^{31}P NMR monitoring of the crude reaction mixture showed the formation of the rearranged product (20 -32 ppm, doublet). DMF was eliminated by rotary evaporation (45°C, 0.5 mmHg) and the residue was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous layer was subsequently extracted with EtOAc (2 x) and the combine organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was suspended in 10 mL of reagent grade toluene and (RO)$_4$Si (1 eq) was added at room temperature. The heterogeneous mixture was heated at reflux temperature for 12 to 16 h and then diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous layer was extracted with two additional portions of EtOAc and the organic layer was washed with saturated $NaHCO_3$ (1 x) and brine (1 x). Drying over $MgSO_4$, concentration, and purification by chromatography on silica gel (hexanes/EtOAc) gave the pure allylic-*H*-phosphinate esters.

(PhO)$_4$Si/ROH Method: A mixture of concentrated H_3PO_2 (1 eq), (PhO)$_4$Si[234] (1 eq) and an allylic alcohol (1 to 2 eq) in dry DMF (0.2 M) was heated at 85°C under N_2, while stirring for 2 h. ^{31}P NMR of the crude reaction mixture revealed the formation of the allylic phosphinate ester in the range of 12 - 20 ppm, as a triplet. The product was used immediately as the DMF solution.

PivCl/ROH Method: To a 0.2 M solution of $PhNH_3OP(O)H_2$ (1 eq) in dry DMF was added pyridine (1.25 eq), an allylic alcohol (1.5 eq) and pivaloyl chloride (1.1 eq) under a N_2 atmosphere at room temperature. The solution is stirred for 1.5 to 2 h and used *in situ* as the DMF solution.

Representative Procedure for the Rearrangement of Allylic Phosphinates: Preparation of Butyl cinnamyl phosphinate (Table 5.1, entry 2c).[66] To a solution of concentrated H_3PO_2 (0.132 g, 2 mmol, 1 eq) in dry DMF (10 mL) was added $(PhO)_4Si$[1] (0.800 g, 2 mmol, 1 eq) and cinnamyl alcohol (0.514 mL, 4 mmol, 2 eq). The resulting solution was heated at 85°C for 2 h. After cooling to room temperature, ^{31}P NMR analysis showed the cinnamyl hypophosphite ester at 14.32 ppm (76%). To the reaction mixture was added Pd_2dba_3 (0.0092 g, 0.01 mmol, 1 mol% Pd) and xantphos (0.0115 g, 0.02 mmol). The resulting mixture was heated at 85°C for 2 h or stirred for 4 h at room temperature. The solution was then concentrated in vacuo and the residue was diluted with EtOAc and washed 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, dried over $MgSO_4$ and concentrated. The residue was dissolved in toluene (10 mL), followed by addition of $(BuO)_4Si$ (0.641 g, 2 mmol). The resulting mixture was stirred at reflux for 12 h, then diluted with EtOAc and washed with brine. Drying, concentration and purification by radial chromatography (4 mm thickness, hexanes/EtOAc 5:1, v/v, EtOAc), afforded the product, butyl cinnamyl phosphinate as a yellow oil (0.286 g, 60%).

Butyl cinnamyl phosphinate (Table 5.1, entry 2c).[57,63,66] See above **(Table 4.1, entries 1c-1d).**

Butyl *(E)*-geranyl phosphinate (Table 5.1, entry 3a).[57] See above **(Table 4.2, entries 3c-d, 3k-l).**

***trans*-Hexen-2-yl (trans-hexen-2-yl) phosphinate (Table 5.1, entry 4).** ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (dq, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 5.76 – 5.90 (m, 1 H), 5.53 – 5.73 (m, 2 H), 5.26 – 5.43 (m, 1 H), 4.42 – 4.63 (m, 2 H), 2.60 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.03 (2 x t, J = 7 Hz, 4 H), 1.42 (2 x sext., J = 7 Hz, 4 H), 0.91 (td, J = 5 Hz, 3 H), 0.89 (td, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.45 (dm J_{PH} = 543 Hz).

General Procedure for the Optimization of the Pd-Catalyzed Allylation of H_3PO_2 with Cinnamyl Alcohol (Table 5.2). Concentrated or 50 wt.% aqueous H_3PO_2 or D_3PO_2 (1 - 3 eq) and an allylic alcohol (1 eq), were dissolved in the appropriate amount of dry (over 4Å molecular sieves) or reagent grade DMF to achieve the desired concentration (0.17 - 4 M). The palladium catalyst, the ligand (0.05 - 2.0 mol% relative to the allylic alcohol) and the additive (0 - 1 eq of Et_3N) were added under air, at room temperature. The reaction was heated at 85 °C or kept at room temperature, either opened into air (using a septum with a needle), or under N_2, while stirring vigorously for 1.5 to 16 h. The advance of the reaction was monitored by ^{31}P NMR on a sample of the crude reaction mixture (δ = 25-30 ppm; from H_3PO_2, doublet; from D_3PO_2, triplet). The resulting solution is allowed to cool to room temperature and concentrated by rotary evaporation (45 - 50°C, 0.5 mmHg). The residue was diluted with EtOAc and then two different procedures were followed: (a) the EtOAc mixture was stirred with activated charcoal (20-30 mg/1 mmol of allylic alcohol) at rt for 30 min, filtered with suction using a Büchner funnel through a celite pad, and then worked up, or (b) the workup was done directly. The extractive workup was done by washing the EtOAc layer with 2 M aqueous HCl. The aqueous layer was then extracted with EtOAc (2 x) and the combined organic layers were washed with brine (1 x). Drying on $MgSO_4$ and concentration afforded the product cinnamyl phosphinic acid in more than 95% purity. The additional treatment with activated charcoal (b) was particularly useful in large-scale processes, to eliminate traces of Pd.

Representative Procedure for the Synthesis of Cinnamyl-*H*-phosphinic acid (or Cinnamyl phosphinic acid) (Table 5.2, entry 9).[66,190] A 1-L, round-bottomed flask (Note 1) equipped with a magnetic stirring bar is charged under air, with a solution of concentrated hypophosphorous acid (19.80 g, 300 mmol, 2 eq) (Notes 2, 3) in *N,N*-dimethylformamide (100 mL) (Note 4), and more of *N,N*-dimethylformamide (200 mL) is poured into the flask via a graduated cylinder.

Mesitylene (20.9 mL, 18.03 g, 150 mmol, 1 eq) (Note 5) and cinnamyl alcohol (19.70 mL, 20.13 g, 150 mmol, 1 eq) (Note 6) are added via syringe (Note 7). The flask is then fitted with a rubber septum and placed on a magnetic stir plate. After stirring for 5 min, $Pd(OAc)_2$ (0.0674 g, 0.300 mmol, 0.002 equiv) (Note 8), and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.1904 g, 0.330 mmol, 0.0022 eq) (Note 9) are added by temporarily removing the septum. Material adhering to the sides of the reaction flask is rinsed into the reaction mixture with 5 mL of *N,N*-dimethylformamide, resulting in a clear brown solution. Stirring is maintained and the reaction flask is equipped with a Claisen adapter fitted with a reflux condenser with nitrogen inlet, and a thermocouple temperature probe adapter. Under a nitrogen atmosphere, the system is placed in a heating mantle filled with sand (Note 10) and the thermocouple is inserted through the adapter. The solution is heated at 85°C (internal temperature) for 7 h (Notes 11, 12). Heating and stirring are then interrupted, and the resulting solution is allowed to cool to room temperature (Notes 13, 14). After removing the nitrogen inlet and the water condenser, the reaction mixture is transferred to a 1-L, round bottomed flask (Note 15) and concentrated for 1 h by rotary evaporation (50°C, 0.5 mmHg). The residue is diluted with ethyl acetate (150 mL) and treated with activated charcoal (3.0 g) (Note 16). The resulting heterogeneous mixture is stirred for 30 min and filtered in *vacuo* through a Celite® pad (Note 17) in a Büchner funnel. The Celite is carefully washed with three 100 mL portions of ethyl acetate (Note 18) and the combined washings are transferred to a 1-L separatory funnel. The organic layer is washed with aqueous HCl (2 M, 250 mL) (Note 19) and the aqueous phase is separated and extracted with two 125 mL portions of ethyl acetate. The combined organic layers are washed with 200 mL of saturated NaCl solution, retreated with charcoal (1.0 g) and $MgSO_4$ (20 g) (Notes 20, 21), filtered through a second Celite pad in a Büchner funnel (Notes 17, 22), and concentrated under reduced pressure (40°C, 0.5 mmHg). The resulting pale yellow solid (around 26 g, 95% yield) (Note 23) is

dissolved in 100 mL of hot dichloromethane (35-38°C), and about 160 mL of hexane (38°C) is added until a light yellow homogeneous solution is obtained. The solution is cooled at -15°C for 2 h and the resulting white crystals (22.4 g) are collected by suction filtration on a Büchner funnel, and washed with ice-cold hexane (100 mL). The filtrate is concentrated under reduce pressure and the residue is dissolved in 20 mL of dichloromethane (35°C), and 30 mL of hexane (35°C). The solution is cooled at -15°C overnight and a second crop of crystals is collected by suction filtration, and washed with ice-cold hexane (20 mL). The two crops of crystals are combined and dried overnight at 0.1 mmHg to provide 25.1 g of cinnamyl-*H*-phosphinic acid (92%) as white crystals (Note 24).

Notes:

1. The success of the reaction does not depend, neither on having previously dried the glassware, nor on adding the reagents under a nitrogen atmosphere.

2. Aqueous hypophosphorous acid (50 wt.%) was purchased from Aldrich Chemical Company, Inc. and concentrated before reaction, according to the following procedure. A 250-mL round bottomed flask is charged with 39.6 g of 50% aqueous hypophosphorous acid. The acid is concentrated for 30 min by rotary evaporation (40°C, 0.5 mmHg) and then diluted with *N,N*-dimethylformamide (80 mL) (see Note 3). The resulting solution is poured into the 1-L reaction flask. The flask was then rinsed with two 10 mL portions of *N,N*-dimethylformamide, which were also poured into the reaction flask. Over-drying H_3PO_2 may result in the formation of a yellow solid of high phosphorus content.

3. H_3PO_2 is used in excess (2 eq) in order to prevent *in situ* oxidation of the products into phosphonic acids.

4. Reagent grade *N,N*-dimethylformamide (≥99.8%) was purchased from Aldrich Chemical Company, Inc. and used as received.

5. Mesitylene (standard for GC, ≥99.8%) was purchased from Fluka and used as received. This reagent does not interfere with the reaction; it works only as internal standard for GC-monitoring of the reaction progress and can be omitted.

6.Cinna myl alcohol (98%) was purchased from Aldrich Chemical Company, Inc. and used with out further purification.

7. Due to the low melting point of cinnamyl alcohol (30-33°C), the reagent was immersed in a water bath at 45°C for 30 min before use to facilitate its addition via syringe. A preheated (45-50°C) 20 mL glass syringe fitted with a short needle (50 mm) was used in order to avoid solidification of the reagent during the addition.

8. Palladium (II) acetate, min. 98% (99.9+%-Pd) was purchased from Strem Chemicals, Inc. and used as received.

9. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) (97%) was purchased from Aldrich Chemical Company, Inc. and used as received.

10. The surface of the solution was below the sand level and good stirring was maintained along the process.

11. A J-KEM Scientific, Inc. temperature controller model 150 with a Teflon-coated thermocouple was used with the heating mantle. The thermocouple was placed inside the solution (1-2 inches) and the temperature was set to 85°C. The reaction time was measured once the internal temperature of the solution was stabilized at 85±3°C, which took about 20-30 min.

12. The reaction was terminated when TLC analysis indicated that all the cinammyl alcohol was consumed. TLC was conducted using Merck silica gel 60 F-254 plates (elution with hexanes/ethyl acetate, 7:1; visualization by UV, and by immersion in anisaldehyde stain (by volume: 93% ethanol, 3.5% sulfuric acid, 1% acetic acid, and 2.5% anisaldehyde) followed by heating; R_f cinnamyl alcohol = 0.27, blue spot on anisaldehyde. The progress of the reaction was

also monitored by gas chromatography. GC analysis was performed on a HP5890 Gas Chromatograph equipped with a HP5 capillary column (30-m x 0.32-mm x 0.25-μm) and FID detector, under the following conditions: inlet temp 200°C; oven temp 60°C, 1 min; ramp1 5°C/min; final temp1: 160°C, final time1: 0 min; then ramp2: 25°C/min; final temp2: 280°C, final time2: 20 min; detector 280°C; split mode with constant make-up. For GC analysis, 3-drops of sample was diluted in 1 mL of diethyl ether. The solution was washed with 1 mL of saturated $NaHCO_3$ solution and 1-μL of the organic solution was injected in the GC; t_R = 18.72 min (cinnamyl alcohol), t_R = 8.69 min (mesitylene).

13. The sand bath was removed and replaced by a water bath.

14. 1 mL of the reaction mixture at room temperature was placed in an NMR tube for analysis. ^{31}P NMR (121.47 MHz, DMF) δ 28.35 ppm ~ 118% (dt, J_{HP} = 529 Hz, J = 19 Hz, Product), 4.70 ppm ~ 48% (t, J_{HP} = 526 Hz, H_3PO_2), 3.02 ~ 34% (d, J_{HP} = 641 Hz, H_3PO_3). The ^{31}P NMR yields were determined by integration of all the resonances in the ^{31}P NMR spectra.

15. The 1-L reaction flask was rinsed with ethyl acetate (20 mL).

16. Activated charcoal (purum p.a.) was purchased from Fluka and used as received to adsorb palladium.

17. Celite 545® was purchased from Fischer Scientific Co. A slurry mixture of 40 g of celite in ethyl acetate (about 50 mL) were placed in a Büchner funnel (7 cm diameter, 10-15 μ).

18. A milky suspension was obtained with some dark gel-like precipitate.

19. An emulsion with some black precipitate is formed at the interphase, which can be broken by using a stirring rod. Some black precipitate goes into the organic phase.

20. Magnesium sulfate (anhydrous, ≥97%) was purchased from Aldrich Chemical Company, Inc.

21. The mixture was stirred with activated charcoal (see Note 15) for 15 min, then $MgSO_4$ was added and stirring was continued for another 15 min.

22. The Celite pad was washed with two 50 mL portions of ethyl acetate.

23. Cinnamyl-*H*-phosphinic acid was pure according to the melting point (84-85°C), and NMR analysis (^{31}P, ^{1}H, ^{13}C). It was recrystallized to remove any trace of Pd.

24. The product is stable and can be stored for several months at rt. Full characterization of the product was as follows: m.p.= 85 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ: 2.77 (dd, J_{HP} = 19.3 Hz, J = 7.0 Hz, 2H), 6.02 – 6.18 (m, 1H), 6.53 (dd, J = 15.8 Hz, J = 5.3 Hz, 1H), 7.04 (d, J_{HP} = 558.2 Hz, 1H), 7.18 – 7.42 (m, 5H), 10.45 (bs, 1H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 34.7 (d, J_{PC} = 91.0 Hz, CH_2), 117.0 (d, J_{PCC} = 10.1 Hz, CH), 126.6 (2xCH), 128.1 (CH), 128.8 (2xCH), 136.3 (d, J_{PCCC} = 14.7 Hz, CH), 136.7 (d, J_{PCCCC} = 4.0 Hz, C); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ: 35.32 (dm, J_{PH} = 557.7 Hz); IR (thin film, KBr), cm^{-1}: 2621 and 1688 (P-O-H); 2422, 2292 and 2181 (P-H); and 1241 (P=O); UV (EtOH, C≈8μM) λ_{max} = 274 nm; HRMS (EI) *m/z* Calcd for $C_9H_{11}O_2P$: 182.0495. Found: 182.0497. Anal. Calcd. for $C_9H_{11}O_2P$: C, 59.34; H, 6.09. Found: C, 59.04; H, 6.02. Analysis by Reverse Phase Ion-Pairing HPLC:[236] Product t_R 1.425 min. Agilent Zorbax® Eclipse XDB-C8 column (4.6 x 150 mm, 5μm) with a guard column (Agilent Zorbax® ODS, 4.6 x 12.5 mm, 5μm), 1 mL/min flow (isocratic), using as mobile phase a Buffer (5 mM hexadecyltrimethylammonium bromide, 50 mM ammonium acetate, and 2% MeOH. pH 4.85, adjusted with acetic acid). Injection volume: 5 μl, C≈0.24 mg/1 mL (EtOH).

Representative Procedure for the Pd-Catalyzed Allylation of H_3PO_2 using Pd_2dba_3/Polystyrene-Supported Nixantphos.[34] Preparation of Cinnamyl phosphinic acid (Table 5.2, entry 10).[66] Multi-run reaction: To a solution of concentrated H_3PO_2 (0.264 g, 4 mmol) in dry DMF (10 mL) was added cinnamyl alcohol (0.274 g, 2 mmol), Pd_2dba_3 (0.0092 g, 0.01 mmol) and polystyrene-supported nixantphos[34] (0.18 mmol/g, 0.111 g, 0.02 mmol). The reaction mixture was heated at 85 °C under N_2 for 4 h. The mixture was suction-filtered in order to separate the resin from the filtrate. The resin was washed with DMF and kept apart to be used

in the next run without further precautions. The filtrates were collected and stored in a stoppered flask. The procedure above was repeated four more times. The resin was filtered, washed and reused each time for the next run. At the end of the sequence, all the filtrates were combined and concentrated under high vacuum. The residue was diluted with EtOAc and washed with 2 M aqueous HCl (1x). The aqueous phase was extracted twice with EtOAc and the combined organic fractions were washed with brine. After drying over $MgSO_4$ and concentration, the product was obtained as a white solid (1.67 g, 92% over 5 runs). For full characterization of the product, see above (Table 5.2, entry 9).[66,190]

General Procedure for the Pd-Catalyzed Allylation of H_3PO_2 (Table 5.3). Unless otherwise noted, the reactions were conducted in dry DMF (over activated 4Å molecular sieves) at 85°C, with 0.5 mol% of catalyst, according to the following procedure: To a solution of concentrated H_3PO_2 (0.132-0.396 g, 2-6 mmol, 1-3 eq) in anhydrous DMF (10 mL) was added the alcohol substrate (2 mmol, 1 eq), followed by Pd_2dba_3 (0.0046 g, 0.005 mmol, 0.5% Pd) and xantphos (0.0063 g, 0.011 mmol, 1.1 eq relative to the amount of Pd) at room temperature, under air. [*Note: In general the reactions were performed under 0.2 M concentration, however allyl alcohol required 2 mol% of Pd/ligand and secondary alcohols required 2 M concentration (1 mL DMF) and 2 mol% of Pd/ligand: Pd_2dba_3 (0.0184 g, 0.02 mmol) and xantphos (0.0254 g, 0.044 mmol)*]. The reaction was heated at 85°C under a N_2 atmosphere for 1.5 to 12 h, until completion (^{31}P NMR monitoring on a sample of the crude reaction mixture). If successful, the reaction mixture was concentrated by rotary evaporation (45°C, 0.5 mmHg) for 30 min. The residue was diluted with EtOAc, treated with activated charcoal (30 mg/1 mmol of allylic alcohol) at rt for 20-30 min, suction-filtered through a celite pad, and washed with 2 M aqueous HCl. The aqueous layer was extracted with EtOAc (2 x) and the combined organic layers were washed with brine. Drying over $MgSO_4$ and concentration gave the product in more than 95% purity.

Representative Procedure for the Pd-Catalyzed Allylation of H_3PO_2: Preparation of *(E, E)*-Farnesyl phosphinic acid (Table 5.3, entry 7b).[66] To a solution of concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) in dry DMF (10 mL) was added *trans-trans*-farnesol (0.51 mL, 0.445 g, 2 mmol, 1 eq) followed by Pd_2dba_3 (0.0046 g, 0.005 mmol, 0.5 mol% Pd) and xantphos (0.0063 g, 0.011 mmol), at room temperature. The reaction was heated at 85°C under N_2 for 8 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 26.4 ppm (100%). The mixture was concentrated under high vacuum. The residue was diluted with EtOAc, treated with activated charcoal for 20 min, filtered through a celite pad, and washed successively with 2 M aqueous HCl. The aqueous phase was extracted with EtOAc (2 x) and the combined organic phase was washed with brine, dried, and concentrated to give 0.508 g of the pure product as a light yellow oil (94%).

General Procedure for the Tandem Pd-Catalyzed Allylation-Esterification (Table 5.3). Unless otherwise indicated, 0.5 mol% of Pd/xantphos was used. (Note: *Allyl alcohol required 2 mol% of Pd/ligand*). To a solution of concentrated H_3PO_2 (0.330-0.396 g, 5-6 mmol, 2.5-3 eq) in dry DMF (10 mL) was added the allylic alcohol (2 mmol, 1 eq), Pd_2dba_3 (0.0046 g, 0.005 mmol, 0.5% Pd) and xantphos (0.0063 g, 0.011 mmol, 0.55 mol%) at room temperature. The resulting solution was heated at 85°C, while stirring vigorously, under N_2 for 1.5 to 12 h. After cooling to room temperature, ^{31}P NMR showed the product in the range of 25-34 ppm (^{31}P-^{1}H coupled, doublet). $(BuO)_4Si$ (1.603-1.923 g, 5-6 mmol, 1 eq relative to the amount of H_3PO_2) was added at rt, and the mixture was heated again at 85°C for 8 to 16 h under N_2. ^{31}P NMR analysis showed the signal from the esterified product shifted downfield with respect to the signal from the acid (δ = 34-40 ppm). The reaction mixture was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous phase was subsequently extracted with two portions of EtOAc and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ and then with brine. The crude

product was purified by chromatography (radial or column) on silica gel, using hexanes/EtOAc mixtures as mobile phase.

Representative Procedure for the Tandem Allylation–Esterification Reaction: Preparation of Butyl allyl phosphinate (Table 5.3, entry 12).[243,57,66] A solution of concentrated H_3PO_2 (0.396 g, 6 mmol, 3 eq) in anhydrous DMF (10 mL) was placed in an Ace Glass® pressure tube fitted with a rubber septum under a N_2 atmosphere. Allyl alcohol (0.14 mL, 0.116 g, 2 mmol, 1 eq) was added via syringe, followed by Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol). The tube was tightly closed with the corresponding PTFE plug and heated at reflux for 3 h in an oil bath at 85 °C. The reaction was allowed to cool to room temperature, the tube was carefully opened and the PTFE plug was replaced by a septum. $(BuO)_4Si$ (2.1 mL, 1.923 g, 6 mmol, 3 eq) was added through the septum under N_2 and the resulting mixture was heated at 85°C for 14 h, when ^{31}P NMR analysis revealed the formation of the esterified product at 37.2 ppm (63%). The solution was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration and purification by column chromatography over silica gel (hexanes/EtOAc 1:1, v/v, EtOAc) afforded 0.140 g of the product as a colorless oil (43%).

Cinnamyl phosphinic acid (Table 5.3, entries 1a-c).[66,190] See above **(Table 5.2, entry 9).**

Butyl cinnamyl phosphinate (Table 5.3, entries 1d-e).[57,63,66] See above **(Table 4.1, entries 1c-1d).**

(*trans*-Hexen-2-yl) phosphinic acid (Table 5.3, entries 2a and 3a).[66] See above **(Table 4.2, entry 10a).**

Butyl (*trans*-hexen-2-yl) phosphinate (Table 5.3, entries 2b, 3b and 3c). See above **(Table**

4.2, entry 10b-c).

(*trans*-Buten-2-yl) phosphinic acid (Table 5.3, entry 4a).[66] See above **(Table 4.2, entry 11a).**

Butyl (*trans*-buten-2-yl) phosphinate (Table 5.3, entry 4b). See above **(Table 4.2, entry 11c).**

(3-Methyl-buten-2-yl) phosphinic acid (Table 5.3, entries 5a and 23a).[66] See above **(Table 2.8, entry 1).**

Butyl (3-methyl-buten-2-yl) phosphinate (Table 5.3, entries 5b and 23b).[57] See above **(Table 4.2, entries 5d, 9a-b).**

(*E*)-Geranyl phosphinic acid (Table 5.3, entry 6a).[66] See above **(Table 4.2, entries 3e-i).**

Butyl *(E)*-geranyl phosphinate (Table 5.3, entry 6b).[57] **(Table 4.2, entries 3c-d, 3k-l).**

***(E*, *E)*-Farnesyl phosphinic acid (Table 5.3, entries 7a-b).**[66] See above **(Table 4.2, entries 4a and 4d).**

Butyl *(E, E)*-farnesyl phosphinate (Table 5.3, entry 7c).[57] See above **(Table 4.2, entry 4c).**

Butyl [(2*E*)-4-(phenylmethoxy)-buten-2-yl] phosphinate (Table 5.3, entry 9b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 – 7.40 (m, 5 H), 7.00 (dt, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 5.79 (ddd, J = 15 Hz, J = 5 Hz, J = 6 Hz, 1 H), 5.68 (ddd, J = 15 Hz, J = 7 Hz, J = 6 Hz, 1 H), 4.51 (s, 2 H), 4.03 (t, J = 10 Hz, 2 H), 3.93 – 4.19 (m, 2 H), 2.66 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 1.69 (quint., J = 7 Hz, 2 H), 1.42 (sext., J = 7 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.0, 132.2 (d, J_{PCCC} = 14 Hz), 127.4 (2 C), 126.7 (2 C), 126.6, 119.4 (d, J_{PCC} = 9 Hz), 71.2, 69.0 (d, J_{PCCCC} = 3 Hz), 65.3 (d, J_{POC} = 7 Hz), 32.3 (d, J_{PC} = 91 Hz), 31.4 (d, J_{POCC} = 6 Hz), 17.7, 12.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.99 (dm, J_{PH} = 543 Hz); HRMS (CI) calcd. for $C_{15}H_{23}O_3P$, ($[M+H]^+$) 283.1463, found 283.1456.

Butyl allyl phosphinate (Table 5.3, entry 12).[243,57,66] See above **(Table 4.2, entry 1b).**

(2-Methyl-3-phenyl-propen-2-yl) phosphinic acid (Table 5.3, entry 15a).[66] m.p. = 62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.15 (bs, 1 H), 7.16 – 7.36 (m, 5 H), 7.11 (d, J_{HP} = 558 Hz, 1 H),

6.39 (d, J = 6 Hz, 1 H), 2.73 (d, J_{HP} = 19 Hz, 2 H), 1.98 (dd, J = 4 Hz, J = 2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.3 (d, J_{PCCCC} = 4 Hz), 130.4 (d, J_{PCC} = 12 Hz), 128.9 (d, J_{PCCCCC} = 3 Hz, 2 C), 128.1, 127.6 (d, J_{PCCC} = 11 Hz), 126.6 (2 C), 41.6 (d, J_{PC} = 89 Hz), 19.6 (d, J_{PCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.87 (dm, J_{PH} = 558 Hz); HRMS (EI^+) calcd. for $C_{10}H_{13}O_2P$, ($[M]^+$) 196.0653, found 196.0654.

Butyl (2-methyl-3-phenyl-propen-2-yl) phosphinate (Table 5.3, entry 15b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 – 7.39 (m, 5 H), 7.12 (dd, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 6.40 (d, J = 6 Hz, 1 H), 4.15 and 4.05 (tdd, J = 12 Hz, J = 8 Hz, J_{HP} = 4 Hz, 2 H), 2.76 (dd, J_{HP} = 19 Hz, J = 6 Hz, 2 H), 2.0 (dd, J = 4 Hz, J = 1 Hz, 3 H), 1.70 (quint., J = 7 Hz, 2 H), 1.42 (sext., J = 7 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.4 (d, J_{PCCCC} = 4 Hz), 130.6 (d, J_{PCC} = 12 Hz), 129.0 (d, J_{PCCCCC} = 3 Hz, 2 C), 128.4, 127.9 (d, J_{PCCC} = 10 Hz), 126.9 (2 C), 66.6 (d, J_{POC} = 7 Hz), 41.3 (d, J_{PC} = 89 Hz), 32.6 (d, J_{POCC} = 6 Hz), 19.8 (d, J_{PCCC} = 3 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.73 (dm, J_{PH} = 543 Hz); HRMS (EI^+) calcd. for $C_{14}H_{21}O_2P$, ($[M]^+$) 252.1279, found 252.1277.

6,6-Dimethyl bicyclo(3.1.1)hept-2-ene-2-(methyl phosphinic acid) (Myrtenyl phosphinic acid) (Table 5.3, entry 16a).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.61 (bs, 1 H), 6.96 (d, J_{HP} = 553 Hz, 1 H), 5.40 – 5.52 (m, 1 H), 2.57 (d, J_{HP} = 19 Hz, 2 H), 2.34 – 2.44 (m, 1 H), 2.20 – 2.34 (m, 2 H), 2.16 (t, J = 6 Hz, 1 H), 2.06 – 2.13 (m, 2 H), 1.28 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.9 (d, J_{PCC} = 10 Hz), 122.9 (d, J_{PCCC} = 14 Hz), 46.7 (d, J_{PCCC} = 3 Hz), 40.2, 38.5 (d, J_{PC} = 91 Hz), 38.2 (d, J_{PCCCC} = 3 Hz), 31.6 (d, J_{PCCCC} = 3 Hz), 31.5 (d, J_{PCCCC} = 4 Hz), 26.2, 21.2; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.59 (dm, J_{PH} = 553 Hz); HRMS (EI^+) calcd. for $C_{10}H_{17}O_2P$, ($[M]^+$) 200.0966, found 200.0964.

6,6-Dimethyl bicyclo(3.1.1)hept-2-ene-2-(methyl-butoxyphosphinoyl) (Myrtenyl phosphinic acid) (Table 5.3, entry 16b). Mixture of diastereoisomers (50/50); ^{1}H NMR ($CDCl_3$, 300 MHz)

δ 6.97 (dq, J_{HP} = 539 Hz, J =2 Hz, 1 H), 5.47 (m, 1 H), 3.98 – 4.11 (tdd, J = 8 Hz, J = 4 Hz, J = 2 Hz, 2 H), 2.46 – 2.73 (m, 2 H), 2.34 – 2.46 (m, 2 H), 2.21 – 2.34 (m, 2 H), 2.05 – 2.20 (m, 2 H), 1.68 (qd, J = 6 Hz, J = 3 Hz, 2 H), 1.42 (sext., J = 7 Hz, 2 H), 1.29 (s, 3 H), 0.94 (td, J = 7 Hz, J = 1 Hz, 3 H), 0.87 (d, J = 3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.0 (d, J_{PCC} = 11 Hz), 136.9 (d, J_{PCC} = 10 Hz), 123.2 (d, J_{PCCC} = 14 Hz), 123.1 (d, J_{PCCC} = 14 Hz), 66.3 (d, J_{POC} = 7 Hz), 66.1 (d, J_{POC} = 7 Hz), 47.1, 47.0, 46.9, 46.8, 40.4 (2 C), 38.3 (d, J_{PCCCC} = 2 Hz, 2 C), 38.1 (d, J_{PC} = 90 Hz), 38.0 (d, J_{PC} = 90 Hz), 32.6 (d, J_{POCC} = 6 Hz, 2 C), 31.8 (d, J_{PCCCC} = 3 Hz), 31.7 (d, J_{PCCCC} = 3 Hz), 26.3 (2 C), 21.4 (d, J_{PCCCCC} = 4 Hz, 2 C), 18.9 (d, J_{POCCC} = 2 Hz, 2 C), 13.8 (2 C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.70 (dq, J_{PH} = 539 Hz, J = 9 Hz) and 38.14 (dq, J_{PH} = 539 Hz, J = 9 Hz); HRMS (EI$^+$) calcd. for $C_{14}H_{25}O_2P$, ([M]$^+$) 256.1592, found 256.1589.

(2-Cyclohexyl-ethen-2-yl) phosphinic acid (Table 5.3, entry 21).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.96 (bs, 1H), 6.93 (d, J_{HP} = 552 Hz, 1H), 5.07 (q, J = 7 Hz, 1H), 2.59 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2H), 2.08 – 2.21 (m, 4H), 1.47 – 1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 146.9 (d, J_{PCCC} = 14 Hz), 107.0 (d, J_{PCC} = 9 Hz), 37.4 (d, J_{PCCCC} = 3 Hz), 29.4 (d, J_{PC} = 92 Hz), 29.3 (d, J_{PCCCC} = 3 Hz), 28.7 (d, J_{PCCCCC} = 3 Hz), 28.0 (d, J_{PCCCCC} = 2 Hz), 26.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.93 (ddd, J_{PH} = 552 Hz, J = 35 Hz, J = 2 Hz); HRMS (EI$^+$) calcd. for $C_9H_{15}O_2P$, ([M]$^+$) 174.0810, found 174.0809.

2-[(*N*-Ethyloxycarbonyl-4-piperidinyl)-ethen-2-yl] phosphinic acid (Table 5.3, entry 22a).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.43 (bs, 1 H), 6.97 (d, J_{HP} = 550 Hz, 1 H), 5.18 – 5.30 (m, 1 H), 4.14 (q, J = 7 Hz, 2 H), 3.38 – 3.55 (m, 4 H), 2.63 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 2.13 – 2.31 (m, 4 H), 1.27 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.7, 141.9 (d, J_{PCCC} = 14 Hz), 110.2 (d, J_{PCC} = 9 Hz), 61.7, 45.6, 44.7, 36.1, 29.4 (d, J_{PC} = 91 Hz), 28.8, 14.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.27 (dm, J_{PH} = 550 Hz); HRMS (EI$^+$) calcd. for $C_{10}H_{18}NO_4P$, ([M]$^+$) 247.0973, found 247.0981.

Butyl [2-(*N*-Ethyloxycarbonyl-4-piperidinyl)-ethen-2-yl] phosphinate (Table 5.3, entry 22b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (d, J_{HP} = 540 Hz, 1H), 5.24 (q, J = 7 Hz, 1H), 4.15 (q, J = 7 Hz, 2 H), 3.94 – 4.20 (m, 2H), 3.38 – 3.56 (m, 4 H), 2.66 (dd, J_{HP} = 18 Hz, J = 8 Hz, 2H), 2.18 – 2.30 (m, 4 H), 1.68 (q, J = 7 Hz, 2 H), 1.41 (sext., J = 7 Hz, 2 H), 1.27 (t, J = 7 Hz, 3H), 0.94 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.6, 141.7 (d, J_{PCCC} = 14 Hz), 110.2 (d, J_{PCC} = 9 Hz), 66.7 (d, J_{POC} = 7 Hz), 61.6, 45.6 (d, J_{PCCCCC} = 3 Hz), 44.7, 36.0, 32.6 (d, J_{POCC} = 6 Hz), 28.8 (d, J_{PC} = 92 Hz), 28.7, 18.9, 14.9, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.24 (dm, J_{PH} = 540 Hz); HRMS (EI^+) calcd. for $C_{14}H_{26}NO_4P$, ($[M]^+$) 303.1599, found 303.1591.

Geranyl phosphinic acid (*E*/*Z*, 50/50) (Table 5.3, entries 24a-b).[66] See above **(Table 2.8, entry 2).**

Butyl geranyl phosphinate (E/Z, 50/50) (Table 5.3, entry 24c). Mixture of diastereoisomers (from crude: 50/50, after column: 54/46); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (ddd, J_{HP} = 537 Hz, J = 3 Hz, J = 2 Hz, 2 H), 5.03 – 5.18 (m, 2 H), 4.10 and 4.0 (dtd, J = 10 Hz, J = 9 Hz, J_{HP} = 7 Hz, 2 H), 2.48 – 2.73 (m, 2 H), 2.03 – 2.13 (m, 4 H), 1.73 (dd, J_{HP} = 24 Hz, J = 6 Hz, 2 H), 1.63 – 1.74 (m, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.41 (sext., J = 8 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.1 (d, J_{PCCC} = 14 Hz), 132.4, 132.0, 123.9, 123.8, 111.3 (d, J_{PCC} = 9 Hz), 110.5 (d, J_{PCC} = 9 Hz), 66.4 (d, J_{POC} = 7 Hz), 39.9 (d, J_{PCCCC} = 3 Hz), 32.6 (d, J_{POCC} = 6 Hz), 32.3 (d, , J_{PCCCC} = 3 Hz), 29.6 (d, J_{PC} = 92 Hz), 29.5 (d, J_{PC} = 92 Hz), 26.6 (d, J_{PCCCCC} = 4 Hz), 26.5 (d, J_{PCCCCC} = 3 Hz), 25.9, 23.7 (d, J_{PCCCC} = 3 Hz), 18.9, 17.9, 16.7 (d, J_{PCCCC} = 3 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.69 and 38.44 (dm, J_{PH} = 537 Hz); HRMS (EI^+) calcd. for $C_{14}H_{27}O_2P$, ($[M]^+$) 258.1749, found 258.1744.

Farnesyl phosphinic acid (*E*/*Z* 50/50, *E*/*Z*) (Table 5.3, entry 25a).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.29 (bs, 1 H), 6.94 (d, J_{HP} = 550 Hz, 1 H), 5.03 – 5.21 (m, 3 H), 2.59 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 1.92 – 2.18 (m, 9 H), 1.56 – 1.83 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz)

δ 142.3 (d, J_{PCCC} = 14 Hz, 2 C), 142.2 (d, J_{PCCC} = 14 Hz, 2 C), 136.1, 136.0, 135.8, 135.6, 131.8, 131.7, 131.6, 131.5, 124.7, 124.6, 124.5, 124.4, 123.9 (2 C), 123.7 (2 C), 111.4 (d, J_{PCC} = 9 Hz), 111.3 (d, J_{PCC} = 9 Hz), 110.7 (d, J_{PCC} = 7 Hz), 110.6 (d, J_{PCC} = 8 Hz), 40.2 (d, J_{PCCCC} = 3 Hz, 2 C), 39.9 (2 C), 32.5 (d, J_{PCCCC} = 3 Hz), 32.3 (d, J_{PCCCC} = 3 Hz), 32.2, 32.1, 30.3 (d, J_{PC} = 92 Hz, 2 C), 30.2 (d, J_{PC} = 92 Hz, 2 C), 27.0, 26.9, 26.8 (2 C), 26.7 (d, J_{PCCCCC} = 4 Hz), 26.5 (d, J_{PCCCCC} = 3 Hz), 26.4 (d, J_{PCCCCC} = 3 Hz), 26.3 (d, J_{PCCCCC} = 3 Hz), 26.0 (2 C), 25.9 (2 C), 23.8 (d, J_{PCCCC} = 3 Hz, 2 C), 23.6 (2 C), 17.9, 17.8, 16.8 (d, J_{PCCCC} = 3 Hz), 16.7 (d, J_{PCCCC} = 3 Hz), 16.2 (4 C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.79 (dm, J_{PH} = 548 Hz); HRMS (EI+) calcd. for $C_{15}H_{27}O_2P$, ($[M]^+$) 270.1754, found 270.1749.

Butyl farnesyl phosphinate (*E/Z*, 50/50, *E/Z*) (Table 5.3, entry 25b). Mixture of diastereoisomers (from crude: 50/50, after column: 62/38); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (d, J_{HP} = 539 Hz, 1 H), 5.03 – 5.20 (m, 3 H), 3.91 – 4.19 (m, 2 H), 2.51 – 2.72 (m, 2 H), 1.92 – 2.17 (m, 9 H), 1.69 – 1.77 (m, 10 H), 1.69 (s, 3 H), 1.41 (sext., J = 7 Hz, 2 H), 0.94 (2 x t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.2 (d, J_{PCCC} = 14 Hz), 136.1, 136.0, 135.8, 135.7, 131.6, 124.6, 124.4, 123.8, 123.6, 111.2 (d, J_{PCC} = 9 Hz), 110.6 (d, J_{PCC} = 9 Hz), 66.4 (d, J_{POC} = 7 Hz), 40.2, 39.9, 32.7 (d, J_{POCC} = 6 Hz), 32.2 (d, J_{POCC} = 6 Hz), 29.7 (d, J_{PC} = 92 Hz), 29.6 (d, J_{PC} = 92 Hz), 26.9, 26.8, 26.6, 26.4, 26.2, 25.9, 23.8, 23.6, 18.9, 17.9, 16.7, 16.3, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.43 and 38.28 (dm, J_{PH} = 539 Hz); HRMS (EI^+) calcd. for $C_{19}H_{35}O_2P$, ($[M]^+$) 326.2375, found 326.2373.

(*trans*-Penten-2-yl) phosphinic acid (Table 5.3, entry 26a).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.85 (bs, 1 H), 6.95 (d, J_{HP} = 555 Hz, 1 H), 5.69 (dt, J = 21 Hz, J = 6 Hz, 1 H), 5.35 (dt, J = 21 Hz, J = 7 Hz, 1 H), 2.57 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.07 (q, J = 7 Hz, 2 H), 0.99 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.4 (d, J_{PCCC} = 14 Hz), 115.5 (d, J_{PCC} = 9 Hz), 34.0 (d, J_{PC} = 92 Hz), 25.8 (d, J_{PCCCC} = 3 Hz), 13.4 (d, J_{PCCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$,

121.47 MHz) δ 37.53 (dm, J_{PH} = 555 Hz); HRMS (EI$^+$) calcd. for $C_5H_{11}O_2P$, ([M]$^+$) 134.0497, found 134.0495.

Butyl (*trans*-penten-2-yl) phosphinate (Table 5.3, entry 26a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (d, J_{HP} = 540 Hz, 1 H), 5.69 (dt, J = 21 Hz, J = 6 Hz, 1 H), 5.35 (dt, J = 22 Hz, J = 7 Hz, 1 H), 4.12 and 4.0 (td, J = 11 Hz, J = 8 Hz, 2 H), 2.59 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H), 2.08 (q, J = 7 Hz, 2 H), 1.69 (quint., J = 7 Hz, 2 H), 1.42 (sext., J = 7 Hz, 2 H), 1.0 (t, J = 7 Hz, 3 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.4 (d, J_{PCCC} = 14 Hz), 115.7 (d, J_{PCC} = 9 Hz), 66.3 (d, J_{POC} = 7 Hz), 33.5 (d, J_{PC} = 91 Hz), 32.5 (d, J_{POCC} = 6 Hz), 25.9, 18.9, 13.7, 13.5 (d, J_{PCCCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.04 (dt, J_{PH} = 540 Hz, J = 6 Hz); HRMS (EI$^+$) calcd. for $C_9H_{19}O_2P$, ([M]$^+$) 190.1123, found 190.1128.

[3-(4-Fluoro-phenyl)-propen-2-yl] phosphinic acid (Table 5.3, entry 27a).[66] m.p. = 99 – 101°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.58 (bs, 1 H), 7.30 (dd, J = 8 Hz, J = 5 Hz, 2 H), 7.01 (d, J_{HP} = 559 Hz, 1 H), 6.98 (t, J = 9 Hz, 2 H), 6.48 (dd, J = 16 Hz, J = 5 Hz, 1 H), 5.90 – 6.12 (m, 1 H), 2.74 (dd, J_{HP} = 19 Hz, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 162.6 (d, J_{FC} = 247 Hz), 135.0 (d, J_{PCCC} = 14 Hz), 132.9, 128.1 (d, J_{FCCC} = 8 Hz, 2 C), 116.6 (d, J_{PCC} = 9 Hz), 115.7 (d, J_{FCC} = 22 Hz, 2 C), 34.6 (d, J_{PC} = 90 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.91 (dm, J_{PH} = 559 Hz); HRMS (EI$^+$) calcd. for $C_9H_{10}FO_2P$, ([M]$^+$) 200.0408, found 200.0402.

Butyl [3-(4-Fluoro-phenyl)-propen-2-yl] phosphinate (Table 5.3, entry 27b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (dd, J = 8 Hz, J = 6 Hz, 2 H), 7.06 (dt, J_{HP} = 543 Hz, J = 2 Hz, 1 H), 7.0 (t, J = 9 Hz, 2 H), 6.52 (dd, J = 16 Hz, J = 6 Hz, 1 H), 6.02 (ddd, J = 16 Hz, J = 15 Hz, J = 8 Hz, 1 H), 4.15 an 4.03 (tdd, J = 10 Hz, J = 8 Hz, J_{HP} = 7 Hz, 2 H), 2.80 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 1.70 (q, J = 7 Hz, 2 H), 1.42 (sext., J = 8 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 162.6 (d, J_{FC} = 247 Hz), 134.9 (d, J_{PCCC} = 14 Hz), 132.9 (dd, J_{PCCCC} = 4 Hz, J_{FCCCC} = 3 Hz), 128.0 (dd, J_{FCCC} = 8 Hz, J_{PCCCCC} = 2 Hz, 2 C), 116.7 (dd, J_{PCC} = 10 Hz,

$J_{FCCCCCC}$ = 2 Hz), 115.7 (d, J_{FCC} = 22 Hz, 2 C), 66.7 (d, J_{POC} = 7 Hz), 34.2 (d, J_{PC} = 91 Hz), 32.6 (d, J_{POCC} = 6 Hz), 19.0, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.94 (dm, J_{PH} = 543 Hz); HRMS (EI^+) calcd. for $C_{13}H_{18}FO_2P$, ($[M]^+$) 256.1028, found 256.1027.

(2*E*),5-Hexadienyl phosphinic acid (Table 5.3, entry 28). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.49 (bs, 1 H), 7.10 (d, J_{HP} = 546 Hz, 1 H), 5.98 – 6.40 (m, 2 H), 5.61 – 5.78 (m, 1 H), 5.13 (d, J = 17 Hz, 1 H), 5.02 (d, , J = 10 Hz, 1 H), 2.39 (dd, J_{HP} = 14 Hz, J = 7 Hz, 2 H), 1.76 – 1.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.7, 132.4 (d, J_{PCCC} = 16 Hz), 132.3, 116.4, 28.8 (d, J_{PC} = 94 Hz), 23.9 (d, J_{PCCCC} = 2 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.59 (dm, J_{PH} = 546 Hz).

Butyl (cylohexen-2-yl) phosphinate (Table 5.3, entry 31).[66] Mixture of diastereoisomers, (50/50); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87 (d, J_{HP} = 529 Hz, 1 H), 5.93 – 6.07 (m, 1 H), 5.57 – 5.79 (m, 1 H), 3.95 – 4.21 (m, 2 H), 2.59 (d, J_{HP} = 25 Hz, 1 H), 1.11 – 2.12 (m, 10 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 132.6 (d, J_{PCCC} = 13 Hz), 132.5 (d, J_{PCCC} = 12 Hz), 119.8 (d, J_{PCC} = 7 Hz), 119.6 (d, J_{PCC} = 6 Hz), 66.5 (d, J_{POC} = 7 Hz), 66.4 (d, J_{POC} = 8 Hz), 36.5 (d, J_{PC} = 94 Hz), 36.4 (d, J_{PC} = 94 Hz), 32.6 (d, J_{POCC} = 6 Hz, 2C), 24.8 (d, J_{PCC} = 4 Hz), 24.7 (d, J_{PCC} = 4 Hz), 21.4, 21.3, 20.7 (d, J_{PCCC} = 9 Hz), 20.6 (d, J_{PCCC} = 9 Hz), 19.0 (2 C), 13.8 (2 C); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.7 (dm, J_{PH} = 529 Hz), 41.9 (dm, J_{PH} = 529 Hz); HRMS (EI^+) calcd. for $C_{10}H_{19}O_2P$, ($[M]^+$) 202.1123, found 202.1118.

3,5,5-Trimethyl-cyclohexen-2-yl phosphinic acid (Table 5.3, entry 32).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.24 (bs, 1 H), 6.76 (dd, J_{HP} = 544 Hz, J = 3 Hz, 1 H), 5.40 (d, J = 10 Hz, 1 H), 2.44 – 2.70 (m, 1 H), 1.79 – 1.92 (m, 1 H), 1.69 (s, 3 H), 1.52 – 1.66 (m, 1 H), 1.23 – 1.41 (m, 2 H), 1.01 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.4 (d, J_{PCCC} = 14 Hz), 111.1 (d, J_{PCC} = 5 Hz), 42.7 (d, J_{PCC} = 3 Hz), 34.5 (d, J_{PC} = 98 Hz), 32.1, 30.4, 28.0 (d, J_{PCCC} = 13 Hz),

23.8, 23.2 (d, J_{PCCC} = 2 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.82 (dm, J_{PH} = 544 Hz); HRMS (EI^+) calcd. for $C_9H_{17}O_2P$, ($[M]^+$) 188.0966, found 188.0968.

((*E*)-1-Methyl-buten-2-yl) phosphinic acid (Table 5.3, entry 35).[66] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.9 (bs, 1 H), 6.81 (d, J_{HP} = 547 Hz, 1 H), 5.64 (ddd, J = 22 Hz, J = 11 Hz, J = 6 Hz, 1 H), 5.38 (dddd, J = 22 Hz, J = 8 Hz, J = 6 Hz, J = 2 Hz, 1 H), 2.52 (dq, J_{HP} = 25 Hz, J = 8 Hz, 1 H), 1.72 (dd, J = 7 Hz, J = 6 Hz, 3 H), 1.26 (dd, J_{HP} = 19 Hz, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 129.9 (d, J_{PCCC} = 13 Hz), 125.4 (d, J_{PCC} = 7 Hz), 37.7 (d, J_{PC} = 92 Hz), 18.4 (d, J_{PCCCC} = 3 Hz), 11.54 (d, J_{PCC} = 3 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.56 (dm, J_{PH} = 547 Hz); HRMS (EI^+) calcd. for $C_5H_{11}O_2P$, ($[M]^+$) 134.0497, found 134.0499.

General Procedure for the Reactivity Screening in Pd-Catalyzed Allylation (Table 5.4). To a mixture of the organophosphorus compound (3 – 6 mmol, 1.5 – 3 eq) in reagent grade CH_3CN or dry DMF (10 mL) was added the allylic alcohol (2 mmol, 1 eq) and the additive, if required (Et_3N-5 mol% or $(BuO)_4Si$, 1 eq relative to the amount of H_3PO_2). (Note: *Butyl phosphinate ($BuOP(O)H_2$) was used as a 0.5 M solution in the corresponding solvent and an excess of solvent was added, if required, to obtain the appropriate concentration [0.17 – 0.2 M]).* The system was placed under nitrogen and Pd_2dba_3 (0.5 – 2 mol% Pd) and xantphos (1.1 eq with respect to the amount of Pd) were added at room temperature. The resulting mixture was heated at 85°C (DMF) or at reflux temperature (CH_3CN) under N_2, with vigorous stirring for 8 to 16 h. ^{31}P NMR analysis of the crude reaction mixture was used to monitor the progress of the reaction. If successful, the crude mixture was concentrated by rotary evaporation (0.5 mmHg, 45°C) and the residue was diluted with EtOAc and washed with 2 M aqueous $NaHSO_4$ or HCl. The aqueous layer was subsequently extracted with EtOAc (2 x). The organic fractions were combined and washed with brine (1 x). Drying over $MgSO_4$ and concentration furnished the crude product. If it

is an acid, traces of aniline can be removed by stirring a solution of the compound with amberlite resin (H^+), followed by filtration and evaporation. If the product is an ester, purification by chromatography on silica gel (Hex/EtOAc, EtOAc) is required to isolate the pure compound.

Butyl cinnamyl phosphinate (Table 5.4, entry 2).[57,63,66] See above **(Table 4.1, entries 1c-1d).**

Butyl propyl phosphinate (Table 5.4, entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (dt, J_{HP} = 527 Hz, J = 2 Hz, 1 H), 3.93 – 4.2 (m, 2 H), 1.55 – 1.85 (m, 6 H), 1.34 – 1.50 (m, 2 H), 1.06 (td, J = 7 Hz, J = 2 Hz, 3 H), 0.80 – 1.0 (m, 2 H), 0.95 (t, J = 7 Hz, J = 3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 66.1 (d, J_{POC} = 7 Hz), 32.4 (d, J_{POCC} = 6 Hz), 30.7 (d, J_{PC} = 94 Hz), 18.8, 15.2 (d, J_{PCCC} = 16 Hz), 14.5, 13.6; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.36 (dt, J_{PH} = 527 Hz, J = 7 Hz).

Butyl (3-methyl-buten-2-yl) phosphinate (Table 5.4, entry 5).[57] See above **(Table 4.2, entry 5d, 9a-b).**

Cinnamyl phosphinic acid (Table 5.4, entry 6).[66,190] See above **(Table 5.2, entry 9).**

Synthetic Application of the Pd-catalyzed Allylation: Preparation of (2-Cyanoethyl)buten-2-yl phosphinate (Scheme 5.3). Allylation: To a solution of concentrated H_3PO_2 (1.39 g, 21 mmol, 3 eq) in dry DMF (35 mL) was added crotyl alcohol (mixture of isomers) (0.60 mL, 0.505 g, 7 mmol), Pd_2dba_3 (0.0160 g, 0.0175 mmol, 0.5 mol% Pd) and xantphos (0.0222 g, 0.0385 mmol). The resulting solution is heated at 85°C under nitrogen for 16 h. The reaction was then concentrated under reduced pressure (0.5 mmHg, 45°C) for 30 min. The residue is diluted with EtOAc and washed with 2 M aqueous HCl and then extracted with EtOAc (2 x). The combined organic layer is washed with brine, dried over $MgSO_4$ and concentrated to afford 0.485 g of the pure (*trans*-buten-2-yl) phosphinic acid (58%). For spectral data, see above, (Table 4.2, entry 6a-c, 11a).[66] Conjugate Addition: To a solution of (*trans*-buten-2-yl) phosphinic acid (0.485 g, 4 mmol, 1 eq) in anhydrous CH_2Cl_2 (25 mL) were added TMSCl (1.2 mL, 0.969 g, 8.92 mmol, 2.23 eq), Et_3N (1.24 mL, 0.903 g, 8.92 mmol, 2.23 eq) and acrylonitrile (0.29 mL, 0.233 g, 4.4

mmol, 1.1 eq) at room temperature under N_2. The solution is stirred at rt for 14 h and then diluted with CH_2Cl_2 and washed with brine (1 x). The aqueous layer is extracted with EtOAc (3 x). The organic layer is dried over $MgSO_4$, filtered, and concentrated to give the product (0.263 g, 38% yield, 93% purity). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.27 (m, 1 H), 5.55 – 5.80 (m, 1 H), 5.32 – 5.53 (m, 1 H), 2.51 – 2.76 (m, 4 H), 2.05 (dt, J_{HP} = 13 Hz, J = 7 Hz, 2 H), 1.72 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 131.9 (d, J_{PCCC} = 13 Hz), 119.07 (d, J_{PCC} = 9 Hz), 33.9 (d, J_{PC} = 93 Hz), 23.6 (d, J_{PC} = 93 Hz), 18.2, 10.5; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 49.88.

Pd-catalyzed dehydrative allylation en route to *P*-heterocycles (Scheme 5.5)

Preparation of (3,6-Dihydro-2-butoxy-2-oxide)-2H-1,2-oxaphosphorin (Molecule 63). To a solution of concentrated H_3PO_2 (0.594 g, 9 mmol, 3 eq) in dry DMF (15 mL) was added *cis*-2-hexenyl alcohol (0.36 mL, 0.300 g, 3 mmol, 1 eq) followed by Pd_2dba_3 (0.0069 g, 0.0075 mmol, 0.5 mol% Pd) and xantphos (0.0095 g, 0.0165 mmol, 0.55 mol%), at room temperature. The reaction was heated at 85°C under N_2 for 8 h and then allowed to warm to room temperature. $(BuO)_4Si$ (3.2 mL, 2.88 g, 9 mmol, 3 eq) was added and the reaction was heated again at 85°C for another 12 h, under N_2. The reaction was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous layer was extracted with EtOAc (2 x). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (hexanes/EtOAc 1:1, v/v, EtOAc) to give 0.600 of *E*-isomer, **61** (98%). To a solution of **61** (0.600 g, 2.94 mmol, 1 eq) in anhydrous CH_3CN (16 mL) was added at room temperature anhydrous CCl_4 (0.57 mL, 0.905 g, 5.88 mmol, 2 eq), allyl alcohol (0.40 mL, 0.342 g, 5.88 mmol, 2 eq) and Et_3N (0.82 mL, 0.595 g, 5.88 mmol, 2 eq) under N_2. The reaction was stirred for 12 h at rt. ^{31}P NMR analysis revealed the formation of the phosphonate **62** (δ = 29.4 ppm (s), 45%). The reaction was diluted with

EtOAc and washed with 2 M aqueous HCl. The aqueous layer was extracted with EtOAc (3 x), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. To a solution of the crude product **62** (1.32 mmol) in anhydrous CH_2Cl_2 (130 mL) was added the 2nd Generation Grubbs catalyst (0.0225 g, 0.0264 mmol, 2 mol%) and the reaction was heated at reflux temperature for 14 h, under a nitrogen atmosphere. After cooling to room temperature, activated charcoal (0.130 g) was added, and the suspension was stirred for 4 h. The mixture was then filtered through a celite pad in a Büchner funnel, and concentrated in vacuo to afford the crude product **63**, which was purified by silica gel chromatography (Hex/EtOAc 5:1, v/v, EtOAc) to give 0.211 g of **63** (1.11 mmol, 37% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63 – 5.89 (m, 2 H), 4.70 – 4.93 (m, 2 H), 4.04 – 4.23 (m, 2 H), 2.36 – 2.69 (m, 2 H), 1.60 – 1.77 (m, 2 H), 1.34 – 1.52 (m, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.35.

Preparation of 1-Butoxy-3-phospholene-1-oxide (Molecule 66).[201] To a solution of concentrated H_3PO_2 (0.594 g, 9 mmol, 3 eq) in dry DMF (4 Å molecular sieves) (15 mL) was added cinnamyl alcohol (0.39 mL, 0.403 g, 3 mmol, 1 eq) followed by Pd_2dba_3 (0.0069 g, 0.0075 mmol, 0.5 mol% Pd) and xantphos (0.0095 g, 0.0165 mmol, 0.55 mol%), at room temperature. The resulting solution was heated at 85°C under N_2 for 1.5 h. After cooling to room temperature, $(BuO)_4Si$ (3.2 mL, 2.88 g, 9 mmol, 3 eq) was added and the resulting mixture was heated at 85°C for 12 h, under N_2. The mixture was then diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration and purification by column chromatography over silica gel (hexanes/EtOAc 1:1, v/v, EtOAc) afforded 0.700 g of **64** (butyl cinnamyl-*H*-phosphinate) as a light yellow oil (98%). A solution of **64** (0.700g, 2.94 mmol, 1 eq) in anhydrous CH_3CN (15 mL) was placed in an Ace Glass®

pressure tube fitted with a rubber septum, under N_2. To the resulting solution was added at room temperature BSA (0.87 mL, 0.72 g, 3.53 mmol, 1.2 eq) and allyl chloride (0.72 mL, 0.675 g, 8.82 mmol, 3 eq). The reaction tube was tightly closed with the PTFE plug and heated at 85°C with stirring during 8 h. After cooling to room temperature, ^{31}P NMR analysis revealed the presence of the product at 49.9 ppm (82%). The reaction mixture was then quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 x). The combined organic phases were washed with 2 M aqueous HCl (1 x) and then with brine (1 x). Drying over $MgSO_4$ and concentration gave the crude product **65** (2.41 mmol), which was dissolved in anhydrous CH_2Cl_2 (150 mL), followed by addition of 2nd Generation Grubbs catalyst (0.0409 g, 0.0482 mmol, 2 mol%) under N_2. The mixture was heated at reflux temperature for 12 h under N_2. The reaction was allowed to cool to room temperature and activated charcoal (0.250 g) was added. The resulting suspension was stirred for 4 h at rt, suction-filtered through a celite pad in a Büchner funnel, and then concentrated in vacuo. Purification by flash chromatography over silica gel (EtOAc, EtOAc/MeOH 90:10, v/v) afforded **66** as a clear oil (0.261 g, 1.5 mmol, 50% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (d, J = 34 Hz, 2 H), 3.98 – 4.14 (m, 2 H), 2.38 – 2.50 (m, 4 H), 1.60 – 1.74 (m, 2 H), 1.41 (sext., J = 8 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 127.2 (d, J_{PCC} = 16 Hz, 2 C), 64.9 (d, J_{POC} = 7 Hz), 32.8 (d, J_{POCC} = 6 Hz), 29.3 (d, J_{PC} = 91 Hz, 2 C), 19.0, 13.8; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 75.83.

General Procedure for the Catalyst Screening in the Pd-Catalyzed Rearrangement of Phenyl Phosphinate (Table 5.5). To a solution of concentrated H_3PO_2 (0.132 g, 2 mmol, 1 eq) in reagent grade CH_3CN (8 mL) was added $(PhO)_4Si$[234] (0.800 g, 2 mmol, 1 eq) and the reaction was heated at reflux temperature for 2 h under N_2,[17] and then allowed to cool to room temperature. ^{31}P NMR analysis of the crude mixture showed the signal corresponding to the

product phenyl phosphinate (δ = 14.0 (t), 100%). The catalyst (2 mol%) was added and the reaction was heated to reflux temperature for 12 h, while stirring vigorously. The reaction was monitored by ^{31}P NMR (product formation) and by GC (transfer hydrogenation product generation: benzene). (Note: *Mesitylene was used as internal standard for GC analyses*).

Chapter 6, Section 6.1

Synthesis of 2-(1-buten-4-ol)-3-methylene-1-oxa-2-phosphacyclopentane-2-oxide (Scheme 6.1) Molecule 69, R = H: To a mixture of anilinium hypophosphite (0.398 g, 2.5 mmol, 1 eq) in reagent grade CH_3CN (10 mL) were added pyridine (0.25 mL, 0.247 g, 3.13 mmol, 1.25 eq), 3-butyn-1-ol (0.28 mL, 0.263 g, 3.75 mmol, 1.5 eq) and pivaloyl chloride (0.34 mL, 0.332 g, 2.75 mmol, 1.1 eq) under N_2 and the mixture was stirred at room temperature for 3 h. ^{31}P NMR analysis revealed the formation of the hypophosphite ester at δ = 16.2 ppm (tt)-100%. $NiCl_2$ (0.010 g, 0.075 mmol, 0.03 eq) were added at room temperature and the solution was heated at reflux temperature for 15 h. ^{31}P NMR of the crude mixture showed a single peak at 39.3 ppm (s). The reaction was diluted with EtOAc and washed with 2 M $NaHSO_4$. The aqueous layer was separated and extracted twice with EtOAc. The organic fractions were combined and subsequently washed with saturated $NaHCO_3$ and then brine. Drying over $MgSO_4$, evaporation and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 2:1, v/v, EtOAc/MeOH 9:1) afforded 0.050 g of the product **69** (R=H) as a colorless oil (11%). (Note: *the low yield is probably due to the easy hydrolysis of the product into the corresponding disubstituted phosphinic acid during the purification*). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93 – 6.32 (m, 2 H), 5.54 – 5.86 (m, 2 H), 4.33 (m, 2 H), 3.65 (t, J = 7 Hz, 2 H), 2.45 – 3.07 (m, 4 H); ^{31}P NMR ($CDCl_3$, 36.44 MHz) δ 41.25; MS (EI^+) for $C_8H_{13}O_3P$, $[M+H_2O]^+$ *m/z* 206.

Chapter 6, Section 6.2

General Procedure for Table 6.2. A stock solution of concentrated H_3PO_2 (3.30 g, 50 mmol) in anhydrous DMF (100 mL, dried over 4Å Sieves or distilled from CaH_2) was prepared under N_2, and used immediately (or within a week) as described next. To a 0.5 M solution of H_3PO_2 in DMF (4 mL, 2 mmol, 1 eq) was added the diamine or amine-alcohol (2 mmol, 1 eq) and the reaction is stirred under N_2 for 0.5 h at room temperature. Then, the alkene (2-6 mmol, 1-3 eq) and the additive (3Å powdered sieves) (0.125 g/mmol H_3PO_2) were added to the reaction, followed by Pd_2dba_3 (0.0184-0.0368 g, 0.02-0.04 mmol, 2-4 mol% Pd) and xantphos (0.0254-0.0508 g, 0.044-0.088 mmol, 1.1 eq with respect to the amount of Pd), and the mixture was heated at 85-110°C for 13-54 h under N_2. ^{31}P NMR analysis was used to monitor the course of the reaction. In the particular case of entry 1, after heating for 13 h, a second catalyst was added *in situ* $(Ph_3P)_3RhCl$/dppb (1.5 mol%) and dppb (5 mol%) and heating was continued for 16 h more. Isolation of the products consisted in an extractive workup, as described next. The reaction was concentrated by rotary evaporation (45°C, 0.5 mmHg), followed by dilution with EtOAc and washing with 2 M aqueous HCl. The organic layer was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. In order to eliminate traces of amine, a CH_2Cl_2 solution of the crude oil was stirred with amberlite resin (3-4 tips of scoopula) for 4-6 h at room temperature, followed by suction filtration on a Büchner funnel and concentration.

Octyl phosphonic acid (Table 6.1, entry 3a).[32] See above **(Table 2.3, entry 13).**

Chapter 6, Section 6.3

General Procedure for the Preparation of *H*-Phosphinate Allylic Esters from *H*-Phosphinic acids (Table 6.2 and Scheme 6.5): a) Using EDC·HCl (Substrates from Entries 2-4 and Molecule 81). A mixture of *H*-phosphinic acid (1 eq) and allylic alcohol (1 eq) and EDC·HCl (1.1 eq) in anhydrous THF (0.33 M) were stirred under N_2 at room temperature for 4 to 8 h. The solution is diluted in EtOAc and washed with saturated aqueous $NaHCO_3$ (1 x). The aqueous layer was separated and extracted with two additional portions of EtOAc. The combined organic fractions were washed with 2 M aqueous HCl (1 x) and then with brine (1 x) to afford the crude product. Depending on the purity of the compound (^{1}H NMR), either the product is used without further purification, or it is purified by silica gel chromatography (Hex/EtOAc 2:1, v/v, EtOAc).

b) By Dean-Stark Esterification (Substrate from entry 1). A mixture of *H*-phosphinic acid (1 eq), allylic alcohol (5 eq) and a drop of H_2SO_4 in reagent grade cyclohexane (0.25 M relative to the acid) is heated at reflux temperature using a Dean-Stark trap (prefilled with cyclohexane) for 48-72 h, according to the progress of the reaction (by ^{31}P NMR analysis). The reaction was concentrated and the residue was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer is extracted with CH_2Cl_2 (2 x) and then the combined organic fractions are washed with brine and concentrated under reduced pressure to furnish the crude product. According to the purity of the compound, it is used directly or purified by chromatography on silica gel.

Procedure for the Preparation of Cinnamyl diphenylphosphinite (Table 6.2, Substrate entry 5). Not isolated, it was used *in situ*. See Reference 205.

Procedure for the Preparation of 1,4-But-2-en-diol phosphonate (Table 6.2, Substrate entry 6). See Reference 147.

General Procedure for the Pd-Catalyzed Rearrangement (Table 6.2). To a solution of the organophosphorus compound (2 mmol, 1 eq) in DMF (4 mL) was added the corresponding additive, followed by Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol). The reaction was heated at 85°C for 12-24 h. Reaction progress was monitored by ^{31}P NMR. The resulting solution was concentrated by rotary evaporation (45°C, 0.5 mmHg) and the residue was diluted with EtOAc and washed with aqueous HCl (1 x). The aqueous layer was extracted with EtOAc (2 x) and then the combined organic fractions were washed with brine (2 x). The organic layer was dried over $MgSO_4$ and concentrated to give the crude product.

Representative Procedure for the Pd-Catalyzed Rearrangement (Table 6.2): Synthesis of Cinnamyl phenyl phosphinic acid (Table 6.2, Product entry 3j). To a solution of cinnamyl phenyl phosphinate (0.516 g, 2 mmol, 1 eq) in anhydrous DMF (4 mL) was added BSA (0.59 mL, 0.488 g, 2.4 mmol, 1.2 eq), followed by Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol). The resulting solution was heated at 85°C for 13 h. DMF was evaporated and the residue was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous layer was extracted with EtOAc (2 x) and the organic layer was washed with brine. Drying and concentration furnished 0.516 g of the phosphinic acid product as clear yellow crystals (100%, >95% purity).

Allyl phenyl phosphinate (Table 6.2, Substrate entry 1).[163,245] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 – 7.92 (m, 2 H), 7.70 (dm, J_{HP} = 565 Hz, 1 H), 7.45 – 7.70 (m, 3 H), 5.98 (m, 1 H), 5.38 (d, J = 37 Hz, 1 H), 5.33 (d, J = 29 Hz, 1 H), 4.49 – 4.70 (m, 2 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.17 (dm, J_{PH} = 565 Hz).

Cinnamyl phenyl phosphinate (Table 6.2, Substrate entries 2 and 3). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 – 7.80 (m, 2 H), 7.68 (dm, J_{HP} = 565 Hz, 1 H), 7.47 – 7.67 (m, 3 H), 7.22 – 7.45

(m, 5 H), 6.69 (d, J = 16 Hz, 1 H), 6.31 (dt, J = 16 Hz, J = 7 Hz, 1 H), 4.64 – 4.83 (m, 2 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.15 (dm, J_{PH} = 565 Hz).

(2(*E/Z*)-Butenyl) 3-(benzyloxycarbonylamino)propyl phosphinate (Table 6.2, Substrate entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 – 7.45 (m, 6 H), 7.11 (d, J_{HP} = 530 Hz, 1 H), 5.73 – 5.91 (m, 1 H), 5.52 – 5.73 (m, 1 H), 5.09 (s, 2 H), 4.38 – 4.59 (m, 2 H), 3.17 – 3.36 (m, 2 H), 1.70 – 1.91 (m, 4 H), 1.73 (m, 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.11 (dm, J_{PH} = 530 Hz).

1,4-But-2-en-diol phosphonate (Table 6.2, Substrate entry 6).[246] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (dd, J_{HP} = 707 Hz, J = 4 Hz, 1 H), 5.59 – 6.08 (m, 2 H), 4.76 (dt, J =48 Hz, J = 16 Hz, 4 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 14.53 (dt, J_{PH} = 707 Hz, J = 17 Hz).

Cinnamyl phenyl phosphinic acid (Table 6.2, Product entry 3j). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.74 (bs, 1 H), 7.61 – 7.82 (m, 2 H), 6.91 – 7.54 (m, 8 H), 6.23 (dd, J = 16 Hz, J = 5 Hz, 1 H), 5.91 – 6.12 (m, 1 H), 2.80 (dd, J_{HP} = 16 Hz, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 136.0 (d, J_{PCCCC} = 3 Hz), 133.7 (d, J_{PCCC} = 13 Hz), 130.9, 130.4 (d, J_{PC} = 133 Hz), 130.3 (d, J_{PCC} = 10 Hz, 2 C), 127.4 (2 C), 127.2 (d, J_{PCCC} = 13 Hz, 2 C), 126.3, 125.2 (2 C), 117.9 (d, J_{PCC} = 10 Hz), 34.9 (d, J_{PC} = 95 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.99 (s).

General Procedure for the Pd-Catalyzed Allylation of *H*-Phosphinic Acids with Allylic Alcohols (Table 6.4). (*Notes:* (a) All reactions were conducted in oven- or flame-dried glassware, under nitrogen or argon. (b) Starting materials *H*-phosphinic acids were synthesized via Pd-catalyzed hydrophosphinylation or dehydrative allylation of H_3PO_2 (Ref. 33 and 66), with the exception of phenyl phosphinic acid, which is commercially available. (c) Allylic alcohols and solvents were generally dried before use according to the procedures indicated at the beginning of this section). To a solution of *H*-phosphinic acid (2 mmol, 1 eq) in the

corresponding solvent (4 mL) was added the allylic alcohol (1-2 eq), Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol% Pd), xantphos (0.0254 g, 0.044 mmol), and the additive, under a nitrogen or argon atmosphere. The resulting mixture was heated at the corresponding temperature for 10-20 h. ^{31}P NMR monitoring of the crude mixture indicated the presence of the product as a singlet (δ: 25-50 ppm). The reaction was concentrated by rotary evaporation (45°C, 0.5 mmHg) and the residue was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous phase was separated and extracted with two additional portions of EtOAc and the combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated. The purity of the crude product was determined by NMR analysis, and if less than 95%, further purification was required. Silica gel chromatography proved to be efficient in the purification of some substrates.

Representative Procedure for the Pd-Catalyzed Allylation of *H*-Phosphinic Acids with Allylic Alcohols (Table 6.4): Preparation of Geranyl phenyl phosphinic acid (mixture of *E/Z* isomers) (entry 3b). To a solution of phenyl phosphinic acid (0.284 g, 2 mmol, 1 eq) in anhydrous *tert*-amyl alcohol (4 mL) was added anhydrous *trans*-3,7-dimethyl-2,6-octadien-1-ol, followed by Pd_2dba_3 (0.0184 g, 0.02 mmol, 2 mol% Pd), and xantphos (0.0254 g, 0.044 mmol). The resulting solution was heated at reflux temperature (102°C) for 24 h under N_2. ^{31}P NMR analysis detected the presence of the product as a mixture of isomers (δ: 38.5 and 38.3 ppm, singlets, 70%). DMF was evaporated under reduced pressure and the resulting residue was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine. Drying, concentration and purification by flash chromatography over silica gel (hexanes/EtOAc 1/1, v/v, EtOAc, EtOAc/MeOH 9/1, v/v) gave 0.345 g of the phosphinic acid (62%).

Cinnamyl phenyl phosphinic acid (Table 6.4, entries 1a-c). See above **(Table 6.2, Product entry 3j).**

Geranyl phenyl phosphinic acid (mixture of *E/Z* isomers) (Table 6.4, entry 3b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.20 (bs, 1 H), 7.71 (dd, J = 11 Hz, J = 7 Hz, 2 H), 7.27 – 7.53 (m, 3 H), 4.9 – 5.19 (m, 2 H), 2.60 (dd, J_{HP} = 19 Hz, J = 8 Hz, 2 H), 1.50 – 2.05 (m, 10 H), 1.29 (d, J = 3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 140.4 (2xd, J_{PCCC} = 14 Hz, 2 C), 132.1 (2 C), 132.0 (2xd, J_{PC} = 132 Hz, 2 C), 131.7 (d, J_{PCC} = 12 Hz, 4 C), 128.2 (d, J_{PCCC} = 14 Hz, 4 C), 124.3 (2 C), 124.2 (2 C), 113.1 (2xd, J_{PCC} = 9 Hz, 2 C), 39.9, 31.9, 31.4 (d, J_{PC} = 78 Hz), 30.3 (d, J_{PC} = 59 Hz), 29.9, 26.7, 25.9, 23.6, 17.9, 16.1; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 42.96 and 42.82 (s).

Scheme 6.5.

(1-Propyl-pent-1-enyl) phosphinic acid (Scheme 6.5, Molecule 80).[35] See above **(Table 2.5, Entry 1).**

Cinnamyl (1-propyl-pent-1-enyl) phosphinate (Scheme 6.5, Molecule 81). ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J_{HP} = 546 Hz, 1 H), 7.15 – 7.45 (m, 5 H), 6.18 – 6.75 (m, 3 H), 4.69 (t, J = 8 Hz, 2 H), 2.02-2.33 (m, 4 H), 1.29 – 1.62 (m, 4 H), 0.94 (t, J = 7 Hz, 6 H); ^{31}P NMR ($CDCl_3$) δ 31.72 (dm, J_{PH} = 546 Hz).

Cinnamyl (1-propyl-pent-1-enyl) phosphinic acid (Scheme 6.5, Molecule 82). (82% purity) ^{1}H NMR ($CDCl_3$) δ 10.69 (bs, 1 H), 7.0 – 7.43 (m, 5 H), 5.96 – 6.55 (m, 3 H), 2.72 (dd, J = 18 Hz, J = 7 Hz, 2 H), 1.91 – 2.32 (m, 4 H), 1.18 – 1.61 (m, 4 H), 0.68 – 1.02 (m, 6 H); ^{31}P NMR ($CDCl_3$) δ 45.72 (s).

Chapter 6, Section 6.4

General Procedures for the Tandem C-P Bond Formation – Oxidation (Table 6.7).

Method A: To a solution of 50% wt. aqueous H_3PO_2 (0.528 g, 4 mmol, 2 eq) in reagent grade DMF (4 ml) was added the alkene (2 mmol, 1 eq), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol) and xantphos (0.0254 g, 0.044 mmol), at room temperature. The resulting solution was heated at

110°C, under air (using a septum with a needle), until completion of the reaction (total oxidation of the intermediate *H*-phosphinic). Reaction progress was monitored by ^{31}P NMR analysis of a sample of the crude reaction mixture. The reaction was then concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous layer was separated and extracted with two additional portions of EtOAc. The combined organic layer was washed with brine (1 x), dried over $MgSO_4$, and concentrated to give the product (phosphonic acid) in more than 95% purity.

Method B:

B-1) Substrate: Alkene, alkyne, allyl alcohol

Aqueous hypophosphorous acid (50% wt.) was concentrated by rotary evaporation (0.5 mmHg, 40°C) for 20-30 min before reaction. Concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) was dissolved in reagent grade DMF (4 ml) and the substrate (2 mmol, 1 eq), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol) and xantphos (0.0254 g, 0.044 mmol) were added at room temperature. The solution was heated at 85°C under N_2 for 12 h. At that time, ^{31}P NMR of the crude mixture showed the formation of the intermediate *H*-phosphinic acid (doublet, between 20-40 ppm) and complete disappearance of the starting material (H_3PO_2). The reaction was then opened to air (capping the reaction flask with a septum fitted with a needle) and heated at 110°C, until completion (total oxidation of the intermediate *H*-phosphinic acid into phosphonic acid), which was checked by ^{31}P NMR analysis of the crude reaction mixture. DMF was evaporated from the reaction (0.5 mmHg, 45°C) and the residue was diluted with EtOAc and washed with 2 M aqueous HCl. The aqueous phase was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine (1 x). Drying over $MgSO_4$ and concentration furnished the product in more than 95% purity.

B-2) Substrate: Aryl halide

To a solution of concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) in reagent grade DMF (4 ml) were added the aryl halide (2 mmol, 1 eq) and triethylamine (0.607 g, 0.84 ml, 6 mmol, 3 eq) followed by $Pd(OAc)_2$ (0.009 g, 0.040 mmol) and dppp (0.0182 g, 0.044 mmol) at room temperature. The solution was heated at 85°C under N_2 for 15 h. At that point, ^{31}P NMR of the reaction mixture revealed the formation of the intermediate *H*-phosphinate salt of triethylamine (δ: 0-20 ppm, doublet). The reaction was then heated under air at 110°C (closing the reaction flask with a septum fitted with a needle in order to release the pressure), until complete oxidation of the intermediate *H*-phosphinate salt, which was checked by ^{31}P NMR analysis of the reaction mixture. The solvent was evaporated from the reaction mixture and the residue was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous layer was extracted with EtOAc (2 x) and the combined organic fractions were washed with brine. After drying over $MgSO_4$, concentration, and recrystallization from dichloromethane-hexanes, the product aryl phosphonic acid was obtained in more than 95% purity.

Representative Procedures for the Tandem C-P Bond Formation – Oxidation (Table 6.7).

Method A: Preparation of Octyl phosphonic acid[32] (Table 6.7, entry 1a). To a solution of aqueous H_3PO_2 (0.528 g, 4 mmol, 2 eq) in reagent grade DMF (4 ml) was added 1-octene (0.225 g, 0.32 ml, 2 mmol, 1 eq), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol, 2 mol% Pd) and xantphos (0.0254 g, 0.044 mmol, 2 mol%), at room temperature. The reaction was heated at 110°C, under air for 20 h or until complete oxidation of the intermediate octyl phosphinic acid, which was performed by ^{31}P NMR monitoring of a sample of the reaction mixture. The reaction is considered to be complete after total disappearance of a signal at 31.8 ppm (doublet), and appearance of a new peak at 29.7 ppm (singlet), corresponding to octyl phosphonic acid. The mixture was then concentrated under reduced pressure. The residue was 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 and concentration afforded 0.338 g of the pure product as a light yellow solid (100%).

Method B-1: Preparation of Cinnamyl phosphonic acid[247] (Table 6.7, entry 4). Concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) was dissolved in reagent grade DMF (4 ml) and cinnamyl alcohol (0.268 g, 0.260 mL, 2 mmol, 1 eq), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol) and xantphos (0.0254 g, 0.044 mmol) were added at room temperature. The resulting solution was heated at 85°C under N_2 for 12 h. At that time, ^{31}P NMR analysis from the reaction mixture showed the formation of cinnamyl-*H*-phosphinic acid at 26 ppm (doublet). The mixture was then opened to air and heated at 110°C for 22 h, until complete disappearance of the peak at 26 ppm (doublet) and appearance of a new peak at 22 ppm (singlet). The reaction was concentrated under reduced pressure and the residue was diluted with EtOAc, and washed with 2 M aqueous HCl (1 x). The aqueous phase was extracted with EtOAc (2 x) and the combined organic layer was washed with brine. Drying and concentration afforded 0.325 g of the product as a white solid (82%).

Method B-2: Preparation of 4-Methoxy-phenyl phosphonic acid[248] (Table 6.7, entry 11). To a 0.5 M solution of concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) in reagent grade DMF (4 ml) were added 4-bromoanisole (0.374 g, 0.250 mL, 2 mmol, 1 eq) and triethylamine (0.607 g, 0.84 ml, 6 mmol, 3 eq), followed by $Pd(OAc)_2$ (0.009 g, 0.040 mmol) and dppp (0.0182 g, 0.044 mmol) at room temperature. The resulting mixture was heated at 85°C under N_2 for 15 h, and then the reaction was opened to air (using a septum with a needle) and heated at 110°C for 22 h. At that moment, the intermediate *H*-phosphinate salt had been completely oxidized into the corresponding phosphonate salt of triethylamine. The reaction was concentrated under high vacuum and the residue was diluted with EtOAc and washed 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. After drying over $MgSO_4$, concentration, and recrystallization from dichloromethane-hexanes, the product aryl phosphonic acid was obtained as a white solid (0.207 g, 55%).

Octyl phosphonic acid (Table 6.7, entry 1).[32] See above **(Table 2.3, entry 13).**

Bicyclo[2.2.1]hept-2-yl-phosphonic acid[249] **(Table 6.7, entry 2).** The product was obtained in more than 95% purity as a light yellow solid after an aqueous acidic workup. m.p. = 173-175°C (lit. 174-175°C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.04 (bs, 2 H), 2.38 (d, J = 8 Hz, 1 H), 2.14 – 2.25 (m, 1 H), 1.28 – 1.72 (m, 6 H), 0.98 – 1.26 (m, 3 H); ^{13}C NMR (DMSO-d_6, 75.45 MHz) δ 39.3 (d, J_{PC} = 96 Hz), 38.2, 36.9, 36.4 (d, J_{PCC} = 4 Hz), 32.3 (d, J_{PCC} = 5 Hz), 31.85 (d, J_{PCCC} = 18 Hz), 28.9; ^{31}P NMR (DMSO-d_6, 121.47 MHz) δ 31.73 (s); MS (EI$^+$) for $C_7H_{13}O_3P$, $[M+H]^+$ *m/z* 177.

4-Phenyl-butyl phosphonic acid[250] **(Table 6.7, entry 3).** The product was obtained in more than 95% purity as a light yellow solid after an aqueous acidic workup. m.p. = 90-92°C (lit. 93°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.3 (bs, 2 H), 6.85 – 7.4 (m, 5 H), 2.48 – 2.64 (m, 2 H), 1.52 – 1.86 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 142.4, 128.7 (4 C), 126.1, 35.8, 32.7, 26.1 (d, J_{PC} = 149 Hz), 22.4; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.84 (s); MS (EI$^+$) for $C_{10}H_{15}O_3P$, $[M+H]^+$ *m/z* 215.

Cinnamyl phosphonic acid[247] **(Table 6.7, entry 4).** m.p. = 162-164°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.5 (bs, 2 H), 7.9 – 7.5 (m, 4 H), 6.46 (dd, J = 16 Hz, J = 4 Hz, 1 H), 6.22 (dd, J = 16 Hz, J = 8 Hz, 1 H), 2.64 (dd, J_{HP} = 22 Hz, J = 7 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 75.45 MHz) δ 137.7 (d, J_{PCCCC} = 3 Hz), 133.3 (d, J_{PCCC} = 14 Hz), 129.3 (2 C), 127.9, 126.5 (2 C), 122.5 (d, J_{PCC} = 11 Hz), 33.6 (d, J_{PC} = 134 Hz); ^{31}P NMR (DMSO-d_6, 121.47 MHz) δ 24.62 (s); MS (EI$^+$) for $C_9H_{11}O_3P$, $[M+H]^+$ *m/z* 199.

(1-Propyl-pent-1-enyl) phosphonic acid[251] **(Table 6.7, entry 7).** The product was obtained in more than 95% purity as a yellow oil after an aqueous acidic workup. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.07 (bs, 2 H), 6.49 (dt, J = 25 Hz, J = 7 Hz, 1 H), 1.9 – 2.4 (m, 4 H), 1.15 – 1.65 (m, 4 H), 0.7 – 1.1 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 144.3 (d, J_{PCC} = 9 Hz), 129 (dd, J_{PC} = 188 Hz, J = 90 Hz), 29.4 (d, J_{PCC} = 19 Hz), 28.2 (d, J_{PCCC} = 12 Hz), 21.5, 20.9, 13.1, 12.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 25.88 (s); MS (EI$^+$) for $C_8H_{17}O_3P$, $[M+H]^+$ *m/z* 193.

Preparation of 3-(Benzyloxycarbonylamino)propyl phosphonic acid[252] **(Table 6.7, entry 8).** To a 0.5 M solution of concentrated H_3PO_2 (0.264 g, 4 mmol, 2 eq) in DMF (4 ml) was added benzyl *N*-(benzyloxycarbonyl)allylamine[20] (0.382 g, 2 mmol, 1 eq), followed by Pd_2dba_3 (0.0184 g, 0.020 mmol) and xantphos (0.0254 g, 0.044 mmol), at room temperature. The solution was heated at 85°C under N_2 for 12 h. At that point, ^{31}P NMR of the reaction mixture showed a peak at 31 ppm (doublet) corresponding to the intermediate *H*-phosphinic acid. The reaction was opened to air and heated at 110°C for 50 h. The reaction was concentrated under reduced pressure and the residue was diluted with water and washed with EtOAc (1 x). The organic phase was extracted with H_2O (2 x) and the combined aqueous fractions were washed with EtOAc (1 x), concentrated, and neutralized to pH 7.0 with aqueous NaOH. The crude was loaded at 5°C (temperature inside the room) on a pad of Bio-Rad AG-1-X8 anion exchange resin (30 mL) which had been pre-washed with 2 M triethylammonium bicarbonate buffer ($Et_3NH^+HCO_3^-$ = TEAB, 150 mL), distilled water (150 mL) and then equilibrated with 0.05 M TEAB. The column was then eluted with a linear gradient (150 mL + 150 mL, 0.05-0.25 M) of TEAB, followed by a final washing with 2M TEAB (300 mL). Fractions containing phosphorus were identified by a 'Total Phosphorus Content Assay' described in the methods published by Avila and Ames.[235] The early phosphorus-positive fractions contained H_3PO_3 and/or H_3PO_4, and were discarded; while the later phosphorus-positive fractions were collected and concentrated to dryness. The

resulting residue was dissolved in water, and passed down a short column of Dowex 50 (H^+). The eluant was concentrated in vacuo to afford the product as colorless crystals (0.470 g, 86%). m.p. = 98-100°C (lit. 98-102°C); ^{1}H NMR (D_2O, 300 MHz) δ 7.07 (s, 5 H), 4.77 (s, 2 H), 2.8 – 3.0 (m, 2 H), 1.35 – 1.65 (m, 4 H); ^{31}P NMR (D_2O, 121.47 MHz) δ 31.83 (s); MS (EI^+) for $C_{11}H_{16}NO_5P$, $[M+H]^+$ *m/z* 274.

3-Chloro-phenyl phosphonic acid[254] **(Table 6.7, entry 10).** The product was obtained as a brown solid in more than 95% purity after an aqueous acidic workup, followed by recrystallization from dichloromethane-hexanes. m.p. = 102-104°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.78 – 9.0 (bs, 2 H), 7.0 – 7.7 (m, 4 H); ^{13}C NMR (DMSO-d_6, 75.45 MHz) δ 137.4 (d, J_{PC} = 178 Hz), 133.8 (d, J_{PCCC} = 18 Hz), 131.5, 131.0 (d, J_{PCCC} = 14 Hz), 130.7 (d, J_{PCC} = 9 Hz), 129.7 (d, J_{PCC} = 7 Hz); ^{31}P NMR (DMSO-d_6, 121.47 MHz) δ 15.06 (s); MS (EI^+) for $C_6H_6ClO_3P$, $[M+H]^+$ *m/z* 192.

4-Methoxy-phenyl phosphonic acid[248] **(Table 6.7, entry 11).** m.p. = 177-178°C (lit. 179°C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.58 (dd, J = 12 Hz, J = 8 Hz, 2 H), 6.98 (dd, J = 8 Hz, J = 2 Hz, 2 H), 6.23 (bs, 2 H), 3.8 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75.45 MHz) δ 161.9 (d, J_{PCCCC} = 3 Hz), 133.1 (d, J_{PCCC} = 11 Hz, 2 C), 126.2 (d, J_{PC} = 188 Hz), 114.2 (d, J_{PCC} = 15 Hz, 2 C), 55.9; ^{31}P NMR (DMSO-d_6, 121.47 MHz) δ 15.06 (s); MS (EI^+) for $C_7H_9O_4P$, $[M+H]^+$ *m/z* 189.

4-(Carboxyphenyl) phosphonic acid[255] **(Table 6.7, entry 12).** The product was obtained as a white solid in more than 95% purity after an aqueous acidic workup, followed by recrystallization from dichloromethane. m.p. >300°C (lit. >300°C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.9 – 8.5 (m, 7 H); ^{13}C NMR (DMSO-d_6, 75.45 MHz) δ 167.6, 139.3 (d, J_{PC} = 179 Hz), 133.4, 131.4 (d, J_{PCCC} = 10 Hz, 2 C), 129.6 (d, J_{PCC} = 14 Hz, 2 C); ^{31}P NMR (DMSO-d_6, 121.47 MHz) δ 13.12 (s); MS (EI^+) for $C_7H_7O_5P$, $[M+H]^+$ *m/z* 203.

Chapter Seven, Section 7.1.1

Palladium(II) [*N,N'*-Bis(3,5-di-tert-butylsalicylidene)-(*R,R*)-1,2-cyclohexanediamine] Molecule 86.[218a] Prepared from $PdCl_2/Et_3N$ according to the procedure described in Ref. 218b. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (s, 2 H), 7.43 (s, 2 H), 6.98 (d, J = 2 Hz, 2 H), 3.41 (bs, 2 H), 2.59 (bs, 2 H), 1.89 (bs, 2 H), 1.10 – 1.75 (m, 40 H).

Chapter Seven, Section 7.1.2

Validation of NMR Assay

(a) Synthesis of Ethyl (1-naphthyl) phosphinate (Scheme 7.1). To a suspension of anilinum hypophosphite (0.382 g, 2.4 mmol, 1.2 eq) and 3-aminopropyltriethoxysilane (0.531 g. 2.4 mmol, 1.2 eq) in CH_3CN (12 ml), was added 1-bromonaphthalene (0.28 mL, 0.414 g, 2 mmol), $Pd(OAc)_2$ (0.009 g, 0.040 mmol, 2 mol% Pd), and BINAP (racemic) or (*R*)-BINAP (0.0288 g, 0.044 mmol). The reaction mixture was heated at reflux temperature for 8 h. After cooling to rt, ^{31}P NMR analysis showed the product at ~28 ppm (100%, doublet). The mixture was then diluted with EtOAc and washed successively with aq. HCl (2 M). The aq. phase was extracted with EtOAc (3 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine. Drying over $MgSO_4$ and concentration afforded pure ethyl (1-naphthyl) phosphinate (0.431 g, 98% yield).

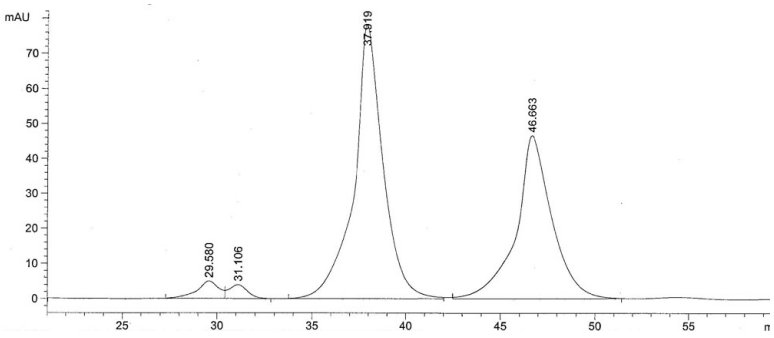
Ethyl (1-naphthyl) phosphinate (Scheme 7.1). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.43 (d, J = 8 Hz, 1 H), 8.09 (dd, J=7, 1Hz, 1 H), 8.07 (d, J = 7 Hz, 1 H), 7.94 (d, J = 563 Hz, 1 H), 7.93 (d, J = 8 Hz, 1 H), 7.75 – 7.89 (m, 1 H), 7.48-7.69 (m, 2 H), 4.05-4.29 (m, 2 H), 1.37 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.76 (dm, J = 563 Hz).

(b) NMR Assay: Derivatization with (*S*)-(-)-(α)-Methylbenzylamine/CCl_4. To a mixture of the crude ethyl (1-naphthyl) phosphinate (~20 mg) in CCl_4 ((~1 mL) in an NMR tube, was added

an excesss of (*S*)-(-)-(α)-methylbenzylamine at room temperature. The solution is stirred for 2-4 h at room temperature, and then ^{31}P NMR analysis is performed on the resulting crude mixture. **From (*R*)-BINAP:** ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 20.94 (s, 60.9%, height: 155.7); 20.53 (s, 39.1%, height: 114.8); $ee_{(heights)}$ = 15%.

HPLC Analysis: Product1 t_R 37.919 min (Area=18.1365 units); Product2 t_R 46.663 min (Area= 13.1633 units); *(S,S)*-Whelk-01 Column (250 × 4.6 mm, 5 μm) from Regis Technologies, which was accompanied with a guard column (Agilent Zorbax® ODS, 4.6 x 12.5 mm, 5μm), 1 mL/min flow (isocratic) at r.t., using as mobile phase a mixture hexanes/isopropanol, 7/3, v/v; ee = 16%.

HPLC

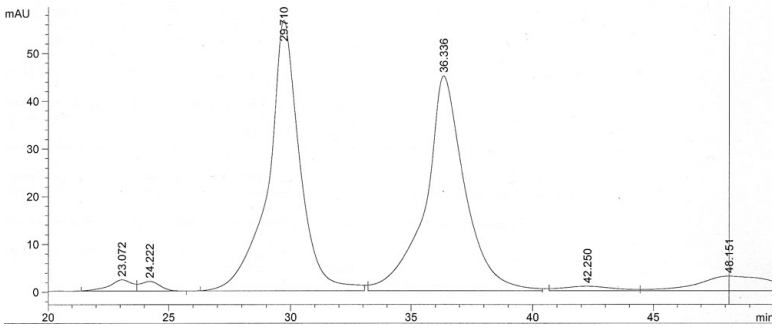


From BINAP (racemic): ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 21.507 (s, height: 104.5); 21.413 (s, height: 110.0); $ee_{(heights)}$ = 2.3%.

HPLC Analysis: Product1 t_R 29.482 min (Area=20.1500 units); Product2 t_R 35.995 min (Area= 20.0855 units); *(S,S)*-Whelk-01 Column (250 × 4.6 mm, 5 μm) from Regis Technologies, which was accompanied with a guard column (Agilent Zorbax® ODS, 4.6 x 12.5 mm, 5μm), 1 mL/min flow (isocratic) at r.t., using as mobile phase a mixture hexanes/isopropanol, 7/3, v/v; ee = 1.6%.

LC/MS: Time range (LC): 30.1-38.2 min, MS (EI^+) for $C_{12}H_{13}O_2P$, $[M]^+$ *m/z* 220.1; $[NaphP(O)(OH)(H)+H]^+$ *m/z* 193; $[NaphP(OH)(H)+H]^+$ *m/z* 175; $[Naph+H]^+$ 129.1.

HPLC



Chapter Seven, Section 7.2.

General Procedures for the Desymmetrization of Chiral and Prochiral Alkyl Phosphinate Esters via Various C-P Bond Forming Reactions

(a) Preparation of Alkyl Phosphinates

Method A: Pivaloyl Chloride-Mediated Esterification.[10,16-17] (Note: *Generally used in metal-catalyzed reactions*). To a suspension of anilinum hypophosphite (0.318 g, 2 mmol, 2 eq) in reagent grade CH_3CN (12 – 15 mL), was added pyridine (0.20 mL, 0.198 g, 2.5 mmol, 2.5 eq) the corresponding alcohol (3 mmol, 3 eq) and pivaloyl chloride (0.27 mL, 0.265 g, 2.2 mmol, 2.2 eq) at room temperature under N_2. The resulting solution is stirred at room temperature for 2 hours. If successful, ^{31}P NMR monitoring of the reaction mixture shows the appearance of the expected alkyl phosphinate in the range of 7 – 20 ppm. The solution is used *in situ* for the next reaction.

Method B: Transesterification with Phenyl Phosphinate.[10,17-18,52] (Note*: Most effective method in general, applicable in metal-catalyzed processes and nucleophilic addition reactions*). To a solution of freshly concentrated H_3PO_2 (0.132 g, 2 mmol, 2 eq) in reagent grade CH_3CN (12 - 15 mL), was added $(PhO)_4Si$[1] (0.800 g, 2 mmol, 2 eq) and the corresponding alcohol (4 mmol, 4 eq). The resulting suspension is heated at reflux temperature for 2 hours under N_2. ^{31}P NMR analysis is used to monitor the progress of the reaction. The appearance of a peak in the range of

7- 20 pppm, with the adequate multiplicity [t(x), x=s, d, t, etc.] indicates a successful formation of alkyl phosphinate. The suspension is cooled to room temperature and used *in situ* for the next reaction. Alternatively, a stock solution can be prepared and used within a period no longer than a week.

Method C: Dean-Stark Esterification.[14] (Note: *Applicable in base-promoted alkylation and free radical-mediated addition reactions. Generally prepared as stock solution and used immediately or within a week. It requires storing under* N_2). A mixture of H_3PO_2 (1 eq), the corresponding alcohol (1.5 – 2 eq) and a drop of H_2SO_4 in reagent grade cyclohexane (0.40 M relative to the amount of acid) is heated at reflux temperature using a Dean-Stark trap (prefilled with cyclohexane) for 12 to 20 h, according to the progress of the reaction (by ^{31}P NMR analysis).

General Procedures for the C-P Bond Forming Reactions (Tables 7.2 & 7.3)

Pd-Catalyzed Hydrophosphinylation.[33] To a solution of alkyl phosphinate (2 mmol, 2 eq) in CH_3CN was added an alkene (1 mmol, 1 eq), Pd_2dba_3 (0.0092 g, 0.01 mmol, 2 mol% Pd) and xantphos (0.0127 g, 0.022 mmol) at room temperature. The solution was heated at reflux (7-14 h), or stirred at room temperature (30-60 h) under nitrogen. After cooling to r.t., ^{31}P NMR analysis was used to detemine the diastereomeric excess (de) achieved. The workup of the reaction was performed as follows: the mixture was diluted with EtOAc and washed with 2 M aqueous HCl (1 x), followed by extraction of the aqueous phase with EtOAc (2 x). The organic fractions were combined and washed with saturated aqueous $NaHCO_3$ (1 x) and brine (1 x). Drying and concentration furnished the crude compound, which was purified by radial or column chromatography using mixtures Hex/EtOAc.

Pd-Catalyzed Cross-Coupling.[62,63] To a solution of alkyl phosphinate (2 mmol, 3 eq) in CH_3CN was added an aryl halide (0.7 mmol, 1 eq), Et_3N (0.28 mL, 0.202 g, 2 mmol, 3 eq),

$Pd(OAc)_2$ (0.0032 g, 0.014 mmol, 2 mol% Pd) and dppp (0.0064 g, 0.0154 mmol) at room temperature. The solution was heated at reflux temperature (7 h), under nitrogen. ^{31}P NMR analysis and/or workup were performed as indicated above for the Pd-catalyzed hydrophosphinylation reaction.

Ni-Catalyzed Hydrophosphinylation.[35] To a solution of alkyl phosphinate (2 mmol, 2 eq) in CH_3CN was added an internal alkyne (1 mmol, 1 eq) and $NiCl_2$ (0.0052 g, 0.04 mmol) at room temperature. The solution was heated at reflux temperature (12 h), under nitrogen. ^{31}P NMR analysis and/or workup were performed as indicated above for the Pd-catalyzed hydrophosphinylation reaction.

Nucleophilic Addition Reactions.[18] To a solution of alkyl phosphinate (2 mmol, 1.2 eq) in CH_3CN was added a carbonyl-containing of an α,β-unsaturated compound (1.7 mmol, 1.0 eq), followed by the corresponding base, either iPr$_2$NEt (0.24 mL, 0.220 g, 1.7 mmol, 1 eq) or TMG (0.22 mL, 0.196 g, 1.7 mmol, 1 eq) and the reactions were stirred at room temperature for 2 to 4 h. ^{31}P NMR analysis and/or workup were performed as indicated above for the Pd-catalyzed hydrophosphinylation reaction.

Et_3B- and AIBN-Mediated Radical Addition.[25,26] A 0.4 M solution of alkyl phosphinate (5 mL, 2 mmol, 3 eq) in cyclohexanes (Dean-Stark esterification) was diluted with reagent grade CH_3CN (5 mL), and an alkene or alkyne (0.7 mmol, 1 eq), followed by the corresponding radical initiator. (a) AIBN (0.2 eq) followed by heating at reflux temperature for 15 h, before another addition of AIBN (0.3 eq) and heating for another 15 h under N_2; or (b) Et_3B (0.7 mmol, 1 eq) followed by stirring at room temperature for 18-24 h under air. ^{31}P NMR analysis, evaporation and/or workup were performed as indicated above for the Pd-catalyzed hydrophosphinylation reaction.

Base-Promoted Alkylation.[57] A 0.4 M solution of alkyl phosphinate (5 mL, 2 mmol, 1.5 eq) in cyclohexanes (Dean-Stark esterification) was diluted with anhydrous THF (5 mL), and an alkyl iodide (1.33 mmol, 1 eq), followed by *n*-BuLi (1.6 M in hexanes, 1.1 mL, 1.73 mmol, 1.3 eq) or a solution of *n*-BuLi/(-)-sparteine (1/1, previously stirred at -78°C for 15 min) were added at -78°C under N_2. After addition of BuLi, the reaction was slowly allowed to reach room temperature (1.5 h). ^{31}P NMR analysis, and/or workup (quenching with 20% aqueous $NaHSO_4$), followed by extraction with EtOAc and purification were performed, as described above for the Pd-catalyzed hydrophosphinylation reaction.

Chapter Seven, Section 7.2.1

Representative Procedure for the Desymmetrization of Alkyl Phosphinates via Pd-Catalyzed Hydrophosphinylation. Preparation of (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2-(2-bromo-phenyl)-ethyl) phosphinate (Table 7.2, entry 23b). To a solution of concentrated H_3PO_2 (0.132 g, 2 mmol, 2 eq) in CH_3CN (15 mL) were added $(PhO)_4Si$[1] (0.800 g, 2 mmol, 2 eq) and (-)-8-phenylmenthol[230] (0.930 g, 4 mmol, 4 eq). The reaction was heated at reflux temperature for 2 hours under N_2 and then cooled down to room temperature. 2-Bromostyrene (0.13 mL, 0.183 g, 1 mmol, 1 eq), Pd_2dba_3 (0.0092 g, 0.01 mmol) and xantphos (0.0127 g, 0.022 mmol) were added at room temperature in that order, and the reaction was stirred at room temperature for 50 h. The diastereomeric excess from the crude mixture was 67% according to the integrals from the ^{31}P NMR spectra. The reaction was diluted with EtOAc and washed with 2 M aqueous HCl (1 x). The aqueous layer was extracted with EtOAc (2 x) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 x) and then brine (1 x). Drying over $MgSO_4$, filtration and concentration gave the crude compound. Purification by radial chromatography (2 mm thickness, hexanes/EtOAc 5:1, v/v,

EtOAc) furnished 0.264 g of the product as a clear oil (57% yield). ^{31}P NMR showed the product as a mixture of diastereoisomers (R_P/S_P) with a de = 70%.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 7.2, entry 23a). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 – 7.41 (m, 8 H), 7.07 – 7.17 (m, 2 H), 7.02 (d, J_{HP} = 519 Hz, 1 H), 6.64 (d, J_{HP} = 528 Hz, 1 H), 4.35 – 4.5 (m, 1 H), 4.12 – 4.3 (m, 1 H), 1.97 – 2.3 (m, 4 H), 1.58 – 1.81 (m, 4 H), 1.0 – 1.57 (m, 44 H), 0.78 – 1.0 (m, 16 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.5, 151.9, 128.1 (2 C), 128.0 (2 C), 125.7 (2 C), 125.5 (2 C), 125.3, 125.1, 79.0 and 78.4 (2xd, J_{POC} = 7 Hz, 2 C), 51.7 and 51.6 (2xd, J_{POCC} = 6 Hz, 2 C), 44.8, 41.8, 39.9, 39.8, 34.6, 31.9, 31.7 (d, J_{PCC} = 11 Hz), 31.5, 30.5 (d, J_{PCCC} = 16 Hz), 29.9, 30.2 (d, J_{PCCC} = 15 Hz), 29.3 (d, J_{PC} = 94 Hz), 29.2, 28.3, 28.2 (d, J_{PC} = 96 Hz), 26.6, 24.9, 24.6, 22.8, 22.0, 21.9, 21.0, 20.4, 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.36 (dd, J_{PH} = 528 Hz, J = 11 Hz, 20.5%), 33.55 (dm, J_{PH} = 519 Hz, 79.5%); HRMS (CI) calcd. for $C_{24}H_{41}O_2P$ $(M+H)^+$ 393.2922, found 393.2916.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2-(2-bromo-phenyl)-ethyl) phosphinate (Table 7.2, entry 23b). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (ddd, J_{HP} = 527 Hz, J = 2 Hz, J = 1 Hz, 1 H), 7.02 – 7.56 (m, 18 H), 6.80 (dt, J_{HP} = 537 Hz, J = 2 Hz, 1 H), 4.38 – 4.53 (m, 1 H), 4.19 – 4.32 (m, 1 H), 3.45 – 3.61 (m, 2 H), 2.51 – 2.85 (m, 2H), 2.0 – 2.15 (m, 4 H), 0.81 – 1.89 (m, 34 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.7, 139.6, 133.2, 130.4, 128.6 (d, J_{PCCC} = 14 Hz), 128.1 (2 C), 127.8, 126.0, 125.8 (2 C), 125.2, 77.4 (d, J_{POC} = 8 Hz), 51.8 (d, J_{POCC} = 7 Hz), 45.5, 41.9, 40.0, 34.6, 31.5, 28.0, 27.9 (d, J_{PC} = 95 Hz), 26.7, 25.0, 22.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.91 (dm, J_{PH} = 537 Hz, 15.5%), 31.09 (dm, J_{PH} = 527 Hz, 85.5%); HRMS (APCI) calcd. for $BrC_{24}H_{32}O_2P$ $(M+H)^+$ 463.1401, found 463.1412.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (3,3,-dimethyl-butyl) phosphinate (Table 7.2, entry 23f). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 – 7.41 (m, 8 H), 7.07 – 7.17 (m, 2 H), 7.02 (d, J_{HP} = 519 Hz, 1 H), 6.64 (d, J_{HP} = 528 Hz, 1 H), 4.35 – 4.5 (m, 1 H), 4.12 – 4.3 (m, 1 H), 1.97 – 2.3 (m, 4 H), 1.58 – 1.81 (m, 4 H), 1.0 – 1.57 (m, 44 H), 0.78 – 1.0 (m, 16 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.36 (dd, J_{PH} = 528 Hz, J = 11 Hz, 20.5%), 33.55 (dm, J_{PH} = 519 Hz, 79.5%).

2-(1-Methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 7.2, entry 26a). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 – 7.43 (m, 8 H), 7.07 – 7.19 (m, 2 H), 7.0 (d, J_{HP} = 524 Hz, 1 H), 6.76 (d, J_{HP} = 530 Hz, 1 H), 4.30 – 4.47 (m, 1 H), 4.07 – 4.28 (m, 1 H), 1.99 – 2.19 (m, 4 H), 1.59 – 1.82 (m, 6 H), 0.98 – 1.50 (m, 48 H), 0.89 (t, J = 7 Hz, 6 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.23 (dm, J_{PH} = 530 Hz, 28.4%), 33.41 (dd, J_{PH} = 524 Hz, J = 6 Hz, 71.6%).

2-[1,1-Dimethyl-1-(3,5-di*iso*-propylphenylmethyl)]cyclohexyl octylphosphinate (Table 7.2, entry 27). Mixture of isomers (R_P/S_P); 78% purity. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 41.43 (dd, J_{PH} = 524 Hz, 19.5%), 35.91 (dm, J_{PH} = 523 Hz, 59.0%). Minor unidentified products: 26.1 (dm, 10.1%), 22.7 (dm, 11.3%).

Chapter Seven, Section 7.2.2

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl phenylphosphinate (Table 7.3, entry 3a). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J_{HP} = 551 Hz, 1 H), 7.26 (d, J_{HP} = 564 Hz, 1 H), 6.93 – 7.61 (m, 20 H), 4.44 – 4.62 (m, 2 H), 1.02 – 2.32 (m, 28 H), 0.78 – 0.96 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.8, 151.6, 133.9 and 132.0 (2xd, J_{PC} = 119 Hz, 2 C), 132.8 (m, 2 C), 130.9 and 130.6 (2xd, J_{PCC} = 12 Hz, 2 C), 129.2 (2 C), 128.7 and 128.6 (2xd, J_{PCCC} = 14 Hz, 4 C), 128.2 (2 C), 127.9 (2 C), 125.7, 125.6, 125.4 (2 C), 124.4,

120.2, 78.9 and 78.3 (2xd, J_{POC} = 7 Hz, 2 C), 52.3 and 52.1 (2xd, J_{POCC} = 6 Hz, 2 C), 44.8, 42.6, 40.3, 40.2, 34.6, 31.7, 28.3, 27.9 (2 C), 27.4, 27.1, 26.9, 26.1, 25.8, 22.0, 21.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.17 (dm, J_{PH} = 564 Hz, 44.6%), 19.34 (dm, J_{PH} = 551 Hz, 55.4%); HRMS (CI) calcd. for $C_{22}H_{29}O_2P$ $(M+H)^+$ 357.1983, found 357.1979.

2-(1-Methyl-1-phenylethyl)cyclohexyl (2-cyanoethyl) phosphinate (Table 7.3, entry 4b). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 – 7.41 (m, 8 H), 7.14 – 7.24 (m, 2 H), 7.10 (ddd, J_{HP} = 539 Hz, J = 4 Hz, J = 1 Hz, 1 H), 6.83 (dd, J_{HP} = 553 Hz, J = 1 Hz, 1 H), 4.34 – 4.48 (m, 1 H), 4.13 – 4.29 (m, 1 H), 2.07 – 2.38 (m, 8 H), 1.69 – 2.02 (m, 6 H), 1.08 – 1.64 (m, 24 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 31.32 (dm, J_{PH} = 553 Hz, 34.3%), 25.0 (dm, J_{PH} = 539 Hz, 65.7%).

2-(1-Methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 7.3, entry 4e). Mixture of isomers (R_P/S_P). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.23 (dm, J_{PH} = 530 Hz, 49.9%), 33.41 (dd, J_{PH} = 524 Hz, J = 6 Hz, 25.4%). Two other unidentified products: δ 44.79 (dm, J_{PH} = 379 Hz, 15.9%), 32.13 (dm, J_{PH} = 556 Hz, 8.9%).

2-(1-Methyl-1-phenylethyl)cyclohexyl methylphosphinate (Table 7.3, entry 4h). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 – 7.38 (m, 8 H), 7.16 (dq, J_{HP} = 532 Hz, J = 2 Hz, 1 H), 7.07 – 7.17 (m, 2 H), 6.89 (dq, J_{HP} = 537 Hz, J = 2 Hz, 1 H), 4.30 – 4.44 (m, 1 H), 4.07 – 4.23 (m, 1 H), 2.08 – 2.32 (m, 4 H), 1.62 – 1.87 (m, 6 H), 1.32 – 1.59 (m, 8 H), 1.18 – 1.30 (m, 10 H), 0.96 – 1.06 (m, 8 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.51 (ddd, J_{PH} = 537 Hz, J = 15 Hz, J = 10 Hz, 60.4%), 27.55 (ddd, J_{PH} = 532 Hz, J = 16 Hz, J = 7 Hz, 39.6%).

REFERENCES

(1) (a) Engel, R.; Cohen, J. I. *Synthesis of Carbon-Phosphorus Bonds* (2nd ed); CRC Press, Boca Raton, FL, 2003.

(b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000.

(c) Hartley, F. R. (Ed.) *The Chemistry of Organophosphorus Compounds*; vol. 4, Wiley: New York, 1996.

(d) Engel, R. *Handbook of Organophosphorus Chemistry*; Marcel Dekker: New York, 1992.

(e) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 301.

(f) Kukhar, V. P. ; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids;* John Wiley & Sons, Inc: New York, 2000.

(g) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.

(h) Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*, CRC Press, Boca Raton, 2003.

(i) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281.

(j) Flett, D. S. *J. Organomet. Chem.* **2005**, *690*, 2426.

(k) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237.

(l) Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287.

(m) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed., Elsevier: Amsterdam, 1995.

(2) For examples of functional group interconversion related to H-phosphinic acids, see:

(a) Nifant'ev, E. E. *Russ. Chem. Rev.* **1978**, *47,* 835.

(b) Yudelevich, V. I.; Sokolov, L. B.; Ionin, B. I. *Russ. Chem. Rev.* **1980**, *49*, 46.

(c) Frank, A. W. *Chem. Rev.* **1961**, *60*, 389.

(d) Sasse, K. (Ed.) *Methoden der Organischen Chemie;* Georg Thieme Verlag: Stuttgart,

1964, Band XII/1, 294-337.

(e) Regitz, M. (Ed,), *Methoden der Organischen Chemie;* Georg Thieme Verlag: Stuttgart. 1982, Vol. E2.

(f) Soulier, E.; Clement, J.-C.; Yaouanc, J.-J.; des Abbayes, H. *Tetrahedron Lett.* **1998**, *39*, 4291.

(g) Frank, A. W.; *J. Org. Chem.* **1961**, *26*, 850.

(h) Anderson, N. G.; Ciaramella, B. M.; Feldman, A. F.; Lust, D. A.; Moniot, J. L.; Moran, L.; Polomski, R. E.; Wang, S. S. Y. *Org. Process Res. Dev.* **1997**, *1*, 211.

(3) For some representative examples of biologically-active phosphinic acids, see:

(a) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.*. **1995**, *38*, 3297.

(b) Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C. Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.

(c) Gill, S. H.; Eisenber, D.; *Biochemistry* **2001**, *40*, 1903.

(d) Cohen, L. H.; Valentijn, A. R. P. M.; Roodenburg, L.; Van Leeuwen, R. E. W.; Huisman, R. H.; Lutz, R. J.; Van der Marel, G. A.; Van Boom, J. H. *Biochemical Pharmacology* **1995**, *49*, 839.

(e) Abdel-Meguid, S. S.; Zhao, B.; Murthy, K. H. M.; Winborne, E.; Choi, J.-K.; DesJarlais, R. L.; Minnich, M. D.; Culp, J. S.; Debouck, C.; Tomaszek, T. A.; Meek, T. D.; Dreyer, G. B. *Biochemistry* **1993**, *32*, 7972.

(f) Feng, Y.; Coward, J. K. *J. Med. Chem.* **2006**, *49*, 770.

(g) Tian, F.; Montchamp, J.-L.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 7373.

(h) Desmet, V.; Vrolix, M.; De Scheerder, I.; Van Lierde, J.; Willems, J. L.; Piessens, J. *Circulation* **1994**, *89*, 385.

(i) Petrillo, E. W.; Karanewsky, D. S.; Thottathil, J. K.; Heikes, J. E.; Grosso, J. A. *Gen. Offen.* **1989**, 20.

(j) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwarz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148.

(4) Collingwood, S. P.; Baxter, A. D. *Synlett* **1995**, *7*, 703.

(5) (a) Farrington, G. K.; Kumar, A.; Wedler, F. C. *J. Med. Chem.* **1987**, *30*, 2062.

(b) Hays, S. J.; Bigge, C. F.; Novak, P. M.; Drummond, J. T.; Bobovski, T. P.; Rice, M. J.; Johnson, G.; Brahce, L. J.; Coughenour, L. L. *J. Med. Chem.* **1990**, *33*, 2916.

(6) (a) Devedjiev, T. T.; Hassan, E. A.; Ganev, V. G. *Bulgarian Chemical Communications* **2002**, *34*, 5863.

(b) Chen, Y.; Helquist, P.; Tenniswood, M.; Miller, M. J.; Wiest, O.; Oliver, J.; Brown, M. *Abstracts of Papers*, 221st ACS ACS National Meeting, San Diego, CA. US, 2001.

(7) Collinsova, M.; Jiracek, J. *Current Medicinal Chemistry* **2000**, *7*, 629.

(8) (a) Rodan, G. A. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 375.

(b) Mundy, G. R. *Annu. Rev. Med.* **2002**, *53*, 337.

(c) Fleish, H. *Bisphosphonates in Bone Disease*; Academic Press: San Diego, 2000.

(9) Gouault-Bironneau, S.; Deprèle, S.; Sutor, A.; Montchamp, J.-L. *Org. Lett.* **2005**, *7*, 5909.

(10) Bravo-Altamirano, K.; Montchamp, J.-L., "Phosphinic Acid, Alkyl Esters" in Encyclopedia of Reagents for Organic Synthesis (eEROS). In press.

(11) Kabachnik, M. I.; Shipov, A. E.; Mastryukova, T. A. *Bull. Acad. Sci., USSR* **1960**, *1*, 138.

(12) Fitch, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 61.

(13) (a) Gallagher, M. J.; Honegger, H. *Tetrahedron Lett.* **1977**, *34*, 2987.

(b) Gallagher, M. J.; Honegger, H. *Aust. J. Chem.* **1980**, *33*, 287.

(c) Gallagher, M. J.; Garbutt, R.; Hua, L. Y.; Lee, G. H. *Phosphorus, Sulfur, and Silicon* **1993**, *75*, 201.

(14) Nifant'ev, E. E.; Levitan, L. P. *J. Gen. Chem. USSR* **1965**, *35*, 762.

(15) (a)Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425.

(b)Kolodyazhnyi, O. I. *Russ. J. Gen. Chem.* **2005**, *75*, 656.

(16) Stawinski, J.; Thelin, M.; Westman, E.; Zain, R. *J. Org. Chem.* **1990**, *55*, 3503.

(17) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388.

(18) Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *643-644*, 154.

(19) Reviews:

(a) Leca, D.; Fensterbank, L.; Lacote, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858.

(b) Walling, C.; Pearson, M. S. *Top. Phosphorus Chem.* **1966**, *3*, 1.

(c) Halmann, H. *Top. Phosphorus Chem.* **1967**, *4*, 49.

(d) Bentrude, W. G. *Free Radicals*, Kochi, J. K. Ed.; Wiley, New York, 1973, Vol. 2, Chapter 22.

(e) Bentrude, W. G. *The Chemistry of Organophosphorus Compounds*, Hartley, F. R. Ed.; Wiley: New York, 1990, Vol. 1, Chapter 14.

(20) Williams, R. H.; Hamilton, L. A. *J. Am. Chem. Soc.* **1955**, *77*, 3411.

(21) Okamoto, Y.; Sakurai, H. *J. Chem. Soc. Jpn. Ind. Chem. Sect.* **1965**, *68*, 2080.

(22) Petrov, K. A.; Lysenko, T. N.; Libman, B. Y.; Pozdnev, V. V. *Chemistry of Organophosphorus Compounds*; Nauka: Moscow, 1967.

(23) (a) Nifant'ev, E. E.; Magdeeva, R. K.; Shchepet'eva, N. P. *J. Gen. Chem. USSR* **1980**, *50*, 1416.

(b) Nifant'ev, E. E.; Solovetskaya, L. A.; Maslennikova, V. I.; Magdeeva, R. K.; Sergeev, N. M. *J. Gen. Chem. USSR* **1986**, *56*, 773. *See also:*

(c) Henderson, W.; Leach, M. T.; Nicholson, B. K.; Sabat, M. *J. Chem. Soc. Dalton Trans.* **1995**, 2109.

(24) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204.

(25) Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745.

(26) Antczak, M. I.; Montchamp, J.-L. *Synthesis* **2006**, *18*, 3080.

(27) Deprèle, S.; Montchamp, J.-L. "Bis-H-Phosphinic Acid Derivatives as Precursors to Therapeutic Bisphosphonates and Uses Thereof", US Patent Number US 6,781,011 B2 (August 24, 2004).

(28) (a) Gautier, A.; Garipova, G.; Salcedo, C.; Balieu, S.; Piettre, S. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 5963. See also:

(b) Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett*. **2002**, *4*, 359

(29) For general references on P-H addition to unsaturated compounds, see:

(a) Beletskaya, I. P.; Kazankova, M. A. *Russ. J. Org. Chem.* **2002**, *38*, 1391.

(b) Tanaka, M.; *Top. Curr. Chem.* **2004**, *232*, 25.

(c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(d) Wicht, D. K.; Glueck, D. S. In *Catalytic Heterofunctionalization*; Togni, A.; Grützmacher, H. Eds. Wiley-VCH: Weinheim, 2001; Chapter 5 and references therein.

(30) For references on transfer hydrogenation with hypophosphorous derivatives, see:

(a) Johnstone, R. A. W.; Wilby, A. H., Entwistle, A. I. *Chem. Rev.* **1985**, *85*, 129.

(b) Boyer, S. K.; Bach, J.; McKenna, J.; Jagdmann, E. *J. Org. Chem.* **1985**, *50*, 3408.

(c) Khai, B. T.; Arcelli, A. *J. Org. Chem.* **1989**, *54*, 949.

(d) Brigas, A. F.; Johnstone, R. A. W. *Tetrahedron* **1992**, *48*, 7735.

(e) Marques, C. A.; Selva, M.; Tundo, P. *J. Chem. Soc. Perkin Trans. 1* **1993**, 529.

(31) (a) Han, L.-B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571.

(b) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407.

(c) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1929.

(d) Zhao, C.-Q.; Han, L.-B.; Tanaka, M. *Organometallics* **2000**, *19*, 4196. See also:

(e) Reichwein, J. F.; Patel, M. C.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 4303.

(f) Stockland, R. A., Jr.; Levine, A. M.; Giovine, M. T.; Guzei, I. A.; Cannistra, J. C. *Organometallics* **2004**, *23*, 647.

(g) Levine, A. M.; Stockland, Jr., R. A.; Clark, R.; Guzei, I. *Organometallics* **2002**, *21,* 3278.

(32) Reichwein, J. F.; Pagenkopf, B. L. *J. Org. Chem.* **2003**, *68*, 1459.

(33) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.

(34) Deprèle, S.; Montchamp, J.-L. *Org. Lett.* **2004**, *6*, 3805.

(35) Ribière, P.; Bravo-Altamirano, K.; Antczak M.; Hawkins, J.; Montchamp, J.-L. *J. Org. Chem.* **2005**, *70,* 4064.

(36) (a) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223.

(b) Boyd, E. A.; Corless, M.; James, K.; Regan, A. C. *Tetrahedron Lett.* **1990**, *31*, 2933.

(c) Boyd, E. A.; Regan, A. C. *Tetrahedron Lett.* **1992**, *33*, 813.

(37) (a) Voronkov, M. G.; Marmur, L. Z.; Dolgov, O. N.; Pestunovich, V. A.; Pokrovskii, E. I.; Popel, Y. I. *J. Gen. Chem. USSR* **1971**, *41*, 2005.

(b) Grobelny, D. *Synthesis* **1987**, 942.

(38) Selected examples on the application of BTSP as synthon:

(a) Ravaschino, E. L.; Docampo, R.; Rodriguez, J. B.; *J. Med. Chem.* **2006**, *49*, 426.

(b) Nan, F.; Bzdega, T.; Pshenichkin, S.; Wroblewski, J. T.; Wroblewska, B.; Neale, J.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 772.

(c) An, H.; Wang, T.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789.

(d) Jones, P. B.; Parrish, N. M.; Houston, T. A.; Stapon, A.; Bansal, N. P.; Dick, J. D.; Townsend, C. A. *J. Med. Chem.* **2000**, *43*, 3304.

(e) Montchamp, J.-L.; Tian, F.; Frost, J. W. *J. Org. Chem.* **1995**, *60*, 6076.

(f) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502.

(39) (a) Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125.

(b) Yamagishi, T.; Suemune, K.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **2001**, *42*, 5033.

(40) For some representative examples, see:

(a) Schmidt, H. *Chem. Ber.* **1948**, *81*, 477.

(b) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2455.

(c) Hamilton, R.; Walker, B.; *Tetrahedron Lett.* **1995**, *36*, 4451.

(41) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510.

(42) Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2003**, *44*, 4243.

(43) (a) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643-644*, 381.

(b) Pirat, J.-L.; Coulombeau, A.; Genevois-Borella, A.; Cristau, H.-J. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 1793.

(c) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *J. Tetrahedron Lett.* **2001**, *42*, 4491.

(44) (a) Natchev, I. A. *Phosphorus, Sulfur* **1988**, *37*, 133.

(b) Natchev, I. A. *Liebigs Ann. Chem.* **1988**, 861.

(45) Maier, L. *Helv. Chim. Acta* **1973**, *56*, 489.

(46) Wroblewski, A. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 10168.

(47) (a) Caldwell, C. G.; Sahoo, S. P.; Polo, S. A.; Eversole, R. R.; Lanza, T. J.; Mills, S. G.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Durette, P. L.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 323.

(b) Broadhurst, M.J.; Handa, B.K.; Johnson, W.H.; Lawton, G.; Machin, P.J. Eur. Pat. 276436-A1, 1988.

(48) (a) Crofts, P. C.; Parker, D. M. *J. Chem. Soc. (C)* **1970**, 332.

(b) Metzger, S. H.; Basedow, O. H.; Isbell, A. F. *J. Org. Chem.* **1964**, *29*, 627.

(49) Kosolapoff, G. M. *J. Am. Chem. Soc.* **1950**, *72*, 4292.

(50) (a) Kabachnik, M. I.; Jung-Yu, C.; Tsvetkov, E. N. *J. Gen. Chem. USSR* **1962**, *32*, 3288.

(b) Kabachnik, M. I.; Tsvetkov, E. N.; Jung-Yu, C. *Dokl. Akad. Nauk. USSR, Div. Khim.* **1960**, *131*, 407.

(51) Xu, Y.; Wei, H.; Xia, J. *Liebigs. Ann. Chem.* **1988***,* 1139.

(52) Montchamp, J.-L. *Specialty Chemicals Magazine* **2006**, *26*, 44.

(53) (a) Coe, D. G.; Perry, B. J.; Brown, R. J. *J. Chem. Soc.* **1957**, 3604.

(b) Balthazor, T. M.; Flores, R. A. *J. Org. Chem.* **1980**, *45*, 530.

(54) Engel, R.; Chakraborty, S. *Synth. Commun.* **1988**, *18*, 665.

(55) Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *Phosphorus, Sulfur, Silicon* **1996**, *115*, 255.

(56) (a) Fookes, C. J. R.; Gallagher, M. J. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1876.

(b) Fookes, C. J. R.; Gallagher, M. J.; Honneger, H. *J. Chem. Soc. Chem. Commun.* **1978**, 324.

(57) Abrunhosa-Thomas, I.; Ribière, P.; Adcock, A. C.; Montchamp, J.-L. *Synthesis* **2006**, *2*, 325.

(58) (a) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G.; Jack, J. *Phosphorus Sulfur* **1987**, *30*, 571.

(b) McCleery, P. P.; Tuck, B. *J. Chem. Soc. Perkin Trans. I* **1989**, 1319.

(c) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787.

(d) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385.

(e) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389.

(f) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc. Trans. 1* **1995**, 1145.

(59) Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393.

(60) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255.

(61) Dumond, Y. R.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *653*, 252.

(62) Huang, Z.; Bravo-Altamirano, K.; Montchamp, J.-L. *Comptes Rendus Chimie* **2004**, *7/8-9*, 763.

(63) Bravo-Altamirano, K.; Huang, Z.; Montchamp, J.-L. *Tetrahedron* **2005**, *61,* 6315.

(64) (a) Huang, C.; Tang X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 5020.

(b) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3636.

(65) (a) Lu, X.; Zhu, J.; Huang, J.; Tao, X. *J. Molecular Catalysis* **1987**, *41*, 235.

(b) Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239.

(c) Lu, X.; Tao, X.; Zhu, J.; Sun, X.; Xu, J. *Synthesis* **1989**, 848.

(d) Lu, X.; Zhu, J. *Synthesis* **1986**, 563.

(66) Bravo-Altamirano, K.; Montchamp, J.-L. *Org. Lett.* **2006**, *8*, 4169.

(67) Schwan, A. *Chem. Soc. Rev.* **2004**, *33*, 218.

(68) (a) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377.

(b) Xu, Y.; Zhang, J. *Synthesis* **1984**, 778.

(c) Xu, Y.; Li, Z.; *Synthesis* **1986**, 240.

(69) (a) Xu, Y.; Zhang, J. *J. Chem. Soc. Chem. Commun.* **1986**, 1606.

(b) Zhang, J.; Xu, Y.; Huang, G.; Guo, H. *Tetrahedron Lett.* **1988**, *29*, 1955.

(c) Xu, Y.; Wej, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949.

(70) (a) Murata, Y.; Woodward, R. M.; Miledi, R.; Overman, L. E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2073.

(b) Ragozzino, D.; Woodward, R. M.; Murata, Y.; Eusebi, F.; Overman, L. E.; Miledi, R. *Mol. Pharmacol.* **1996**, *50*, 1024.

(71) Schuman, M.; Lopez, Z.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299.

(72) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W.; *J. Org. Chem.*, **1994**, *59,* 4206.

(73) Han, L.-B.; Zhao, C.-Q.; Onozawa, S.-y.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842.

(74) (a) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080.

(b) Han, L.-B.; Ono, Y.; Yazawa, H. *Org. Lett.* **2005**, *7*, 2909.

(75) For radical reactions of *H*-phosphinates, see:

(a) Piettre, S. R.; *Tetrahedron Lett.* **1996**, *37*, 2233.

(b) Zeiss, H.-J. *Tetrahedron Lett.* **1992**, *38*, 8263.

(c) Dingwall, J. G.; Tuck, B. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2081.

(d) Pudovik, A. N.; Konovalova, I. V.; Guryleva, A. A. *J. Gen. Chem. USSR* **1963**, *33*, 2850.

(e) Finke, M.; Kleiner, H.-J. *Liebigs Ann. Chem.* **1974**, 741.

(f) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Chem. Soc., Chem. Commun*. **1971**, 146.

(76) Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* **2005**, *70*, 10121.

(77) Hirai, T.; Han, L.-B. *Org. Lett.* **2007**, *9*, 53.

(78) Stockland, R. A.; Taylor, R. I.; Thompson, L. E.; Patel, P. B. *Org. Lett.* **2005**, *7*, 851.

(79) Stockland, R. A., Jr.; Lipman, A. J.; Bawiec, J. A., III; Morrison, P. E.; Guzei, I. A.; Findeis, P. M.; Tamblin, J. F. *J. Organomet. Chem.* **2006**, *691*, 4042.

(80) (a) Pudovik, A. N.; Gur'yanova, I. V.; Banderova, L. V. *Khim. Org. Soedin, Fosfara. Akad. Nauk SSSR*, *Otd. Obshch. Tekh. Khim.* **1967**, 21; *C. A.* **1968**, *69*, 67485.

(b) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81.

(81) (a) Yamashita, M.; Tsunekawa, K.; Sugiura, M.; Oshikawa, T. *Synthesis* **1985**, 896.

(b) Hansen, H. I.; Kehler, J. *Synthesis* **1999**, 1925.

(82) Review: (a) Bhattacharya, A. K.; Thyagarajan, G.; *Chem. Rev.* **1981**, *81*, 415.

(b) Kosolapoff, G. M. *J. Am. Chem. Soc.* **1945**, *67*, 1180.

(83) (a) Yamagishi, T.; Suemune, K.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2002**, *58*, 2577.

(b) Yamagishi, T.; Kusano, T.; Yokomatsu, T.; Shibuya, S. *Synlett* **2002**, 1471.

(84) Yamagishi, T.; Kusano, T.; Kaboudin, B.; Tsutomu, Y.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767.

(85) Pudovik, A. N.; Pudovik, M. A. *Zhurnal Obshchei Khimii* **1966**, *36*, 1467.

(86) Cristau, H.-J.; Hervé, A.; Virieux, D. *Tetrahedron* **2004**, *60*, 877.

(87) Jackson, P. F.; Tays, K. L.; Maclin, K. M.; Ko, Y.-S.; Weixing, L.; Vitharana, D.; Tsukamoto, T.; Stoermer, D.; Lu, X.-C. M.; Wozniak, K.; Slusher, B. S. *J. Med. Chem.* **2001**, *44*, 4170.

(88) Szabó, A.; Petneházy, I.; Jászay, Z. M. *Heteroatom Chem.* **2003**, *14*, 235.

(89) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502.

(90) Ravaschino, E. L.; Docampo, R.; Rodriguez, J. B. *J. Med. Chem.* **2006**, *49*, 426.

(91) Lecerclé, D.; Sawlckl, M.; Taran, F. *Org. Lett.* **2006**, *8*, 4283.

(92) Selected publications: (a) Michaelis, A.; Kaehne, R. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1408.

(b) Arbuzov, A. E.; *J. Russ. Phys. Chem. Soc.* **1906**, *38* 687.

(c) Flisch, W.; Rußkamp, P.; Langer, W. *Liebigs Ann. Chem*. **1985**, 1413.

(d) Yao, Q.; Levchik, S. *Tetrahedron Lett.* **2006**, *47*, 277.

(93) (a) Renard, P.-Y.; Vayron, P.; Leclerc, E.; Valleix, A.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 2389.

(b) Renard, P.Y., Vayron, P.; Mioskowski, C. *Org Lett*. **2003** *5*, 1661.

(94) Thottathil, J. K.; Przybyla, C. A.; Moniot, J. L. *Tetrahedron Lett.* **1984**, *25*, 4737.

(95) Majewsky, P. *Phosphorus, Sulfur, and Silicon* **1989**, *45*, 151.

(96) Gallagher, M. J.; Ranasinghe, M. G. *J. Org. Chem.* **1996**, *61*, 436.

(97) Demange, L.; Dugave, C. *Tetrahedron Lett.* **2001**, *42*, 6295.

(98) Thottathil, J. K.; Ryono, D. E.; Przybyla, C. A.; Moniot, J. L.; Neubeck, R. *Tetrahedron Lett.* **1984**, *25*, 4741.

(99) Vassiliou, S.; Mucha, A.; Cuniasse, P.; Georgiadis, D.; Lucet-Levannier, K.; Beau, F.; Kannan, R.; Murphy, G.; Knauper, V.; Rio, M.-C.; Basset, P.; Yiotakis, A.; Dive, V. *J. Med. Chem.* **1999**, *42*, 2610.

(100) Georgiadis, D.; Matziari, M.; Yiotakis, A. *Tetrahedron* **2001**, *57*, 3471.

(101) Buchardt, J.; Meldal, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3306.

(102) (a) Chen, H.; Noble, F.; Mothé, A.; Meudal, H.; Coric, P.; Danascimento, S.; Roques, B. P.; George, P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **2000** *43*, 1398.

(b) Chen, H.; Bischoff, L.; Fournié-Zaluski, M.-C.; Roques, B. P. *J. Labelled Cpd.*

Radiopharm. **2000**, *43*, 103.

(103) Some representative examples:

(a) Farnham, W. B.; Murray, R. J.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 5809.

(b) Baillie, A. C.; Cornell, C. L.; Wright, K. *Tetrahedron Lett.* **1992**, *33*, 5133.

(c) Magnin, D. R.; Biller, S. A.; Dickson, Jr., J. K.; Logan, J. V.; Lawrence, R. M.; Chen, Y.; Sulsky, R. B.; Ciosek, Jr., C. P.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Rich, L. C.; Slusarchyk, D. A. *J. Med. Chem.* **1995**, *38*, 2569.

(d) Fairhurst, R. A.; Collingwood, S. P.; Lambert, D.; Taylor, R. J. *Synlett* **2001**, 467.

(e) McKittrick, B. A.; Stamford, A. W.; Weng, X.; Ma, K.; Chackalamannil, S.; Czarniecki, M.; Cleven, R. M.; Fawzi, A. B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1629.

(104) Abrunhosa-Thomas, I.; Sellers, C. E.; Montchamp, J.-L. *J. Org. Chem.* **2007**, *72*, 2851.

(105) (a) Nifant'ev, E. E.; Shchepet'eva, N. P.; Magdeeva, R. K. *Zhurnal Obshchei Khimii* **1979**, *49*, 1905.

(b) Andreev, N. A.; Grishina, O. N.; Enikeev, K. M.; *J. Gen. Chem. USSR* **1982**, *52*, 1352.

(c) Magdeeva, R. K.; Borunova, E. B.; Samkharadze, L. O.; Vasyanina, L. K.; Dolidze, A. V.; Ninfat'ev, E. E. *Russ. Gen. Chem.* **1996**, *66*, 1087.

(106) (a) Fastrez, J.; Jespers, L.; Lison, D.; Renard, M.; Sonveaux, E. *Tetrahedron Lett.* **1989**, *30*, 6861.

(b) Hamilton, R.; Walker, B.; Walker, B. J. *Tetrahedron Lett.* **1995**, *36*, 4451.

(c) Belyankin, A. V.; Khomutov, A. R.; Zhukov, Y. N.; Kartasheva, O. N. *Russ. Chem. BI* **1997**, *46*, 133.

(d) Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1998**, *63*, 7223.

(e) Willems, H. A. M.; Veeneman, G. H.; Westerduin, P. *Tetrahedron Lett.* **1992**, *33*, 2075.

(107) Osipova, T. I.; Belyankin, A. V.; Khomutov, A. R.; Zhukov, Y. N.; Khurs, E. N.; Khomutov, R. M. *Russ. Chem. BI* **1996**, *11*, 2588.

(108) Michaelis, P. *Justus Liebigs Ann. Chem.* **1896**, *293*, 265.

(109) Belakhov, V. V.; Yudelevich, V. I.; Ionin, B. I. *J. Gen. Chem. USSR* **1986**, *56*, 1548.

(110) Seth, M.; Mathur, A.; Banerji, K. K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3640.

(111) Vitharana, D.; France, J. E.; Scarpetti, D.; Bonneville, G. W.; Majer, P.; Tsukamoto, T. *Tetrahedron: Assymetry* **2002**, *13*, 1609.

(112) Dorfman, Y. A.; Aleshkova, M. M. *Kinetics and Catalysis* **1998**, *39*, 852.

(113) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**,660.

(114) Mucha, A.; Kafarski, P. *Tetrahedron* **1994**, *50*, 12743.

(115) (a) Sampson, N. S.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500.

(b) Bartlett, P. A.; Giangiordano, M. A. *J. Org. Chem.* **1996**, *61*, 3433.

(116) Emmick, T. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459.

(117) Wife, R. L.; Van Oort, A. B.; Van Doorn, J. A.; Van Leeuwen, P. W. N. M. *Synthesis* **1983**, 71.

(118) Hall, R. G.; Riebli, P. *Synlett* **1999**, 1633.

(119) (a) Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275.

(b) Krawiecka, B.; Michalski, J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 377.

(c) Krawiecka, B.; Wojna-Tadeusiak, E. *J. Chem. Soc. Perkin Trans. 1* **1991**, 229.

(120) (a) Aaron, H. S.; Braun, J.; Shryne, T. M.; Frack, H. F; Smith, G. E.; Uyeda, R. T.; Miller, J. I. *J. Am. Chem. Soc.* **1959**, *82*, 596.

(b) Yoshitake, A.; Mohri, Z.-I.; Kamada, T.; Yasuda, T.; Nakatusa, I. *J. Label. Compounds Radiopharm.* **2006**, *17*, 137.

(121) (a) Van Wazer, J. R. *Phosphorus and its Compounds.* Vol. 2: Chemistry. Interscience Publishers, New York: 1958.

(b) Maier, L. *Helv. Chim. Acta* 1**964**, *47*, 2137.

(c) Fontal, B.; Goldwhite, H.; Rowsell, D. G. *J. Org. Chem.* **1966**, *31*, 2424.

(d) Ginsburg, V.; Privezentseva, N. *Zh. Obhch. Khim*. **1958**, *28*, 736.

(122) Berrigan, R. A.; Russell, D. K.; Henderson, W.; Leach, M. T.; Nicholson, B. K.; Woodward, G.; Harris, C. *New J. Chem.* **2001**, *25*, 322.

(123) (a) Fritzsche, H.; Hasserodt, U.; Korte, F.; Friese, G.; Adrian, K.; Arenz, H. J. *Chem. Ber.* **1965**, *98*, 1681.

(b) Soulier, E.; Yaouanc, J.-J.; Laurent, P.; des Abbayes, H.; Clément, J.-C. *Eur. J. Org. Chem.* **2000**, 3497.

(124) Gruber, M.; Schmutzler, R.; Ackermann, M.; Seega, J.; Hagele, G. *Phosphorus, Sulfur, and Silicon* **1989**, *44*, 109.

(125) (a) Kolodiazhnyi, O. I.; Grishkun, E. V. *Phosphorus, Sulfur, and Silicon* **1995**, *103*, 191.

(b) Kolodiazhnyi, O. I.; Grishkun, E. V. *Zhurnal Obshchei Khimii* **1993**, *63*, 1188.

(126) Nifant'ev, E. E.; Koroteev, M. P. *Zhurnal Obshchei Khimii* **1967**, *37*,1366.

(127) Pudovik, M. A.; Terent'eva, S. A.; Pudovik, A. N. *Zhurnal Obshchei Khimii* **1981**, *51*, 518.

(128) Some representative examples:

(a) Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784.

(b) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90,* 4842.

(c) Nudelman, A.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 3869.

(d) Juge, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, 2783.

(e) Oshiki, T.; Hikosaka, T.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32,* 3371.

(f) Koide, Y.; Sakamoto, A.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32,* 3375.

(g) Horner, L.; Balzer, W. D. *Tetrahedron Lett.* **1965**, *6*, 1157.

(h) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

(i) Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265.

(j) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625.

(k) Imamoto, T.; Kikuchi, S; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.

(129) Reviews on the asymmetric synthesis of phosphorus compounds, including P-chiral phosphorus compounds:

(a) Pietrusiewicz, K. M.; Zablocka, M. *Chem Rev.* **1994**, 1994, *94*, 1375.

(b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, 9, 1279.

(c) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391.

(d) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.,* **2003**, *229*, 1.

(e) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25.

(130) Some representative examples:

(a) Korpiun O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4847.

(b) Vineyard, B. D.; Knowles, W. S.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(c) Hall, C. R.; Inch, T. D. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1104.

(d) Kolodiazhnyi, O. I.; Grishkun, E. V. *Tetrahedron: Asymmetry* **1996**, *7*, 967.

(e) Benabra, A.; Alcudia, A.; Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron: Asymmetry* **1996**, *7*, 3353.

(f) Schmidt, U.; Riedl, B.; Griesser, H.; Fitz, C. *Synthesis* **1991**, 655.

(g) Juge, S.; Wakselman, M.; Stephan, M.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 4443.

(h) Leung, P. H. *Acc. Chem. Res.* **2004**, *37*, 169.

(131) (a) Kolodiazhnyi, O. I.; Grishkun, E. V.; Golovatyi, O. R.; Ustenko, S. N. *Phosphorus, Sulfur, and Silicon* **1996**, *109/110*, 485.

(b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.

(c) Kolodiazhnyi, O. I.; Grishkun, E. V.; Otzaluk, V. M. *Zhurnal Obshchei Khimii* **1997**, *67*, 1210.

(d) Valentine, Jr., D.; Scott, J. W. *Synthesis* **1978**, 329.

(132) (a) Chodkiewicz, W.; Guillerm, D. *Tetrahedron Lett.* **1979**, 3573.

(b) Hall, C. R.; Inch, T. D. *Tetrahedron Lett.* **1976**, 3645.

(c) Cooper, D. B.; Hall, C. R.; Inch, T. D. *Tetrahedron Lett.* **1974**, 2697.

(d) Whitsell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(e) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.

(133) Sasaki, M. *Agr. Biol. Chem.* **1986**, *50*, 741.

(134) (a) Vitharana, D.; France, J. E.; Scarpetti, D.; Bonneville, G. W.; Majer, P.; Tsukamoto, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1609.

(b) Reiter, L. A.; Jones, B. P. *J. Org. Chem.* **1997**, *62*, 2808.

(135) (a) Deshmukh, M.; Dunach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 3467.

(b) Pakulski, Z.; Demchuk, O. M.; Pietrusiewicz, K. M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217.

(136) (a) Kielbasinski, P.; Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry*, **1998**, *9*, 3283.

(b) Kielbasinski, P.; Albrycht, M.; Luczak, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry*, **2002**, *13*, 735.

(c) Albrycht, M.; Kielbasinsky, P.; Drabowicz, J.; Mikolajczyk, M.; Matsuda, T.; Harada, T.; Nakamura, K. *Tetrahedron: Asymmetry*, **2005**, *16,* 2015.

(137) Shioji, K.; Tashiro, A.; Shibata, S.; Okuma, K. *Tetrahedron Lett.* **2003**, *44*, 1103.

(138) Yamagishi, T.; Miyamae, T.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **2004**, *45*, 6713.

(139) Nowlan, C.; Li, Y.; Hermann, J. C.; Evans, T.; Carpenter, J.; Ghanem, E.; Shoichet, B. K.; Raushel, F. M. *J. Am. Chem. Soc.* **2006**, *128*, 15892.

(140) Review on hydrophosphination: O. Delacroix and A.-C. Gaumont, *Curr. Org. Chem.,* **2005**, *9*, 1851.

(141) (a) Costa, E.; Pringle, P. G.; Smith, M. B.; Worboys, K. *J. Chem. Soc. Dalton Trans.* **1997**, 4277.

(b) Costa, E.; Pringle, P. G.; Worboys, K. *Chem. Commun.* **1998**, 49.

(c) Wicht, D. K.; Kourkine, I. V.; Kovacik, I.; Glueck, D. S.; Concolino, T. E.; Yap, G. P. A.; Incarvito, C. D.; Rheingold, A. L. *Organometallics* **1999**, *18*, 5381.

(d) Trofimov, B. A.; Arbuzova, S. N.; Gusarova, N. K. *Russ. Chem. Rev.* **1999**, *68*, 215.

(142) (a) Douglass, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 1824.

(b) Douglass, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10221.

(c) Douglass, M. R.; Ogasawara, M.; Hong S.; Metz, M. V.; Marks, T. J. *Organometallics* **2002**, *32*, 283.

(d) Kawaoka, A. M.; Douglass, M. R.; Marks, T. J. *Organometallics* **2003**, *22*, 4630.

(e) Takaki, K.; Takeda, M.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* **2001**, *42*, 6357.

(f) Takaki, K.; Komeyama, K.; Takehira, K. *Tetrahedron* **2003**, *59*, 10381.

(g) Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* **2003**, *68*, 6554.

(h) Komeyama, K.; Kawabata, T.; Takehira, K.; Takaki, K. *J. Org. Chem.* **2005**, *70*, 7260–7266.

(i) Komeyama, K.; Kobayashi, D.; Yamamoto, Y.; Takehira, K.; Takaki, K. *Tetrahedron* **2006**, *62*, 2511.

(j) Kazankova, M.; Shulyupin, M. O.; Borisenko, A. A.; Beletskaya, I. P. *Russian J. Org. Chem.* **2002**, *38*, 1479.

(k) Shulyupin, M. O.; Kazankova, M. A.; Beletskaya, I. P. *Org. Lett.*, **2002**, *4*, 761.

(l) Kazankova, M. A.; Efimova, I. V.; Kochetkov, A. N.; Afanas'ev, V. V.; Beletskaya, I. P.; Dixneuf, P. H. *Synlett* **2001**, 497.

(m) Kazankova, M.; Efimova, I. V.; Kochetkov, A. N.; Afanas'ev, V. V.; Beletskaya, I. P. *Russian J. Org. Chem.* **2002**, *38*, 1465.

(n) Shulyupin, M. O.; Trostyanskaya, I. G.; Kazanova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2006**, *42*, 17.

(o) Shulyupin, M. O.; Franco, G.; Beletskaya, I. P.; Leitner, W. *Adv. Synth. Catal.* **2005**, *347*, 667.

(p) Jérôme, F.; Monnier, F.; Lawicka, H.; Dérien, S.; Dixneuf, P. H. *Chem. Commun*. **2003**, 696.

(q) Ohmiya, H., Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 2368.

(143) (a) Mimeau, D.; Gaumont, A.-C. *J. Org. Chem.* **2003**, *68*, 7016.

(b) Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun*., **2003**, 2928.

(c) Join, B.; Delacroix, O.; Gaumont, A.-C. *Synlett,* **2005**, 1881.

(d) Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2006**, 3249.

(144) (a) Shulyupin, M. O.; Francio, G.; Beletskaya, I. P.; Leitner, W. *Adv. Synth. Catal.* **2005**, *347*(5), 667.

(b) Goulioukina, N. S.; Dolgina, T. M.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 319.

(c) Goulioukina, N. S.; Dolgina, T. M.; Bondarenko, G. N.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Russ. J. Org. Chem.* **2002**, *38*, 600.

(d) Allen, A., Jr.; Manke, D. R.; Lin, W. *Tetrahedron Lett.* **2000**, *41*, 151.

(145) (a) Han, L.-B.; Choi, N.; Tanaka, M. *Organometallics* **1996**, *15*, 3259.

(b) Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 94.

(d) Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, *66*, 5929.

(d) Allen, A., Jr.; Ma, L.; Lin, W. *Tetrahedron Lett.* **2002**, *43*, 3707.

(e) Van Rooy, S.; Cao, C.; Patrick, B. O.; Lam, A.; Love, J. *Inorganic Chimica Acta* **2006**, *359*, 2918.

(f) Niu, M.; Fu, H.; Jian, Y.; Zhao, Y. *Chem. Commun.* **2007**, 272.

(146) Zwierzak A. *Can. J. Chem.* **1967**, *45*, 2501.

(147) Munoz, A.; Hubert, C.; Luche, J-L. *J. Org. Chem.* **1996**, *61*, 6015.

(148) (a) Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.***2001**, *34*, 895.

(b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(c) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 8291.

(149) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(150) Skelton, B. W. *Aust. J. Chem.* **2004**, *57*, 345.

(151) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757.

(152) Scott, S.; Li, Y.; Nassim, B.; Robert Lopes, M.-T.; Tran, P. T.; Crabbé, P. *J. Chem. Soc. Perkin Trans. I* **1984**, 747.

(153) Tsuji, J.; Suguira, T.; Minami, I. *Synthesis* **1987**, 603.

(154) (a) Trost, B. M. *Science* **1991**, *256*, 1471.

(b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(c) Van Aken, K.; Strekowski, L.; Patiny, L. *Beilstein J. Org. Chem.* **2006**, 2:3, and references cited therein.

(155) Reviews: (a) De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Adv. Org. Synth.* **2005**, *1*, 119.

(b) Wolkenberg, S. E.; Shipe, W. D.; Lindsley, C. W.; Guare, J. P.; Pawluczyk, J. M. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 701.

(c) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66.

(d) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

(156) (a) Noyori, R. *Chem. Commun.* **2005**, 1807.

(b) Van Aken K.; Strekowski L., Patiny L. *Beilstein Journal of Organic Chemistry*, **2006** 2:3.

(c) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 767.

(157) (a) F. Diederich and P. J. Stang, and Eds., *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, 1998.

(b) Beller, M., Bolm, C., Eds. *Transition Metals for Organic Synthesis;* Wiley-VCH: Weinheim, Germany, 1998; Vol. 1.

(c) Cárdenas, D. J. *Angew. Chem. Int. Ed* **2003,** 42, 384.

(d) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000,** 100, 3187.

(e) Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999,** 38, 3018.

(158) (a) A. R. Muci and S. L. Buchwald, in *Practical Palladium Catalysts for C–N and C–O Bond Formation*, ed. N. Miyaura, Springer-Verlag, New York, 2002, p. 133.

(b) Corbet, J.-P.; Mignani, G. *Chem Rev.* **2006**, *106*, 2651.

(c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(d) Barañano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287.

(159) (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595.

(b) Hirao, T.; Masunaga, T.; Yamada, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.

(160) For examples of transition metal catalyzed P-C bond formation via cross-coupling:

(a) Vallette, H.; Pican, S.; Boudou, C.; Levillain, J.; Plaqueventa, J.-C.; Gaumont, A.-C. *Tetrahedron Letters* **2006**, *47*, 5191.

(b) Pican, U. H.; Levillain, B. C.; Plaquevent, J. C.; Gaumont, A. C. *Indian J. Chem. Section B* **2006**, *45B*, 2286.

(c) Toffano, M.; Dobrota, C.; Fiaud, J.-C. *Eur. J. Org. Chem.* **2006**, 650-656.

(d) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315.

(e) Pican, S.; Gaumont, A. C. *Chem. Commun.* **2005**, 2393.

(f) Korff, C.; Helmchen, G. *Chem. Commun.* **2004**, 530.

(g) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. *J. Am. Chem. Soc.* **2002**, *124*, 13356.

(h) Martorell, G.; Garcías, X.; Janura, M.; Saá, J. M. *J. Org. Chem.* **1998**, *63*, 3463.

(i) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033.

(j) Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 569.

(k) Kurtz, L.; Lee, G.; Morgans Jr., D.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321.

(l) Zhong, P.; Huang, X.; Xiong, Z.-X. *Synlett* **1999**, *6*, 721.

(m) Malet, R.; Moreno-Manas, M.; Pleixats, R. *Synth. Commun.* **1992**, *22*, 2219.

(n) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc. Trans. 1* **1995**, 1145.

(o) Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom Chem.* **1992**, *3*, 563.

(p) Al-Masum, M.; Kumuraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776.

(q) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033.

(r) Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069.

(s) Maffei, M.; Buono, G. *Phosphorus, Sulfur, Silicon* **1993**, *79*, 297.

(161) Ma, D.; Tian, H. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3493.

(162) Abbas, S.; Bertram, R. D.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3365.

(163) Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. *Org. Lett.* **2000**, *2*, 3341.

(164) Representative examples of esterification of *H*-phosphinic acids with activating agents:

RCOCl/alcohol: (a) Bravo-Altamirano, K.; Montchamp, J.-L. *Poster 313*, 231st National Meeting of the American Chemical Society, Atlanta, March, 2006.

(b) Qiao, L.; Nan, F.; Kunkel, M.; Gallegos, A.; Powis, G.; Kozikowski, A. P. *J. Med. Chem.* **1998**, *41*, 3303.

Carbodiimides: (c) Karanewsky, D. S.; Badia, M. C. *Tetrahedron Lett.* **1986**, *27*, 1751.

(165) Reviews: (a) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.

(b) Dunina, V. V.; Gorunova, O. N. *Russ. Chem. Rev.* **2004**, *73*, 309.

(c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

(e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(f) Shilov, a. E.; Shul'pin, G. *Chem. Rev.* **1997**, *97*, 2879.

(g) Arndtsen, B. A.; Bergman, R. G.; Mobley, A.; Peterson, T. H. *Acc. Chem. Res.* **1995,** *28*, 154.

(h) Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91.

Selected papers: (i) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

(j) Godula, K.; Dalibor, S. D. *Science* **2006**, *312*, 67.

Handbook: (l) Dyker, G. *Handbook of C-H Transformations: Applications in Organic Synthesis;* Wiley: New York, 2000.

(166) Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* **2004**, *6*, 2101.

(167) (a) Galamb, V.; Gopal, M.; Alper, H. *Organometallics* **1983**, *2*, 801.

(b) Hudrlik, P. F.; Kulkarni, A. K.; Jain, S.; Hudrlik, A. M. *Tetrahedron* **1983**, *39*, 877.

(c) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85.

(d) Summerville, R. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 1112.

(e) Wustrow, D. J.; Wise, L. D.; *Synthesis* **1991**, *11*, 993.

(168) Books: (a) Tsuji, J.; *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000.

(b) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995.

(c) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; Wiley-VCH: New York, 2000.

(d) Davis, J. A. *In Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 9, p 291.

(e) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol. 3, p 585.

Review: (f) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(169) Reviews: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179.

(b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

For allylation with allylic alcohols in the presence of additives, see for example:

(c) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, *62*, 3949.

(d) Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333.

(e) Fontana, G.; Lubineau, A.; Scherrmann, M.-C. *Org. Biomol. Chem.* **2005**, *3*, 1375.

(f) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241.

(g) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968.

(h) Yang, S.-C.; Tsai, Y.-C. *Organometallics* **2001**, *20*, 763.

(i) Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506.

(j) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.

(170) Examples of direct allylation without additives: (a) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabo, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588.

(b) Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* **2004**, 4989.

(c) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.*, **2004**, 4085.

(d) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595.

(e) Trost, B. M. Spagnol, M. D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2083.

(f) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535.

(171) Fiaud, J. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1055.

(172) Ram, R. N.; Meher, N. K. *Tetrahedron* **2002**, *58*, 2997.

(173) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley, New York, 2002; pp. 366-379.

(b) Inomata, K.; Kinoshita, H. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley, New York, 2002; Vol. 2, Chapter V. 2.3.1.

(c) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.

(d) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017.

(174) Berry, J. P.; Isbell, A. F.; Hunt, G. E. *J. Org. Chem.* **1972**, *37*, 4396.

(175) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J. Sweeney, J. B. *J. Chem. Soc., Chem. Commun.***1988**, 1030.

(176) (a) Subadolni, R. J. *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1970.

(b) Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55.

(177) A representative example: Yamagishi, T.; Fujii, K.; Shibuya, S.; Yokomatsu, T. *Synlett* **2004**, *14*, 2505.

(178) A representative example: Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1998**, 110, 5411.

(179) CGP36742/SGS742: (a) Chebib, M.; Vandenberg, R. J.; Froest, W.; Johnston, G. A. R. *Eur. J. Pharmacol.* **1997**, *329*, 223.

(b) Pittaluga, A.; Vaccari, D.; Raiteri, M. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 82.

(c) Steulet, A.-F.; Moebius, H.-J.; Mickel, S. J.; Stoecklin, K.; Waldmeier, P. C. *Biochem. Pharmacol.* **1996**, *51*, 613.

(180) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H. *Organometallics* **2004**, *23*, 1698.

(181) Lumin, S.; Falck, J. R.; Capdevila, J.; Karara, A. *Tetrahedron Lett*. **1992**, *33*, 2091.

(182) Lu, X.; Lu, L.; Sun, J. *J. Mol. Catal.* **1987**, *41*, 245.

(183) Lu, X.; Jiang, X.; Tao, X. *J. Organomet. Chem.* **1988**, *344*, 109.

(184) Tsay, S.; Lin, L. C.; Furth, P. A.; Shum, C. C.; King, D. B.; Yu, S. F.; Chen, B.; Hwu, J. R. *Synthesis* **1993**, 329.

(185) (a) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627.

(b) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401.

(c) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234.

(186) Stary, I.; Stará, I. G.; Kocovsky, P. *Tetrahedron Lett.* **1993**, *34*, 179.

(187) (a) Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4473.

(b) Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* **1995**, 1121.

(188) (a) Itoh, K.; Hamaguchi, N.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2833.

(b) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877.

(c) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000.

(d) Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* **2003**, *44*, 1481.

(189) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1065.

(190) Bravo-Altamirano, K.; Montchamp, J.-L. *Palladium-Catalyzed Dehydrative Allylation of Hypophosphorous Acid with Allylic Alcohols. Preparation of Cinnamyl-H-Phosphinic Acid Org. Synth. (Submitted)*

(191) For example: (a) Mark, V. *In Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 319-437.

The rearrangement of propargyl phosphinates is well-known: (b) Ionin, B. I.; Petrov, A. A. *Phosphorus, Sulfur Silicon* **1990**, *49/50*, 243.

(c) Belakhov, V. V.; Yudelevich, V. I.; Komarov, E. V.; Ionin, B. I.; Komarov, V. Y. Zakharov, V. I.; Lebedev, V. B.; Petrov, A. A. *J. Gen. Chem. USSR* **1983**, *53*, 1345.

(192) (a) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.

(b) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219.

(193) (a) Zhang, H.; Tsukuhara, R.; Tigyi, G.; Prestwich, G. D. J. Org. Chem. **2006**, *71*, 6061.

(b) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2219.

(c) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowsky, C. *Org. Lett.* **2000**, *2*, 1517.

(d) Majewski, P. *Phosphorus, Sulfur Silicon* **1989**, *45*, 151.

(e) Kurdyumova, N. R.; Ragulin, V. V.; Tsvetkov, E. N. *Russ. J. Gen. Chem.* **1994**, *64*, 380.

(194) Guthrie, J. P. *Can. J. Chem.*, **1979**, *57*, 236.

(195) Kozlova, S. G.; Gabuda, S. P.; Blinc, R. *Chem. Phys. Lett.*, **2003**, *376*, 364.

(196) Montchamp, J.-L. *Unpublished results.*

(197) (a) Cohen, L. H.; Valentijn, A. R. P. M.; Roodenburg, L.; Van Leeuwen, R. E. W.; Huisman, R. H.; Lutz, R. J.; Van der Marel, G. A.; Van Boom, J. H. *Biochemical Pharmacology* **1995**, *49*, 839.

(b) Pompliano, D. L.; Rands, E.; Schaber, M. D.; Mosser, S. D.; Anthony, N. J.; Gibbs, J. B. *Biochemistry* **1992**, *31*, 3800.

(198) Jeanmaire, T.; Hervaud, Y.; Boutevin, B. *Phosphorus, Sulfur Silicon Relat. Elem*. **2002**, *177*, 1137.

(199) Fletcher, S. P.; Clive, D. L. J.; Peng, J.; Wingert, D. A. *Org. Lett.* **2005**, 7, 23.

(200) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.

(201) (a) Shell Internationale Research Maatschappij NV. *Separation of mixtures of organic compounds* (1965). 24 pp. NL 298567 19651125. Application: NL 19630930. CAN 64:67518.

(b) Felcht, U. H. *Epoxy-1-oxo-phospholanes*. Ger. Offen. (1981). 25 pp. CODEN:

GWXXBX DE 2927914 19810129. Application: DE 79-2927914 19790711. CAN 95:25268

(202) Review: Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

(203) Bravo-Altamirano, K.; Montchamp, J.-L. *Unpublished results.*

(204) Cherbuliez, E.; Weber, G.; Rabinowitz, J. *Helv. Chim. Acta* **1963**, *46*, 2464.

(205) (a) Liron, F.; Knochel, P. *Chem. Commun.* **2004**, 304.

(b) Pollok, T.; Schimidbaur, H. *Tetrahedron Lett.* **1987**, *28*, 1085 and referenced cited intherein.

(206) Nifant'ev, E. E.; Kil'disheva, V. R.; Nasonovskii, I. S. *Zh. Prikl. Khim.* **1969**, *42*, 2590.

(207) Kers, A.; Kers, I.; Stawinski, J.; Sobkowski, M.; Kraszewski, A. *Synthesis* **1995**, 427.

(208) Loewus, D. I. *J. Am. Chem. Soc.* **1981**, *103,* 2292.

(209) Selected Reviews: (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(b) Ma, J.-A. *Chem. Soc. Rev.,* **2006**, *35*, 630.

(c) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Related Elem.* **1991**, *63*, 193.

(d) Dembitsky, V. M.; Al Quntar, A. A. A.; Haj-Yehiaa, A.; Srebnik, M. *Mini-Rev. Org. Chem.* **2005**, *2*, 91.

(e) Freedman, L. D.; Doak, G. O. *Chem. Rev.;* **1957**; *57*(3); 479-523.

(f) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

(g) Edmundson, R. S. *Compr. Org. Chem.* **1979**, *2*, 1189.

(h) Kolodiazhnyi, O. I. *Tetrahedron Asymm.* **2005**, *16*, 3295.

(i) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868.

(j) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.

(j) Failla, S.; Finocchiaro, P.; Consiglio, G. A. *Heteroatom Chem.* **2000**, *11*, 493.

(k) Blackburn, M. G. *Chem. Ind. (London)* **1981**, 134.

(l) Eckstein, F.; Thomson, J. B. *Methods Enzymol.* **1995**, *262*, 189.

(210) Reviews: (a) Grapov, A. F. *Reaktsii i Metody Issledovaniya Organicheskikh Soedinenii* **1966**, *15*, 41.

(b) Salvatore, R. N. In *Organophosphorus Reagents: A Practical Approach in Chemistry* Murphy, P. J., Ed.; Oxford University Press Inc., New York, 2004; pp.188-212.

(c) Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13109.

Selected publications: (d) Cohen, R. J.; Fox, D. L.; Eubank, J. F.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 8617.

(e) Kem, K. M.; Nguyen, N. V.; Cross, D. J. *J. Org. Chem.* **1981**, *46*, 5188.

(f) Tomilov, A. P.; Martynov, B. I.; Pavlova, N. A. *J. Electroanal. Chem.* **2001**, *507*, 46.

(211) (a) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M. C. *J. Tetrahedron Lett.* **1997**, 155.

(b) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, *16*, 739.

(c) Salomon, C. J.; Breuer, E. *Tetrahedron Lett.* **1995**, *36*, 6759.

(d) Kumar, G. D. K.; Saenz, D.; Lokesh, G. L.; Natarajan, A. *Tetrahedron Lett.* **2006**, *47*, 6281.

(212) Some representative publications:

(a) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. *J. Am. Chem. Soc.* **2002**, *124*, 13356.

(b) Moncarz, J. R.; Brunker, T. J.; Glueck, D. S.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 1180.

(c) Moncarz, J. R.; Brunker, T. J.; Jewett, J. C.; Orchowski, M.; Glueck, D. S.; Sommer, R. D.; Lam, K.; Incarvito, C. D.; Concolino, T. H.; Ceccarelli, C.; Zakharov, L. V.; Rheingold, A. L. *Organometallics,* **2003**, *22*, 3205.

(d) Scriban, C.; Glueck, D. S. J. *Am. Chem. Soc.* **2006**, *128*, 2788.

(e) Brunker, T. J.; Anderson, B. J.; Blank, N. F.; Glueck, D. S.; Rheingold, A. L. *Org. Lett.* **2007**, *9*, 1109.

(f) Korff, C.; Helmchen, G. *Chem. Commun.* **2004**, 530.

(g) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc*. **2006**, *128*, 2786.

(h) Lebel, H.; Morin, S.; Paquet, V. *Org. Lett.* **2003**, *5*, 2347.

(i) Pican, S.; Gaumont, A. C. *Chem. Commun.* **2005**, 2393.

(j) Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chemm. Commun.* **2006**, 3249.

(k) Malisch, W.; Klüpfel, B.; Schumacher, D.; Nieger, M. *J. Organomet. Chem.* **2002**, *661*, 95.

(l) Miyake, Y.; Yamauchi, A.; Nishibayashi, Y.; Uemura, S. *Bull. Chem. Soc, Jpn.* **2003**, *76*, 381.

(213) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

(214) Wolfe, B.; Livinghouse, T. *J. Org. Chem.* **2001**, *66*, 1514.

(215) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894.

(216) (a) de Vaumas, R.; Marinetti, A.; Ricard, L.; Mathey, F. *J. Am. Chem. Soc.* **1992**, *114*, 261.

(b) Marinetti, A.; Bauer, S.; Ricard, L.; Mathey, F. *Organometallics* **1990**, *9*, 793.

(217) Oohara, N.; Imamoto, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1359.

(218) (a) DiMauro, E. F.; Kozlowski, M. C. *Organometallics* **2002**, *21*, 1454.

(b) Leung, W.-H.; Chan, E. Y. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S.-M. *J. Chem. Soc., Dalton Trans.* **1996**, 1229.

(219) Selected publications/reviews: (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.

(b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(c) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

(d) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003,** *103,* 3071.

(d) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.

(220) Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1984**, *25*, 5383.

(221) Bacque, E.; Paris, J. M. *Synth. Commun.* **1992**, *22*, 2259.

(222) Sands, R. D. *J. Org. Chem.* **1994**, *59*, 468.

(223) Tlahuext, H.; Contreras, R. *Tetrahedron: Asymmetry* **1992**, *3*, 727.

(224) (a) Jongh, C. P de; Modro, T. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *79*, 161.

(b) Lambert, J. B.; Emblidge, R W.; Zhao, Y. *J. Org. Chem.* **1994**, *59*, 5397.

(225) Montchamp, J.-L.; Migaud, M. E.; Frost, J. W. *J. Org. Chem.* **1993**, *58*, 7679.

(226) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(227) Dvedjiev, I.; Petrova, K.; Glavchev, I. *Synth. Commun.* **2000**, *30*, 4411.

(228) Rausch, M.; Vogel, M.; Rosenberg, H. *J. Org. Chem.* **1957**, *22*, 903.

(229) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.

(230) Ort, O. *Org. Synth.* **1993**, *Coll. Vol. 8,* 522; **1987**, *65,* 203.

(231) Takahashi, T.; Kurose, N.; Koizumi, T. *Heterocycles* **1993**, *36*, 1601.

(232) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.

(233) Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818.

(234) Malatesta, L. *Gazz. Chim. Ital.* **1948**, *78*, 747.

(235) (a) Avila, L. Z. Ph.D. Dissertation, Stanford University, CA, 1990.

(b) Ames, B. N. *Meth. Enzymol.* **1966**, *8*, 115.

(236) Richardson, D.; Sadi, B. B. M.; Caruso, J. A. in *Ultra-Trace Analysis of Organophosphorus Chemical Warfare Agent Degradation Products by HPLC-ICP-MS.* Agilent Technologies, Online Literature at www.agilent.com/chem.

(237) Maier, L; Rist, G. *Phosphorus Sulfur* **1983**, *17*, 21.

(238) (a) Lewin, G. *J. Gen. Chem. USSR* **1967**, *37*, 2604.

(b) Shagidul, R. R.; Chernova, A. V.; Galeev, V. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1971**, *20*, 1082.

(239) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth.Commun.* **1991**, *21*, 2341.

(240) Kabatschnik, M. I.; Tsvetkov, E. N.; Chang, C.-Y. *Dokl. Chem.* **1959**, *124-129*, 309.

(241) Levin, Y. A.; Galeev, V. S. *J. Gen. Chem. USSR* **1967**, *37*, 2604.

(242) Razumov, A. I.; Liorber, B. G.; Gazizov, M. B.; Khammatova, Z. M. *Zhurnal Obshchei Khimii* **1964**, *34*, 1851.

(243) Kabachnik, M. I.; Chang, J.-Y.; Tsvetkov, E. N. *J. Gen. Chem. USSR* **1962**, *32*, 3351.

(244) Petnehazy, I.; Jaszay, Z.M.; Szabo, A.; Everaert, K. *Synth. Commun.* **2003**, *33*, 1665.

(245) Afarinkia, K.; Yu, H. *Tetrahedron Lett.* **2003**, *44*, 781.

(246) Schlemminger, I.; Saida, Y.; Groeger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem*. **2000**, *65*, 4818.

(247) Kumar, G. D. K.; Saenz, D.; Lokesh, G. L.; Natarajan, A. *Tetrahedron Lett.* **2006**, *47*, 6281.

(248) (a) Berdnik, I. V.; Sentemov, V. V.; Shagvaleev, F. Sh.; Zykova, T. V.; Krasil'nikova, E. A. *Zhurnal Obshchei Khimii* **1988**, *58*, 302.

(b) Przychodzén, W. *Eur. J. Org. Chem.* **2005**, *10,* 2002.

(249) Peterson, A. C.; Levsen, S. M.; Cremer, S. E. *Phosphorus, Sulfur and Silicon and the Related Elements* **1996**, *115*, 241.

(250) Thottathil, J. K. (E. R. Squibb and Sons, Inc., USA) **1987**, U.S. 4670193 A.

(251) Ono, Y.; Han, L.-B. *Tetrahedron Lett.* **2006**, *47*, 421.

(252) Yamauchi, K.; Une, F.; Tabata, S.; Kinoshita, M. *J. Chem. Soc. Perkin Trans. I* **1986**, *5*, 765.

(253) Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E.; Watson, L.; Bednarski, M.; Whitesides, G. *J. Org. Chem.* **1988**, *53*, 3457.

(254) Hideo, S. (Nissan Chemical Industries, Ltd., Japan) **1998**, JP 10045779.

(255) Gul, S.; Sonkaria, S.; Pinitglang, S.; Florez-Alvarez, J.; Hussain, S.; Thomas, E. W.; Ostler, E. L.; Gallacher, G.; Resmini, M.; Brocklehurst, K. *Biochem. J.* **2003**, *376*, 813.

VITA

Karla Bravo-Altamirano was born May 25, 1979, in Oaxaca, Mexico. She is the daughter of Rosa Maria Altamirano Bonecchi and Carlos Bravo Fernandez. In 1997, she graduated with honors from Blaise Pascale High School in Oaxaca, Mexico. In the same year, she participated in the Third Iberoamerican Chemistry Olympiad at Rio de Janeiro, Brazil, where she got bronze medal. She received a Bachelor of Science degree with a major in Chemistry from Universidad de las Américas Puebla, Mexico, *magna cum laude*, in 2002.

In August 2002, she enrolled in graduate study at Texas Christian University, Fort Worth, TX, to pursuit a Ph.D. in Organic Chemistry. While working on her doctorate in Chemistry, she worked as a Graduate Teaching Assistant for four semesters and was awarded the Graduate Student Teaching Award from the Chemistry Department in the spring of 2004.

She is married to Carlos Cordero-Sanchez.

ABSTRACT

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

by Karla Bravo-Altamirano, Ph.D., 2007
Department of Chemistry
Texas Christian University

Dissertation Advisor: Jean-Luc Montchamp, Associate Professor

The work developed in this dissertation consists in the development of new methodologies for the preparation of *H*-phosphinic acid derivatives and their *P*-chiral counterparts. Special emphasis is given to the role of *H*-phosphinates as useful synthons for organophosphorus compounds via tandem processes. A review of the most relevant literature in terms of the preparation methodologies and reactivity of *H*-phosphinic acid derivatives is provided in Chapter I. The following chapter describes the addition of hypophosphorous compounds to unsaturated substrates in presence of metal-catalysts. The mechanism, regioselectivity on alkynes, and reactivity of substituted alkenes, allenes, allenols, and 1,3-dienes as substrates in a palladium-catalyzed hydrophosphinylation was investigated. A novel alkyne hydrophosphinylation catalyzed by nickel chloride or its hydrate in the absence of added ligand was discovered and exploited in the synthesis of various important organophosphorus compounds. The third chapter details a tandem esterification – cross-coupling reaction of alkyl phosphinates with aryl, heteroaryl, alkenyl, and benzylic halides and triflates. Thus the reaction of the electrophilic substrate with a hypophosphorous acid salt, in the presence of a silicate, a base and the palladium catalyst provided directly a wide variety of *H*-phosphinates, which were not accessible previously. In the following chapter, transition metal-catalyzed reactions of hypophosphorous compounds with allylic electrophiles are disclosed. Allylic acetates, benzoates and carbonates undergo an effective cross-coupling in the presence of palladium catalysts where pure *H*-

phosphinic acids can be isolated by a simple acidic work-up or esterified *in situ* to the corresponding *H*-phosphinate esters. Chapter V describes a palladium-catalyzed dehydrative allylation of hypophosphorous acid with allylic alcohols, in the absence of additives. The next chapter focuses on P-H bond activation of *H*-phosphinates through catalytic allylation and oxidation strategies, which lead to disubstituted phosphinic acid and phosphonic acids, respectively. In the last chapter, desymmetrization strategies to access *P*-chiral *H*-phosphinates are reported. Two different avenues are explored: the use of chiral ligands in palladium-catalyzed reactions and the use of chiral auxiliaries by means of esterification of hypophosphorous acid with chiral alcohols, where 8-phenylmenthol provides, in a palladium-catalyzed hydrophosphinylation reaction, our best result with around 70% diastereomeric excess.