CARBON-PHOSPHORUS AND OXYGEN-PHOSPHORUS BOND FORMATION

NEW METHODOLOGIES FOR THE PREPARATION OF ORGANOPHOSPHORUS COMPOUNDS

by

HENRY C. FISHER

Bachelor of Arts, 2003
Baylor University
Waco, Texas

Master of Science, 2005
Baylor University
Waco, Texas

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Author's Declaration

This is an original work, except where references have been made. No part of this work has been previously submitted as part of a requirement for an academic degree.

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LIST OF ABBREVIATIONS

AA	Acetic acid
Ac	Acetyl
AHP	Anilinium Hypophosphite
AIBN	2,2′-Azobis(2-methylpropionitrile), 2-(azo(1-cyano-1-methylethyl))-2-methylpropane nitrile
ALB	Aluminum-lithium BINOL
Alk	Alkyl
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
BA	Benzoic acid
BDE	Bond dissociation energy
BINOL	1,1’-Bi-2-naphthol
B/L	Branched/linear
Bn	Benzyl
BOC	*tert*-Butyl carbamate
BSA	N,O-Bis(trimethylsilyl)acetamide
BTSP	bis(trimethylsilyl)phosphine
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
Cbz	Benzylcarbonyl

conc.	Concentrated
Cy	Cyclohexyl
dba	*trans,trans*-1,5-Diphenyl-1,4-pentadien-3-one
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diasteromeric excess
DFT	Density functional theory
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DOPO	6*H*-Dibenzo[*c*,*e*][1,2λ^5]oxaphosphinine 6-oxide
dppe	1,1'-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
D/S	Dean-Stark
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
GABA	γ-Aminobutyric acid
GLC	Gas liquid chromatography
HCl	Hydrochloric acid
Hex	Hexyl

HMDS	Hexamethyldisilazane
HRMS	High resolution mass spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazane
M. P.	Melting point
Me	Methyl
Men	Menthyl
MRI	Magnetic resonance imaging
MW	Microwave
MW/t	Megawatt per ton
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Oct	Octyl
PCl_3	Phosphorus trichloride
Pent	Pentyl
PET	Positron emission tomography
Ph	Phenyl
Pht	Phthalimide
Piv	Pivaloyl
PPAPM	Pyrrolidine-1-phosphonic acid phenyl monoester
Pr	Propyl
Pyr	Pyridine
r.t.	Room temperature
Xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

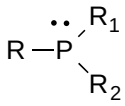
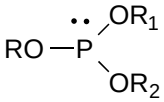
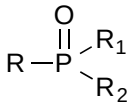
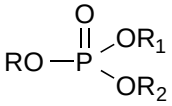
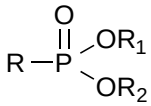
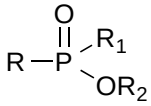
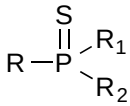
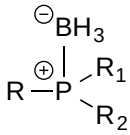
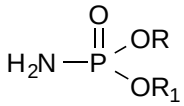
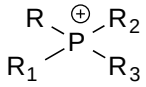
TBA	Thiobenzoic acid
TBDMS	tert-Butyldimethylsilyl
Tf	Triflate
ThFA	Thioformic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosylate
TS	Thiosaccharin
Z (CBZ)	Benzyl carbamate

Chapter One: **Background, Preparation and Reactivity of Organophosphorus Compounds**

The preparation of organophosphorus compounds is of vital importance due to their many applications in agriculture (herbicides and pesticides), pharmaceuticals, detergents, additives for oilfield production, flame retardants, extractants for metals, chain transfer agents in polymer synthesis, and ligands in organometallic catalysis.[1] The preparation of all organophosphorus compounds on a large scale involves the use of phosphorus-halogen reagents such as phosphorus trichloride (PCl_3). Industrial processes involving PCl_3, which is derived from elemental phosphorus P_4, give off large amounts of hydrogen chloride (HCl), which is toxic to the environment and causes corrosion problems.[2] Therefore, the study of alternative methods to prepare organophosphorus compounds via P-C and P-O bond formation is not only important in reducing hazardous waste products, but also in understanding how to increase efficiency of reactions and obtain unique phosphorus-containing substrates that might not be obtainable with established methods. The following dissertation will summarize the continued examination of hypophosphorous acid, $(HO)P(O)H_2$, as an alternative feedstock to prepare relevant organophosphorus compounds.

Organophosphorus compounds (**1a – 1h**) are classified into a variety of different groups as summarized in Chart 1.1. Various organophosphorus compounds are also identified by their unique coordination number with the σ bond representing the number of direct bonds to the phosphorus and λ representing the valency or total number of bonds (σ and π bonds). For example, $(HO)P(O)H_2$ is described as σ^4, λ^5. This dissertation will primarily focus on the preparation of the class of σ^4, λ^5 phosphorus compounds: *H*-phosphonates (**1e**) and *H*-phosphinates (**1f**). These particular classes of compounds contain the phosphinylidene moiety [P(O)H] through which they can tautomerize between the P(V) and P(III) forms with the

Chart 1.1 Classification and Nomenclature of Selected Organophosphorus Compounds

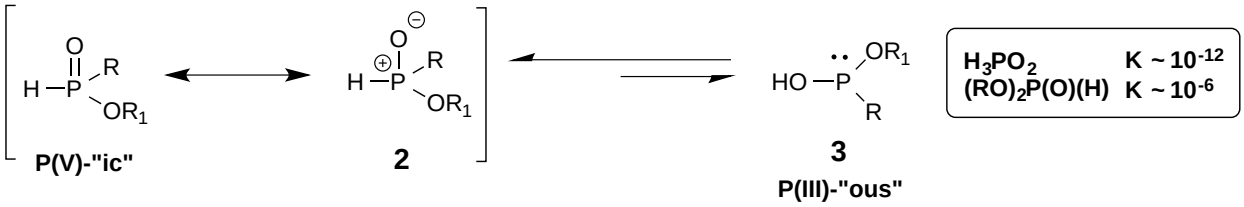
	**1a**	Phosphines	σ^3, λ^3	R, R_1, R_2 = H, alkyl or aryl
	**1b**	Phosphite	σ^3, λ^3	R, R_1, R_2 = H, alkyl or aryl
	**1c**	Phosphine Oxides	σ^4, λ^5	R, R_1, R_2 = alkyl or aryl
	**1d**	Phosphates	σ^4, λ^5	R, R_1, R_2 = H phosphoric acid R, R_1, R_2 = alkyl or aryl
	**1e**	Phosphonates	σ^4, λ^5	R, R_1, R_2 = H phosphorous acid R = H; R_1, R_2 = alkyl, aryl *H*-Phosphonate or dialkyl phosphite
	**1f**	Phosphinates	σ^4, λ^5	R, R_1, R_2 = H hypophosphorous acid R, R_1 = H; R_2 =alkyl, aryl alkyl hypophosphite or alkyl phosphinate
	**1g**	Phosphine Sulfides	σ^4, λ^5	R, R_1, R_2 = H, alkyl, aryl; also –OR (H, alkyl, aryl)
	**1h**	Phosphine Boranes	σ^4, λ^4	R, R_1, R_2 = H, alkyl, aryl; also –OR (H, alkyl, aryl)
	**1i**	Amidophosphinate	σ^4, λ^5	R, R_1 = H, alkyl or aryl
	**1k**	Phosphonium	σ^4, λ^4	R, R_1, R_2, R_3 = H, alkyl or aryl

equilibrium highly favoring the P(V) form (Scheme 1.1). The phosphinylidene tautomeric equilibrium is an important thermodynamic and kinetic barrier to overcome in the development

of P-C and P-O forming reactions, and the initial study of this phenomenon will be discussed further in Chapter 2.

To note, although the depiction of P=O bond is well established and considered conventional in the field, the simple resonance representation (**2**) is a more useful one because of the electronegativities of oxygen and phosphorus (Scheme 1.1).

Scheme 1.1 Tautomerization of Phosphinylidene Compounds



1.1 Preparation of *H*-phosphinic Acid Compounds as Flexible Organophosphorus Intermediates

The last few years has seen the continued development of *H*-phosphinic acid derivatives as targeted intermediates primarily due to their versatility. They can be converted to a variety of useful phosphorus-containing compounds such as phosphinates, phosphonates, phosphine oxides, thiophosphonates and phosphoramidites (Scheme 1.2). As biological targets, mono- and di-substituted phosphinic acid compounds are interesting isosteres of their carboxylic acid analogs for the inhibition of enzymes because they can form similar tetrahedral transition state geometries and hinder a normal reaction pathway.[3] Phosphinic acid compounds also make hydrolytically and enzymatically stable replacements of phosphates like oligonucleotides for anti-sense DNA and RNA molecules.[4] Chart 1.2 illustrates some interesting examples of biologically active phosphinic acid compounds.

Scheme 1.2 Conversion of *H*-phosphinate substrates to other useful phosphorus functional groups.

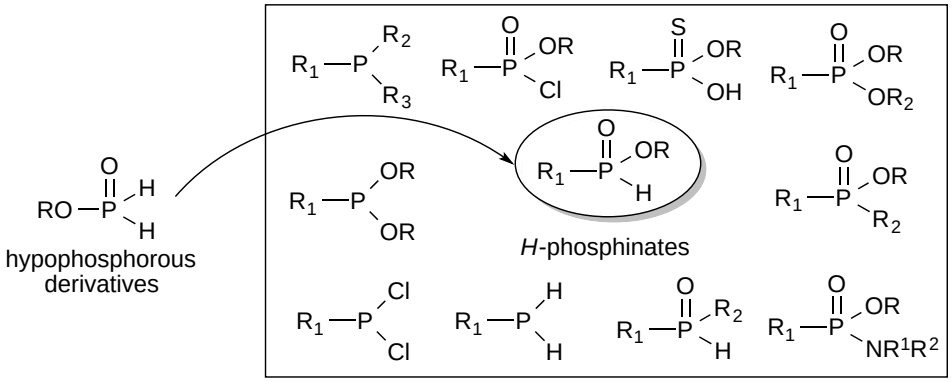
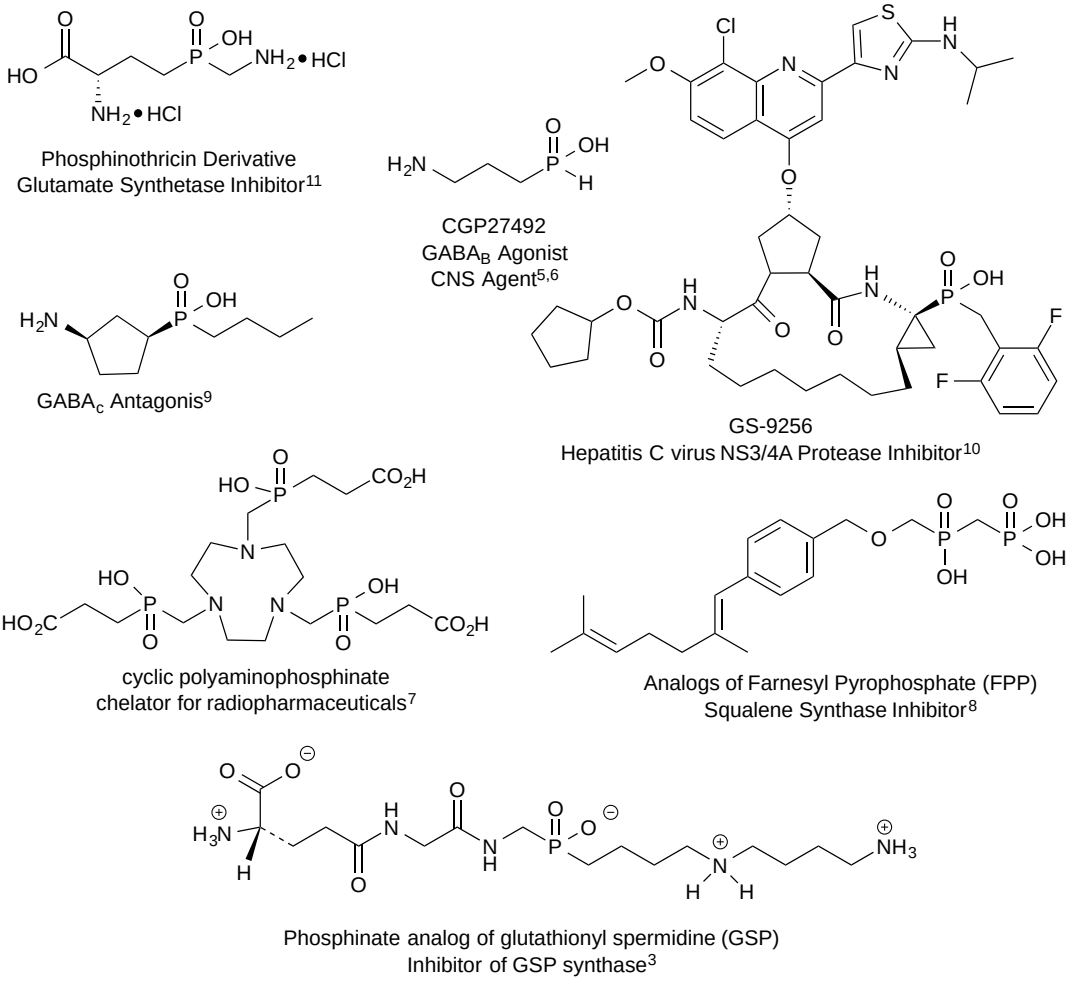


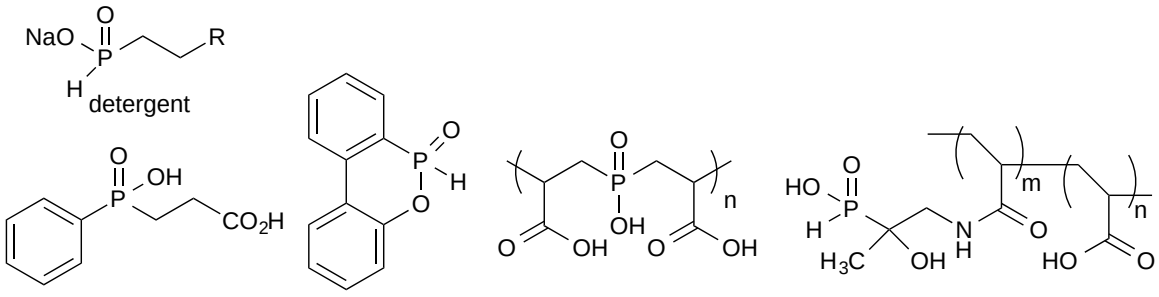
Chart 1.2 Examples of phosphinic acid compounds used for biological applications.[3,5–11]



The *H*-phosphinic acid analog of GABA (CGP27492) displayed an order of magnitude increase of biological activity as potent inhibitor of the $GABA_B$ receptor.[8,9] The development and study of Hepatitis C protease inhibitor GS-9256, currently in FDA stage 2B clinical trials, is another example of a phosphinic acid bioisostere having similar activity as Ciluprevir, the carboxylate lead compound.[10] Sheng et al easily customized the phosphinate with different benzylic groups to complete structural-activity relationship studies to ascertain that the ortho-difluorobenzyl group provided the most potent inhibitor.[10] Also of note are the easily customizable cyclic polyaminophosphinates as lanthanide chelators for use as radiopharmaceuticals for tissue selective MRI or PET imaging applications.[5]

As mentioned previously, phosphinates have many industrial applications. Chart 1.3 shows a few examples of phosphinates used for various purposes. Long chain alkyl phosphinates prepared using radical methods make good anionic surfactants in detergent

Chart 1.3 Phosphinic acid compounds used in industrial applications.[12–15]



chemistry.[12] DOPO and its structural derivatives are high performing halogen free flame retardants for epoxy resins which mechanistically work as a hydroxyl radical scavenger in the gas phase and form thermally stable polymers at charring temperatures.[13] Phosphinate containing

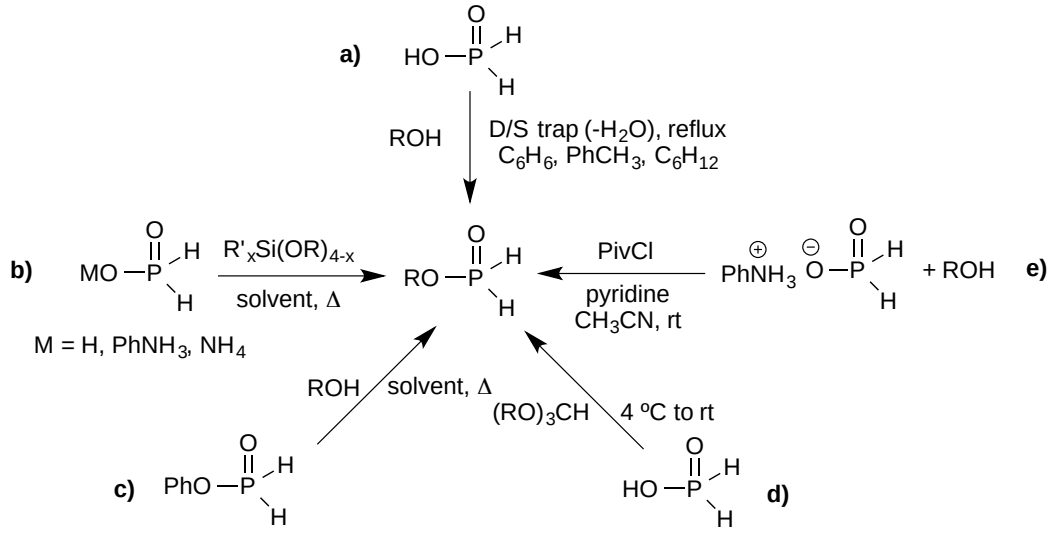
monomers co-polymerized with polyacrylate or polymaleic acid are effective for many applications such as water treatment sequestration agents to prevent the crystallization of mineral scale (ie. $CaCO_3$, $BaSO_4$) under reduced temperature and pressure conditions[14] and also as additives to control setting times for cement used to seal metal casings that line a newly drilled oil well.[15]

1.2 Synthesis of *H*-phosphinic Acid Compounds through the Formation of P-C Bonds

1.2.1 Preparation of Alkyl Hypophosphite Starting Materials

Alkyl phosphinates (also known as hypophosphite esters, $(RO)P(O)H_2$) are important intermediates in the preparation of *H*-phosphinic acid derivatives.[1,16] Due to the extreme reactivity of these compounds, they are highly sensitive to moisture, air oxidation and thermal decomposition, and therefore only used in solution. Many methods have been developed to prepare alkyl hypophosphites, but only a few are consistently utilized. The easiest procedures for the preparation of alkyl phosphinates are the Dean-Stark esterification developed by Nifant'ev

Scheme 1.3 Various methods to prepare alkyl hypophosphites.

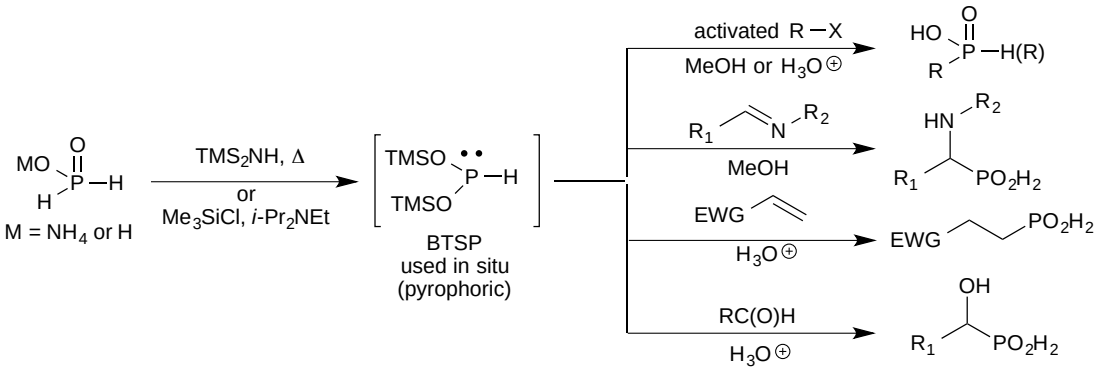


(Scheme 1.3a)[17] and the alkoxysilane-mediated esterification developed by Montchamp (Scheme 1.3b).[18,19] When a specific orthosilicate is not commercially available, phenyl hypophosphite, initially prepared by using tetraphenoxysilane, can be transesterified *in situ* with a specific alcohol (Scheme 1.3 c).[20] Methyl and ethyl hypophosphite esters may be prepared via the esterification of anhydrous crystalline hyposphosphorous acid with the corresponding trialkyl orthoformate (Scheme 1.3 d).[21,22] In addition to fact that excessively dried H_3PO_2 can degrade to dangerous phosphine gas, this protocol also forms P-alkylated by-products via a P(III) mechanism.[23,24] Finally, Montchamp developed a modified Stawinski method[25] using pivaloyl chloride as a condensing agent with anilinium hypophosphite, pyridine and an alcohol to form the desired alkyl phosphinate (Scheme 1.3 e).[20,26]

1.2.2 Nucleophilic Addition and Substitution Reactions of Silyl Phosphonites

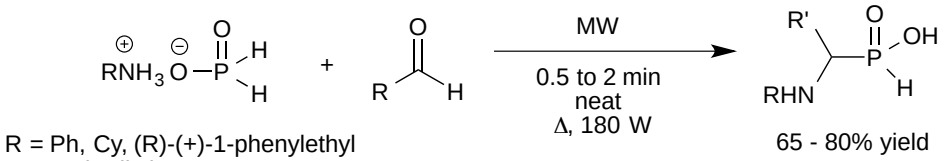
The preparation and extensive use of bis(trimethylsiloxy)phosphine (BTSP) was reported by several groups for synthesis of *H*-phosphinic acids. Although an efficient way to trap the P(III) tautomer via silylation, BTSP is pyrophoric and it must be prepared and used in solution. Scheme 1.4 shows the initial preparation of BTSP and subsequent reactions with alkyl halides,[27] imines,[28] activated alkenes[29–31] and aldehydes.[32]

Scheme 1.4 Preparation of *H*-phosphinic acids using BTSP.



1.2.3 Nucleophilic Addition Reactions of Hypophosphorous Compounds

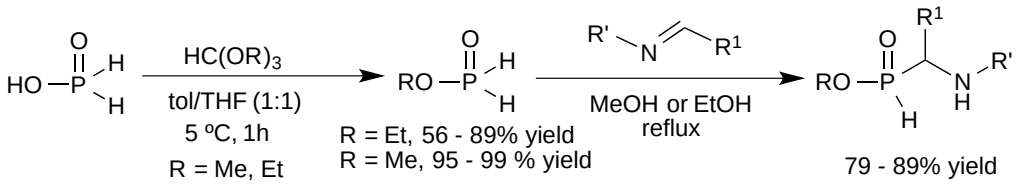
Alkyl phosphinates can nucleophilically add to carbonyl-containing compounds (aldehydes, ketones) or activated alkenes (Michael acceptors).[18] Preparation of α-aminophosphinic acids may be completed at reflux using the phospha-Mannich or Kabachnik-Fields reaction typically with an aldehyde, an amine and hypophosphorous acid or one of its salts.[33] A more efficient method was reported by Kaboudin using an alkylammonium hypophospite salt with an aldehyde under microwave irradiation for up to 2 minutes (Eq. 1.1).[34]



R = Ph, Cy, (R)-(+)-1-phenylethyl
R'= Aryl, Alkyl

(Eq. 1.1)

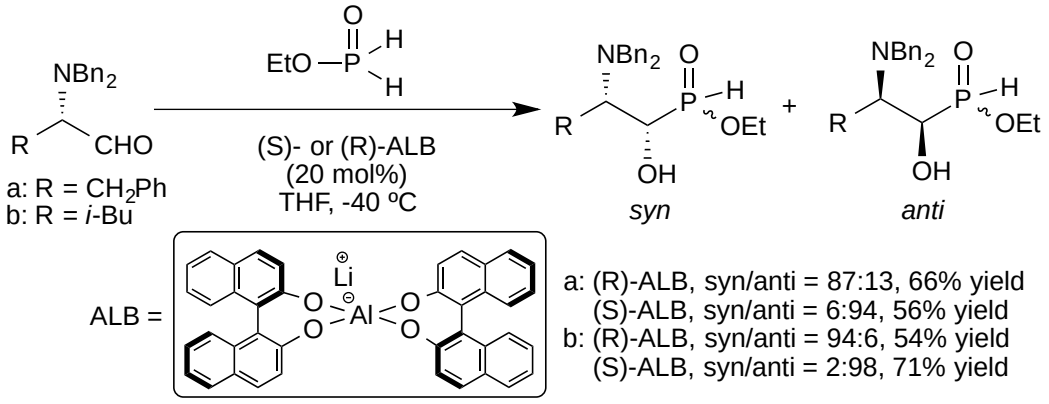
Cristau published a series of papers detailing the synthesis of phosphinopeptides using alkyl phosphinates and subsequently reacted with imines or hexahydrotriazines (Eq. 1.2).[35–37] To note, an effort to optimize the yield of ethyl phosphinate prepared by the orthoformate method[21,22] was also accomplished in this study.



(Eq. 1.2)

Finally, an asymmetric nucleophilic addition of methylphosphinate to aldehydes was developed using a chiral aluminum-lithium BINOL (ALB) complex as a catalyst.[38] In the following studies by Yokomatsu, α-aminoaldehydes were used to prepare derivatives of ß-amino-α-

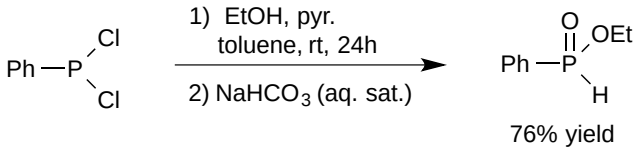
hydroxyphosphinic acid diastereoselectively for potential applications as HIV protease inhibitors (Eq. 1.3).[39,40]



(Eq. 1.3)

1.2.4 Hydrolysis or Alcoholysis of Chlorophosphines

Alkyl- or aryl-*H*-phosphinic acids such as PhP(O)(OH)H may be simply prepared from the hydrolysis of their corresponding dichlorophosphine ($RPCl_2$).[41] In a recent application to prepare ligands for dinuclear Ni(II) complexes, PhP(O)(OH)H was prepared by slow addition of $PhPCl_2$ to cold degassed deionized water and stirred until a white precipitate formed.[42] The ethyl ester, PhP(O)(OEt)H, was synthesized in a similar way with an ethanol and pyridine solution added slowly to $PhPCl_2$ and allowed to sit without stirring for 24 hours (Eq. 1.4).[43]

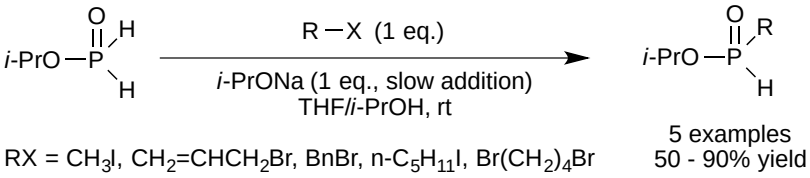


(Eq. 1.4)

1.2.5 Direct Alkylation of Alkyl Phosphinates

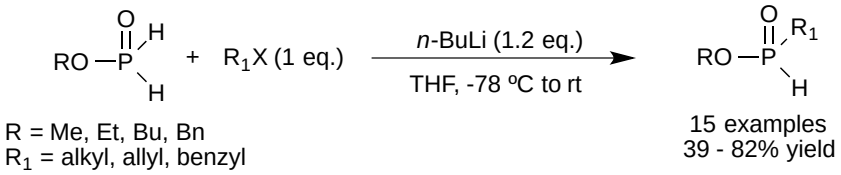
Gallagher et al. examined the alkylation of isopropyl phosphinate (*i*-$PrOP(O)H_2$) with alkyl halides and using sodium isoproxide as the base (Eq. 1.5).[44] Only more hindered secondary alkyl phosphinate esters can be used under these conditions because they are less reactive

towards dealkylation from the strong base and forming a hypophosphite anion. For this reason, more robust methodology needed to be developed to alkylate alkyl hyposphosphites.

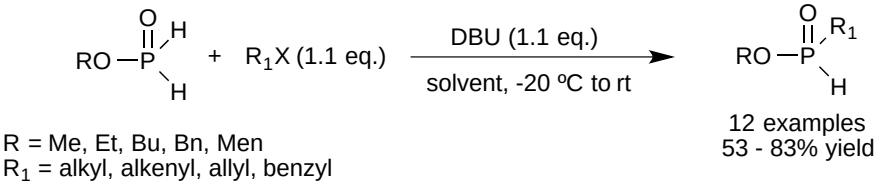


(Eq. 1.5)

Montchamp and co-workers also developed an *n*-butyllithium-promoted alkylation procedure between primary alkyl hypophospites and reactive electrophiles like alkyl iodides and allyl/benzylic bromides (Eq. 1.6).[45] Furthermore, the use of DBU as a base was also reported. This method showed versatility between types of phosphorus compounds studied (phosphinates and phosphonates) and less reactive alkyl halides (Eq. 1.7).[46]



(Eq. 1.6)



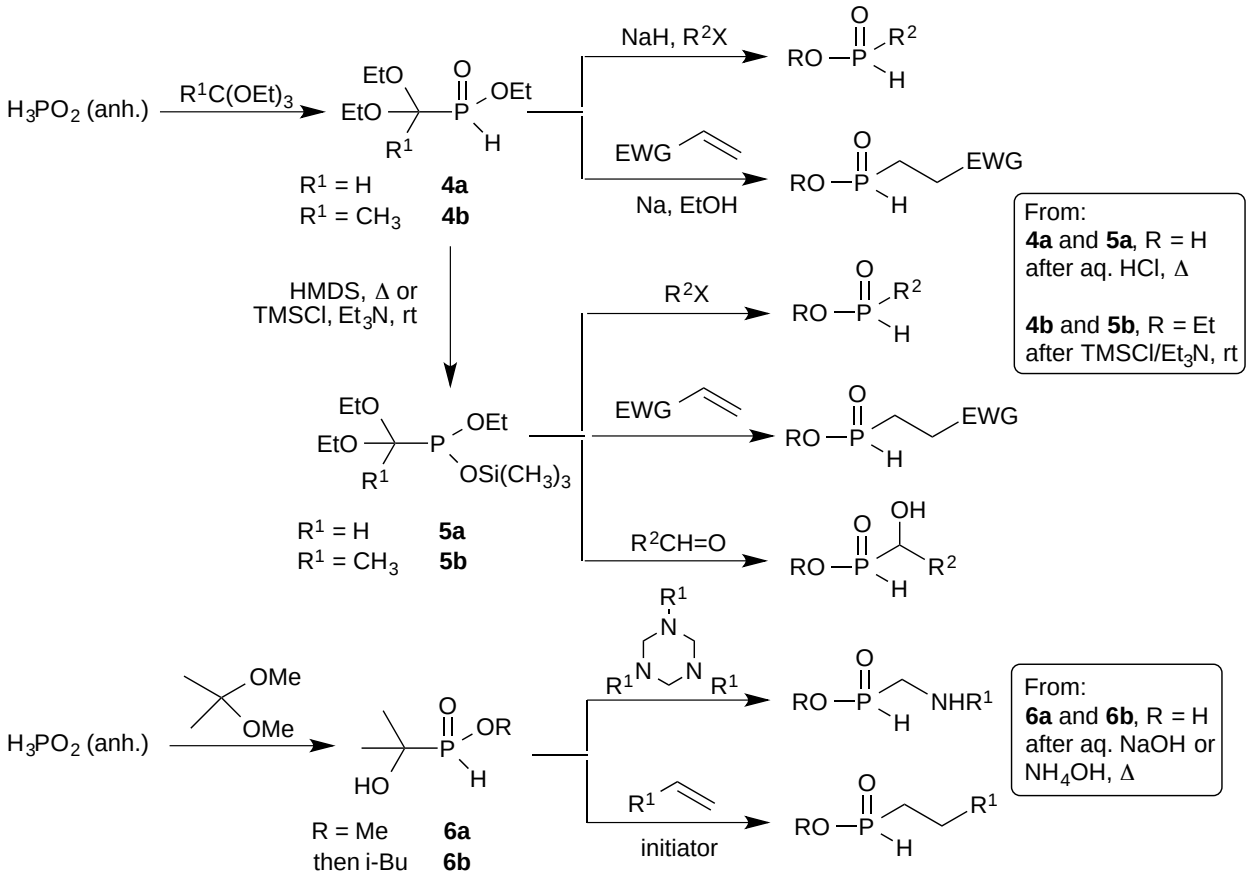
(Eq. 1.7)

1.2.6 Ciba-Geigy Methodology

Gallagher introduced the dialkoxymethylation of phosphinic and phosphonic acids using trialkoxyorthoformate under acidic conditions.[23,24] The chemists at the former Ciba-Geigy corporation realized the opportunity to protect a P-H bond in H_3PO_2 with a series of different reagents (**3**, **4**, **5**, Scheme 1.5) whereby the P-H bond could be unmasked when needed in the

next step of the synthetic sequence.[8,9,47–52] An addition of a protection/deprotection step, however, may not be ideal as the acidic condition to remove the acetal protecting group may not be compatible with more complex compounds with acid labile groups.

Scheme 1.5 Reactions with Ciba-Geigy Reagents and conversion to *H*-phosphinates.

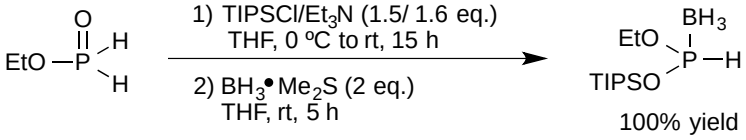


The first Ciba-Geigy reagents used 1,1-diethoxymethyl as the protecting group (**4a** and **5a**, Scheme 1.4) but its removal requires treatment under very acidic conditions with aqueous hydrochloric acid and heating at 100 ºC which causes hydrolysis of phosphinate ester too.[47–49] The subsequent reagents developed were a ketal protecting group (1, 1-diethoxyethyl, **4b** and **5b**, Scheme 1.5) which can be mildly cleaved using excess TMSCl in chloroform at room temperature.[51] Baylis developed the 1-hydroxy-2,2-dimethyl protecting group that is stable in

acidic conditions, but may be removed with aqueous base like ammonium or sodium hydroxide with slight heating (**6**, Scheme 1.4).[50]

1.2.7 Borane-protected Phosphonites

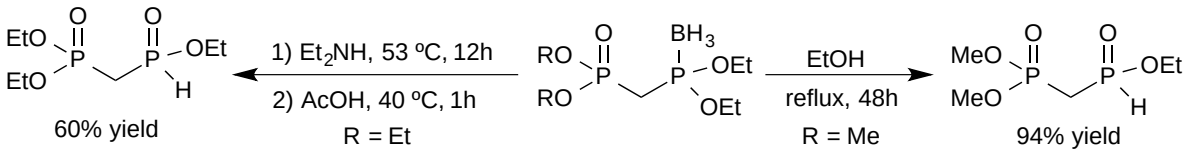
Alkyl phosphinates may also be protected as complexes with borane (Eq. 1.8).[53] Typical preparation first involves reacting the hypophosphite with a chlorosilane and base, which silylates the hydroxyl of the P(III) tautomer locking it in as the more reactive phosphonite. The silyl intermediate is then reacted with BH_3•Me_2S to form the stable borane complex.



(Eq. 1.8)

These compounds have similar reactivities compared with *H*-phosphinates, and can be efficiently alkylated under basic conditions, added as a nucleophile to carbonyls or undergo radical addition to alkenes. Deprotection of the borane complex is accomplished by using a strong acid such as HBF_4•Et_2O or a large excess of amine base followed by acetic acid (Scheme 1.6).[54] It was observed by Van der Eycken that simple refluxing in ethanol was enough to deprotect the phosphine-borane,[55] and this strategy was utilized successfully by Montchamp and Ortial to prepare bisphosphorus compounds containing a *H*-phosphinate.[56]

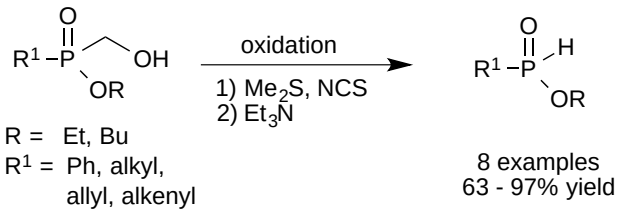
Scheme 1.6 Deprotection of Phosphonite-Borane Complexes.



1.2.8 Oxidation of Hydroxymethyl Phosphinates

Up until recently, the deprotection of (hydroxymethyl)phosphinate compounds to the corresponding *H*-phosphinate was not fully realized.[57] A neutral oxidative conversion was investigated and it was determined that the Corey-Kim oxidation was the optimal method (Eq. 1.9).

A polymer-supported version of the reaction using a polystyrene attached 4-(methylthio)-1-butanol was also studied briefly giving excellent results even after several successive runs.

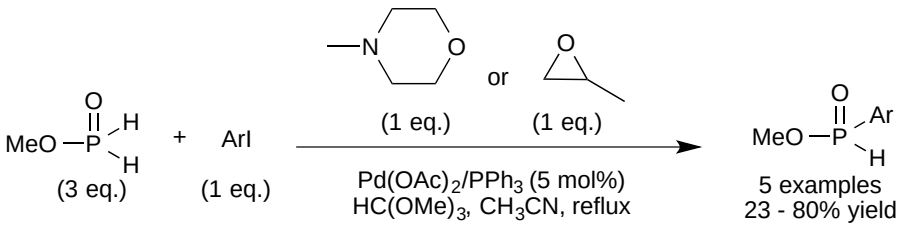


(Eq. 1.9)

1.2.9 Cross-coupling Reactions of Various Csp^2-X Containing Electrophiles

The cross-coupling reactions of hypophosphorous compounds is continuing to be expanded rapidly in the literature. An example of cross-coupling between triethylammonium hypophosphite with a steroid-derived dienyl triflate was reported by Holt;[58] however, the generality of the reaction was not examined.

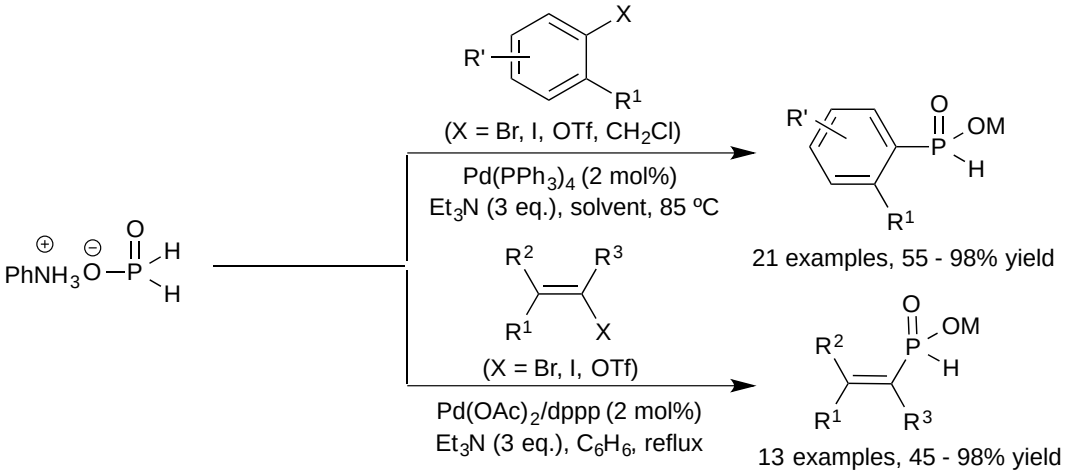
Using methyl- or *tert*-butyl phosphinate prepared by Fitch's orthoformate method,[21,22] Schwabacher and co-workers developed a palladium-catalyzed cross-coupling of aryl iodides (Eq. 1.10).[59]



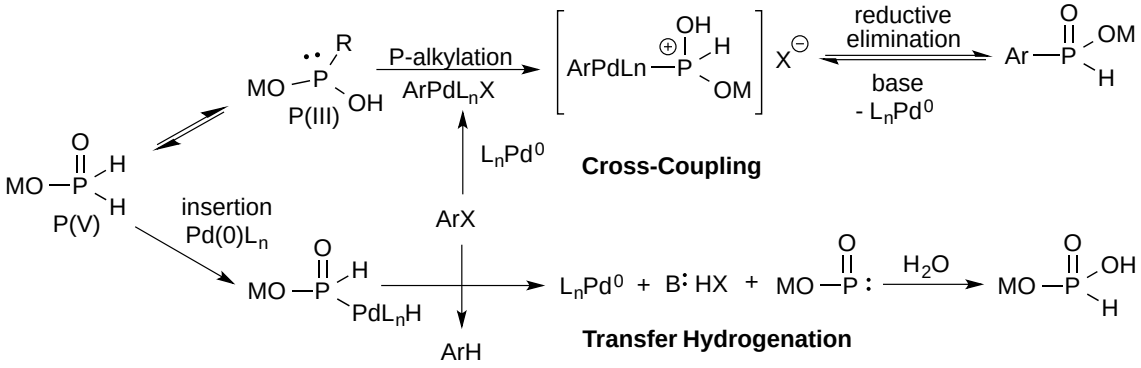
(Eq. 1.10)

The Montchamp Group's first contributions in this field involved the development of Pd-catalyzed cross-coupling reactions between hypophosphite salts and aryl halides, and alkenyl bromides and triflates (Scheme 1.7).[60,61] Consideration of possible mechanistic pathways indicate that the 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 partitition between them. (Scheme 1.8).

Scheme 1.7 Palladium-catalyzed cross-coupling of anilinium hypophosphite with aryl and alkenyl electrophiles.

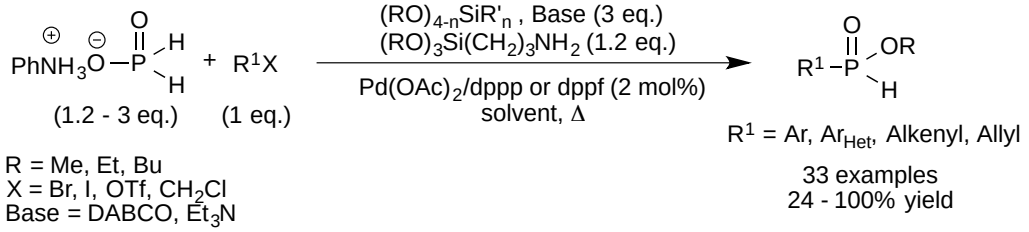


Scheme 1.8 Cross-coupling and transfer hydrogenation pathways.



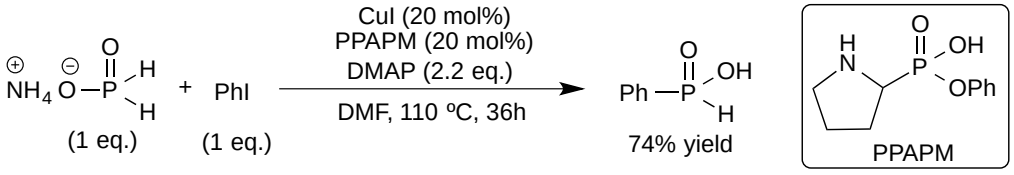
The competitive reduction was found to decrease significantly when $Pd(OAc)_2$/dppp (2 mol% or less) is used as the catalyst in place of $Pd(PPh_3)_4$. Changing the ligand from dppp to dppf was needed to accommodate the Z-substitution for alkenyl electrophiles, and the modification afforded the product in good yield.[61]

Furthermore, Montchamp and co-workers developed a "one pot" cross-coupling of alkyl phosphinates with a wide variety of aryl, heteroaryl, alkenyl and a few allylic electrophiles through the use of their alkoxysilane esterification method (Eq. 1.11).[62,63]



(Eq. 1.11)

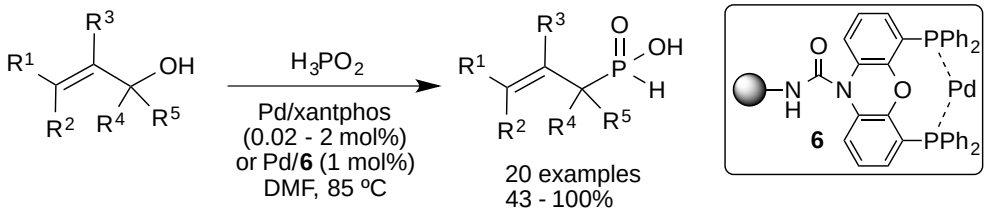
Another example on cross-coupling of hypophosphorous compounds is the copper-catalyzed reaction of ammonium hypophosphite with iodobenzene using CuI and pyrrolidine-1-phosphonic acid phenyl monoester (PPAPM) as the ligand (Eq. 1.12).[64]



(Eq. 1.12)

The only reports on cross-coupling of hypophosphorous acid derivatives with allylic electrophiles have been published by the Montchamp group.[63,65] Allylic chlorides and acetates function as excellent leaving groups in the cross-coupling. Of particular relevance is an elegant and environmentally friendly cross-coupling reaction between H_3PO_2 and allylic alcohols (Eq. 1.13).

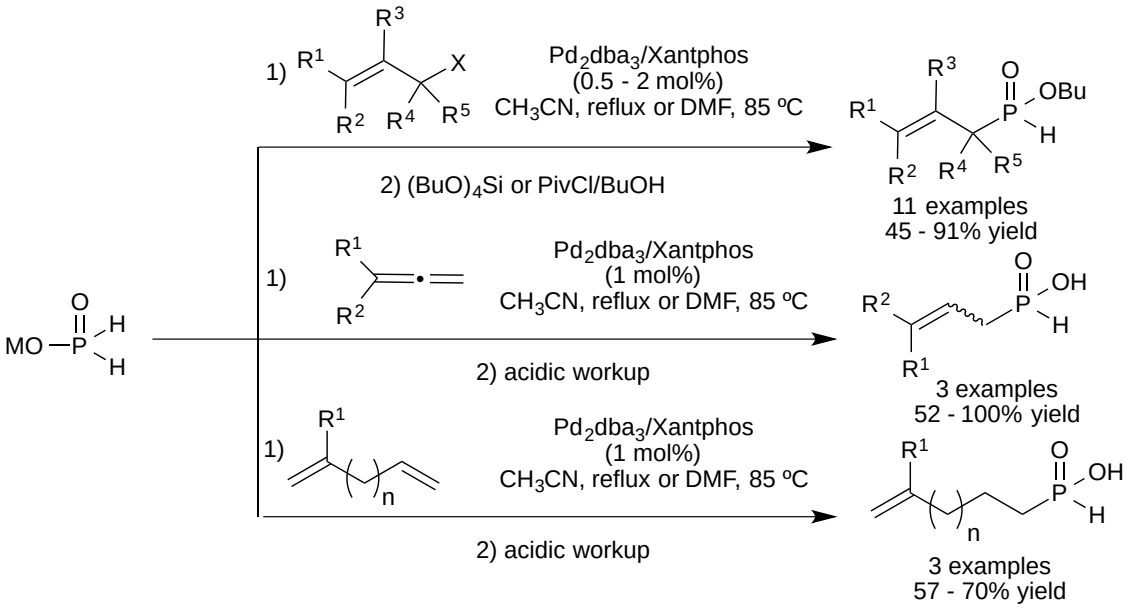
Functioning by first esterifying the alcohol to the phosphorus, the hydroxyl group can then be eliminated as water and removed by molecular sieves or a Dean-Stark trap. The reaction also works using a polystyrene supported catalyst **6**, allowing recovery by filtration and recycling of the palladium catalyst.[65]



(Eq. 1.13)

Cross-coupling reactions of hypophosphorous acid derivatives with allylic electrophiles yield allylic *H*-phosphinates (Scheme 1.9). Based on mechanistic studies, a general catalytic

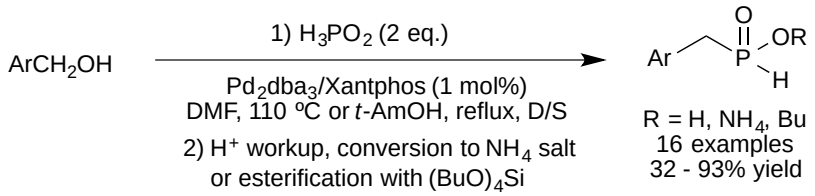
Scheme 1.9 Palladium-catalyzed reactions of hypophophosphorous compounds with allenes, dienes, and allylic electrophiles.



system for the cross-coupling of hypophosphorous compounds with activated allylic electrophilic (i.e. acetates, benzoates and carbonates) was elucidated, leading to the development of an effective and practical synthesis of allylic *H*-phosphinic acids.[66] The acid products can be isolated in good yields by simple extractive workup, esterified *in situ* to the *H*-phosphinic ester, or oxidized to the allylic phosphonates.

In a follow-up report, the direct benzylation of hypophosphorous acid was developed (Eq. 1.14).[67] The benzylic alcohols are employed without prior activation (ie. as esters, carbonates, or halides, etc.).

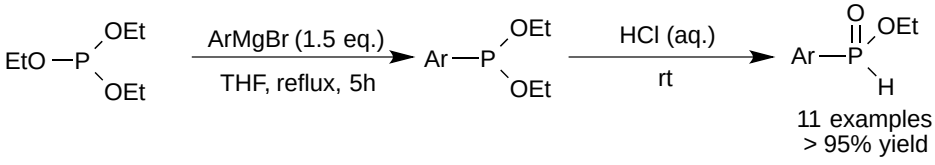
In cases when DMF acted as a poor solvent, *tert*-amyl alcohol (t-AmOH) was used. This methodology is a good representation of a greener, PCl_3-free method to obtain benzylic *H*-phosphinate building blocks.



(Eq. 1.14)

1.2.10 Addition of Grignard to Trialkyl Phosphite followed by Acid Hydrolysis

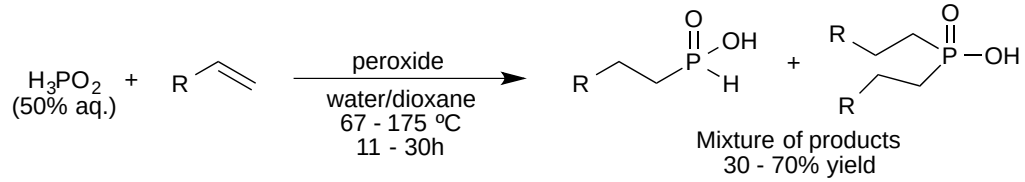
Volle, Virieux and Pirat recently completed a systematic study of the preparation of aryl-*H*-phosphinates using reaction conditions originally developed and optimized by Sander and Petnehazy, respectively (Eq. 1.15).[68] It involves the direct addition of triethyl phosphite with a Grignard reagent, and hydrolysis in the second step to produce the desired compounds in high yields and purities.



(Eq. 1.15)

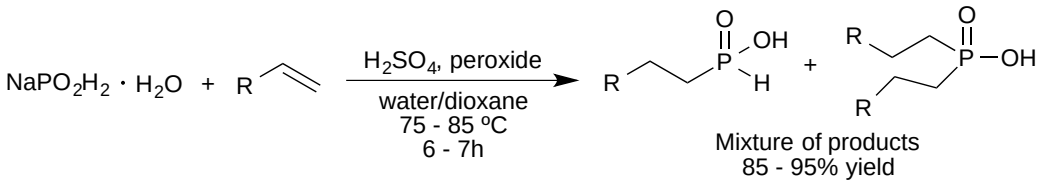
1.2.11 Free-radical Hydrophosphinylation Reactions of Alkenes and Alkynes

The addition of phosphorus-centered radicals to olefins is well documented in the literature.[69] Williams and Hamilton reported the addition of aqueous H_3PO_2 to olefins initiated by organic peroxides at high temperatures (Eq. 1.16),[70] where the reaction yields could be increased by using hazardous crystalline H_3PO_2.[71] In parallel work, hydrophosphinylation of olefins with salts of H_3PO_2 in an autoclave at 120-150 ºC was also reported.[72] As a result, mixtures mono- and disubtituted of phosphinic acids were obtained.



(Eq. 1.16)

Nifant'ev and coworkers contributed significantly to the development of radical addition methodology using hypophosphorous acid.[73] Addition of H_3PO_2 or sodium or potassium hypophosphite salts to alkenes (Eq. 1.17) is performed in the presence of peroxides and mineral or organic acids. The use of acid catalysts enables lowering the temperature of the reaction by assisting the breakdown of the peroxide initiators. Karanewsky found that the use of AIBN in refluxing ethanol provided the desired products;[74] however, the conditions were harsh and ultimately incompatible with acid-sensitive functional groups.

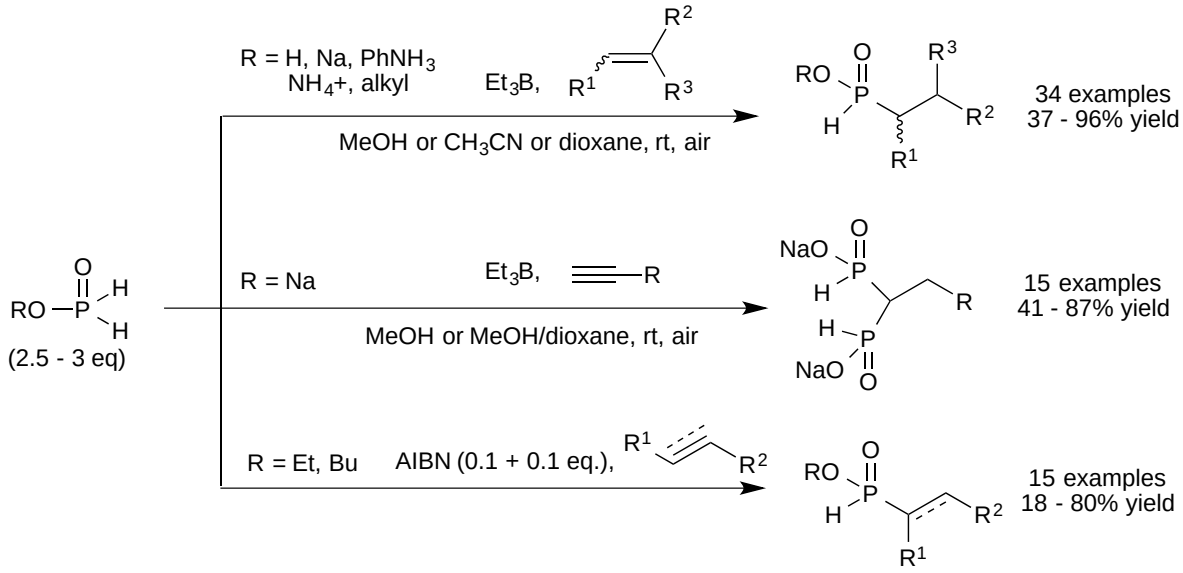


(Eq. 1.17)

Montchamp et al. developed more efficient approaches for the free-radical addition of hypophosphorous compounds to unsaturated substrates (Scheme 1.10). Using Et_3B as initiator

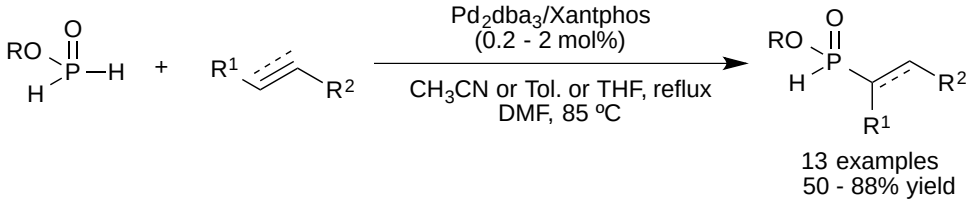
under aerobic conditions, addition of H_3PO_2, its salts anilinium hypophosphite (AHP) and $NaOP(O)H_2$ or even alkyl phosphinates to alkenes occurs at room temperature in a flask open to air.[75] AIBN-initiated hydrophosphinylation of alkenes and alkynes with alkyl phosphinates also proceeds effectively in refluxing acetonitrile.[76] Furthermore, room temperature radical addition of $NaOP(O)H_2$ to terminal alkynes produces the previously unknown 1-alkyl-1,1-bis-*H*-phosphinates,[77] which are novel precursors of the biological important 1,1-bisphosphonates.[78]

Scheme 1.10 Free radical reactions of hypophosphorous compounds.



1.2.12 Metal-catalyzed Hydrophosphinylation

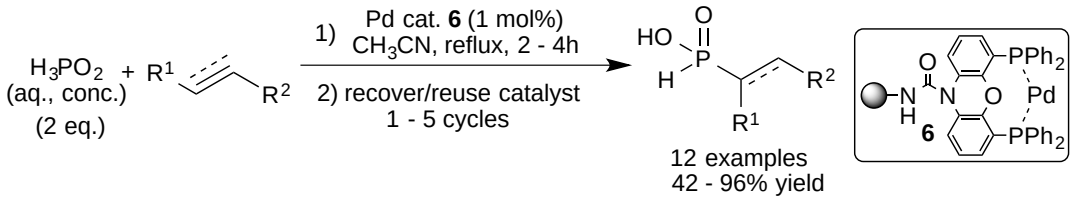
Transition metal-catalyzed additions of P-H bonds across unsaturated substrates have received significant focus in the recent literature, and it was Montchamp's group that developed the first hydrophosphinylation of hypophosphorous compounds with unsaturated substrates.[2,26] A remarkably broad Pd-catalyzed addition of H_3PO_2, AHP and alkyl phosphinates to alkenes and alkynes under homogeneous catalytic conditions was studied yielding *H*-phosphinic acid derivitives in high yields (Eq. 1.18).[79] Of note, the reaction does not require strict anhydrous conditions.



(Eq. 1.18)

A more thorough discussion about the proposed mechanism of metal-catalyzed hydrophosphinylation will be discussed in Chapter 3; however, like the palladium-catalyzed cross-coupling reactions, the competing transfer hydrogenation (Scheme 1.8) was also observed.

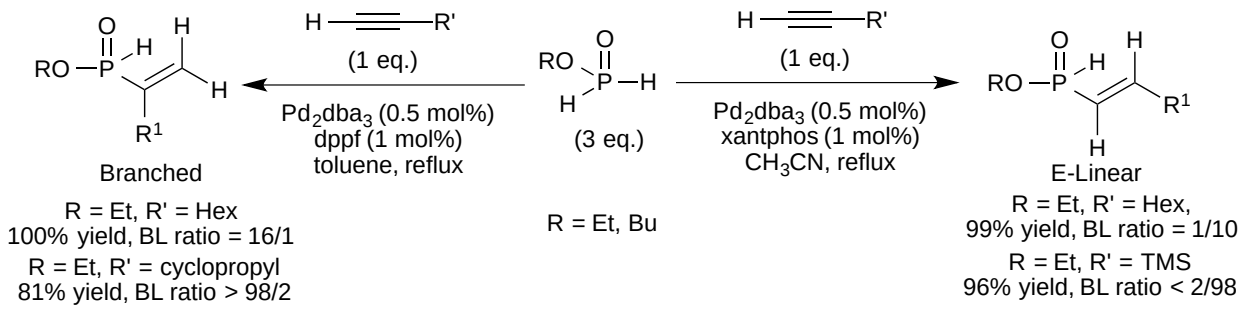
Although the Pd/xantphos catalyst system is used sparingly at low loading, costs of the palladium metal and ligand are still significant. An environmentally and cost-effective variant of hydrophosphinylation was developed using a water-tolerant, recyclable polystyrene supported catalyst **6** (Eq. 1.19).[80] The ligand can also be used with Pd/C for a possible two-fold reusable heterogeneous catalyst system. In a continuing effort to reduce cost of the catalyst system while maintaining efficiency, nickel-catalyzed hydrophosphinylation reactions of alkenes and alkynes were developed and will be the focus of Chapter 3.



(Eq. 1.19)

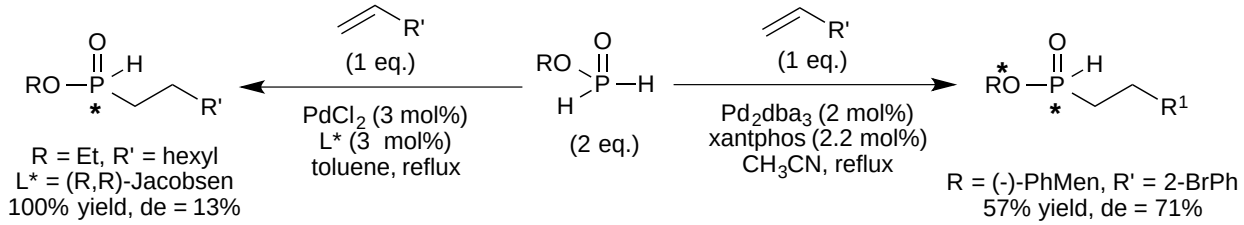
An extension of the Pd-catalyzed hydrophosphinylation work was conducted to understand the regioselectivity for linear vs branched isomers of alkenyl-*H*-phosphinates based on ligand and solvent selection (Scheme 1.11).[81] It was observed that selectivities varied based on the alkyne employed and the conditions for phosphinate synthesis but selectivities are generally better than 5:1 and sometimes reach 98:2, with either the linear or branched isomer dominating.[81]

Scheme 1.11 Regioselectivity on addition of alkynes based on reaction conditions



The asymmetric synthesis of *H*-phosphinates through the desymmetrization of hyposphosphite esters, $ROP(O)H_2$, was also investigated through an enantioselective version of Pd-catalyzed hydrophosphinylation (Scheme 1.12).[20] In a two-tiered study, both chiral hypophosphites prepared by esterification methods of H_3PO_2 using chiral alcohols (Scheme 1.3) and chiral ligands were examined. Diastereomeric excess as determined by ^{31}P NMR and validated by chiral HPLC showed little desymmetrization of non-chiral phosphinates using chiral ligands. Palladium-catalyzed hydrophosphinylation of (-)-8-phenylmenthol hypophosphophite with 2-bromostyrene showed the most promising desymmetrization at 71% de.

Scheme 1.12 Desymmetrization of alkyl phosphinates via chiral auxillary or ligand



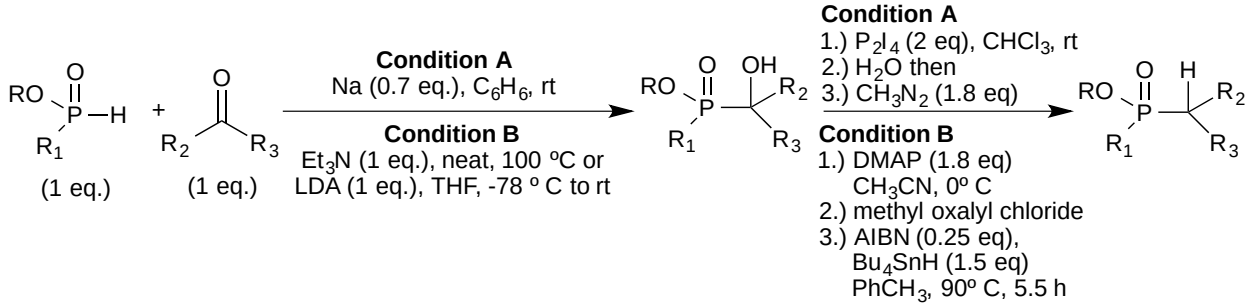
1.3 Reactivity of *H*-phosphinic Acid Derivatives

The following section briefly describes the second functionalization of *H*-phosphinates, which is of great interest due to product stability and many applications in industry, medicine and agriculture. When functionalizing or "activating" the second P-H bond, the decreased reactivity must be considered especially with non-aromatic *H*-phosphinates. A selected non-comprehensive review of methods for functionalization of *H*-phosphinates into disubsituted products is given.

1.3.1 Nucleophilic Addition

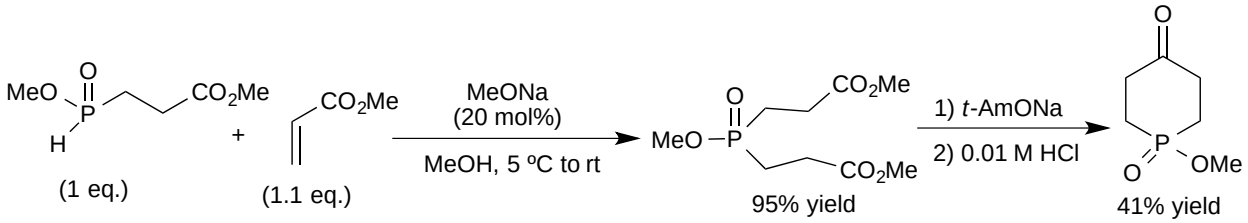
Pudovik reported for the first time the addition of *H*-phosphonates to aldehydes or ketones using heat and base-catalyzed conditions, typically with alkoxides or tertiary amines.[82] Yamashita[83] and Hansen[84] applied this approach to *H*-phosphinates in order to prepare, via addition-deoxygenation processes, alkyl or sec-alkyl phosphinates, which are otherwise difficult to obtain by Arbuzov or Michaelis-Becker reactions of secondary alkyl halides (Scheme 1.13).[27,44,85] However, Hansen et al. discovered under amine catalysis, *H*-phosphinates exclusively undergo addition to aldehydes and reactive ketones, which acyclic ketones are unreactive, even under forcing conditions.[84]

Scheme 1.13 Addition of *H*-phosphinates to carbonyl compounds followed by deoxygenation

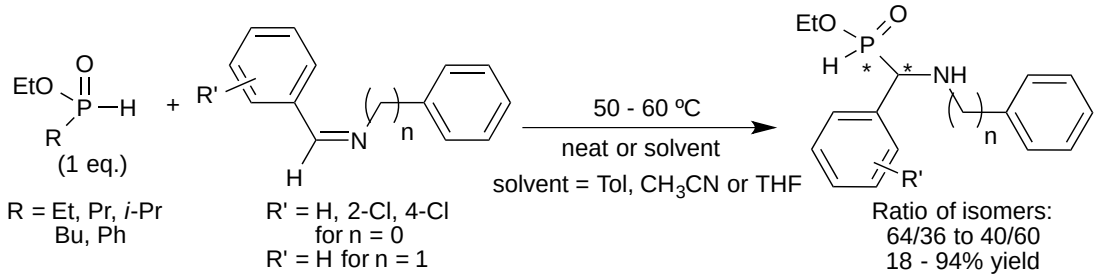


Conjugate addition reactions of *H*-phosphinate alkyl esters to acrylate esters and acrylonitrile, using catalytic amounts of sodium alkoxides was initially reported by Pudovik.[86] Verkade used this reaction in the synthesis of 1-methoxy-1-oxophosphorinan-4-one (Scheme 1.14).[87]

Scheme 1.14 Conjugate addition reaction of *H*-phosphinate with methyl acrylate



Phosphoryl analogues of glycine that exhibit herbicidal and antitumor activity have been prepared by thermal addition of *H*-phosphinates to triazines. Szabo studied the thermal reaction of ethyl alkyl- and ethyl phenyl-*H*-phosphinates with imines, and observed a small effect of the substituents on the C=N on the diastereoselectivity of the reaction (Eq. 1.20). Cristau has also synthesized α-amino-alkyl hydroxymethylphosphinic acids by thermal addition of *H*-phosphinates to imines.[88]

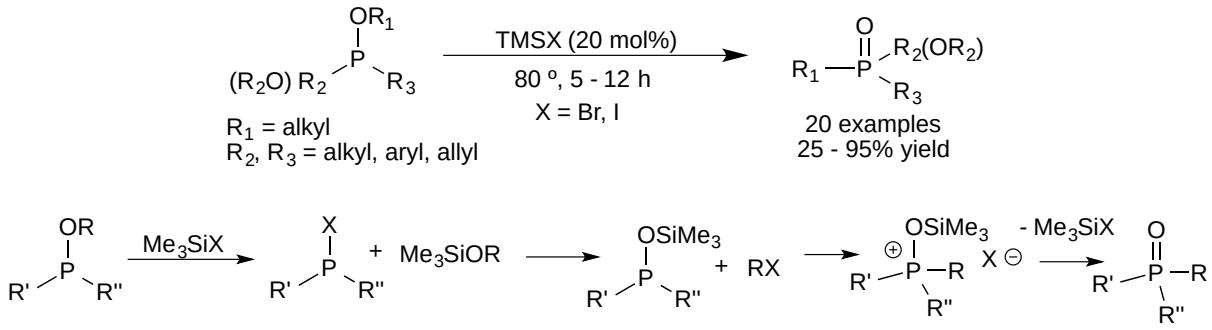


(Eq. 1.20)

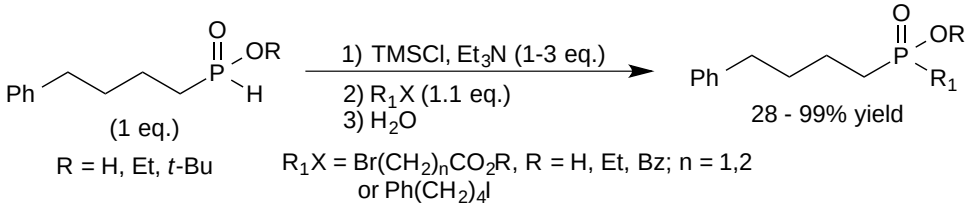
1.3.2 Arbuzov-like Reactions of *H*-phosphinic Acid Derivatives

In a recent publication, Michalski demonstrated the synthesis of disubstituted phosphinates using the Michaelis-Abruzov rearrangement, which involves the thermal reaction of a phosphonite, $R^2P(OR^1)(R^3)$ with a catalytic amount of trimethylsilyl halide (Scheme 1.15).[89]

Scheme 1.15 TMS-X-catalyzed Michaelis-Arbuzov rearrangement of phosphonites



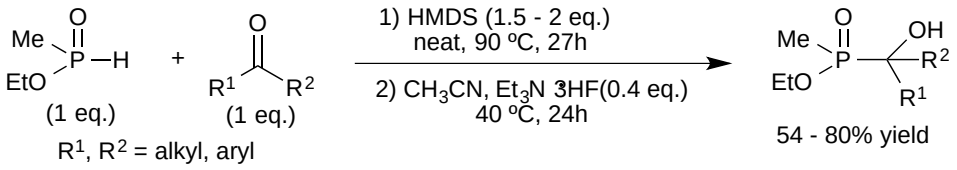
Stepwise silylation and alkylation of *H*-phosphinates (silyl-Arbuzov reaction) was initially demonstrated by Thottathil using reactive bromocarboxylates as electrophiles (Eq. 1.21).[90]



(Eq. 1.21)

Majewski reported the formation of symmetrical disubstituted phosphinates by reaction of BTSP with highly reactive halides (benzyl, allyl and a-carbonyl).[91] Subsequently, Boyd and Regan prepared both symmetrical and unsymmetrical disubstituted phosphinic acids using reactive halides.[27] This methodology has been widely applied in synthesis, such as in the preparation of γ-aminopropyl-*H*-phosphinic acids (GABA analogs),[8,9] synthesis of phosphorus-

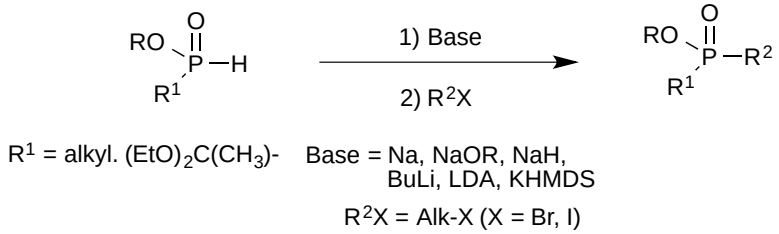
containing sugar derivatives[92] and mono-, di-, and spirocyclic phosphinic acid analogues of phosphodiesters in the preparation of the commercial heart drug monopril (fosinopril sodium), and of pseudopeptides that inhibit the human cyclophilin hCyp-19,[93] as well as in the synthesis of MMP inhibitors.[94] As a final example, Hansen has reported an efficient reaction involving the use of trimethylsiloxy derivatives of *H*-phosphinates with aldehydes and ketones (Eq. 1.22).[84]



(Eq. 1.22)

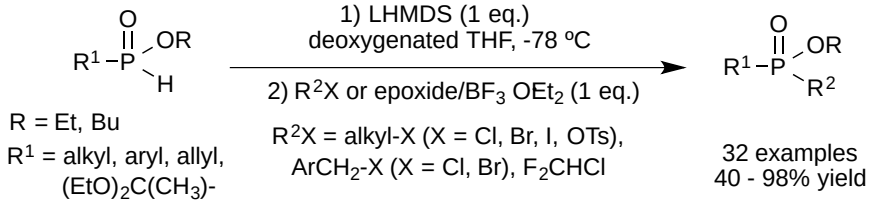
1.3.3 Based-catalyzed Alkylations

Several examples of base-promoted *H*-phosphinate alkylation (Michaelis-Becker type reactions) have been reported, employing various bases (Na, RONa, NaH, BuLi, LDA, KHMDS) (Eq. 1.23). [8,9,47]



(Eq. 1.23)

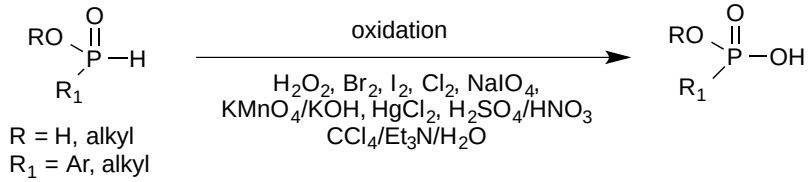
Montchamp et al. developed a general protocol for the direct alkylation of *H*-phosphinates using LiHMDS as the base (Eq. 1.24).[95] The phosphorus nucleophile, base and electrophile were used in equimolar amounts. The reaction works with alkyl halides, including primary alkyl chlorides. The effectiveness of the reaction was demonstrated in the synthesis of several GABA analogs or their precursors.



(Eq. 1.24)

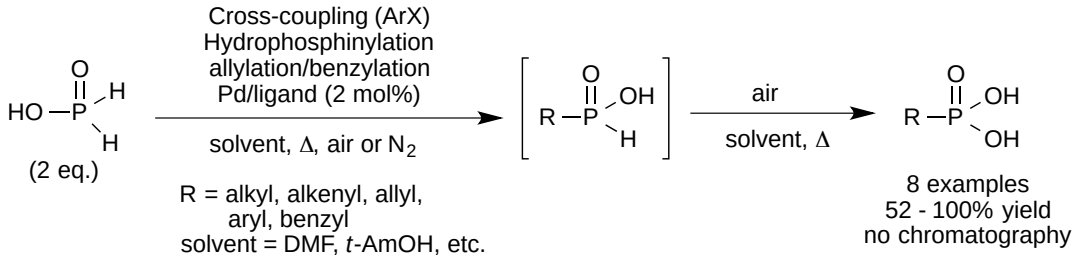
1.3.4 Oxidation reactions

The preparation of phosphonic acids through oxidation of H-phosphinic acids in a well-known methodology (Eq. 1.25), which generally requires harsh conditions and strong oxidative agents such as H_2O_2 (30%, 80 – 90 ºC);[96] Br_2, I_2 or Cl_2 in H_2O/DMSO or in concentrated HI/HCl (20 – 75 ºC);[97] $HgCl_2$ or HgO in H_2O (90 – 95 ºC);[97] $KMnO_4$/KOH in H_2O (50 – 250 ºC);[98] H_2SO_4/HNO_3 (100 – 110 ºC);[98] $CCl_4/Et_3N/H_2O$ (35 ºC); PCC/TsOH in DMSO;[99] or $NaIO_4$ (50 ºC).[100]



(Eq. 1.25)

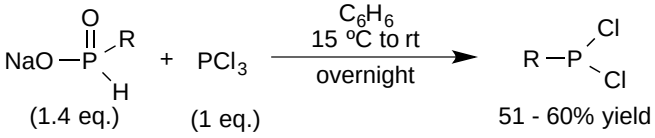
Montchamp and coworkers developed a tandem palladium-catalyzed oxidation of *H*-phosphinates to phosphonates in response to the lack of generality in the literature methods up to that point (Eq. 1.26).[101] In a one-pot reaction, a single catalytic system accomplishes both hydrophosphinylation and oxidation. This method is the first reported catalytic oxidations of *H*-phosphinates in tandem with the formation of a P-C bond.



(Eq. 1.26)

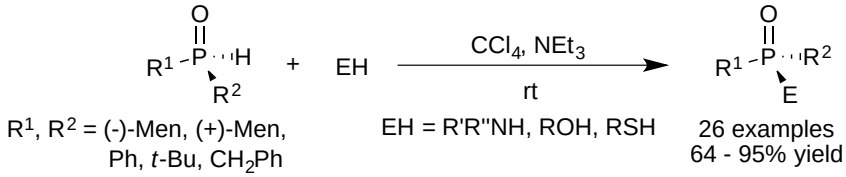
1.3.5 Halogenation Reactions

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). A few examples of fluorophosphonic acids have been successfully isolated and characterized. The reductive halogenation of sodium *H*-phosphinate salts with PCl_3 or $SOCl_2$, instead of their isolation, as described by Nifant'ev (Eq. 1.27).[102] *H*-phosphinate esters have also been converted to dichlorophosphines by treatment with PCl_3.[103]



(Eq. 1.27)

Han developed a stereospecific coupling reaction between *H*-phosphinates and amines, alcohols and thiols using the Atherton-Todd reaction (Eq. 1.28).[104] As mentioned above, the phosphinate chloride is first generated in solution before the addition of the electrophile, and the synthesis of the desired substrates occurs in good yield. The developed reaction, although not original in its concept, showed that the Atherton-Todd reaction continues to be robust.

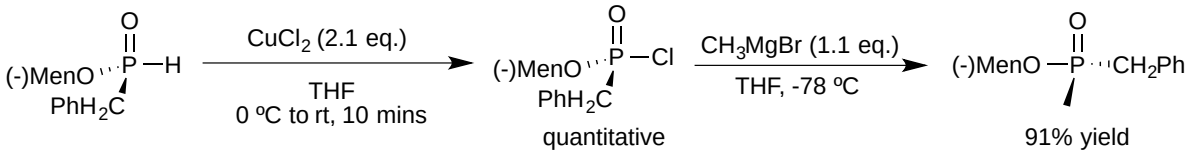


(Eq. 1.28)

Finally, Han et al. developed a protocol to chlorinate and isolate optically active *H*-phosphinate chlorides using stoichiometric $CuCl_2$ (Scheme 1.16).[105] The reaction is stereospecific and a multiple types of nucleophiles from alkyl Grignard reagents, alkyl lithium, alcohols, thiols and amines were tested in the reaction scope showing very good yields for all

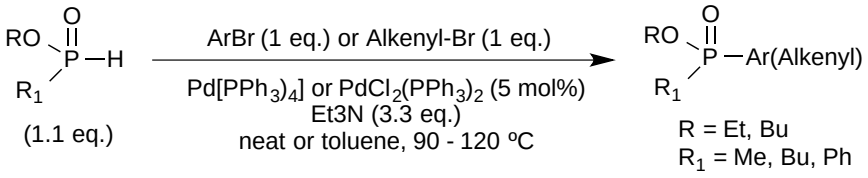
substrates prepared. The reactions with the nucleophiles caused an inversion of stereochemistry at the phosphorus.

Scheme 1.16 Chlorination of *H*-phosphinate with stoichiometric $CuCl_2$ at room temperature



1.3.6 Cross-coupling Reactions

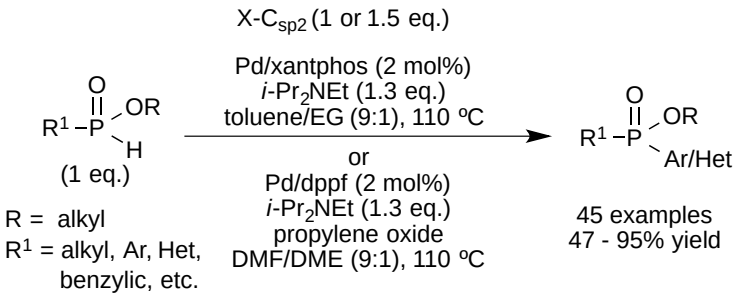
The first studies on cross-coupling reaction of H-phosphinate esters with aryl halides was reported by Xu et al. By applying the classic Hirao conditions, it was discovered that aryl and alkenyl bromides cross-couple with phenyl-H-phosphinate[106,107] and alkyl *H*-phosphinate esters[107,108] in the presence of Pd-catalysts and a base (Eq. 1.29). Xu also showed that enantiomerically pure (S)- and (R)-isopropyl methyl-*H*-phosphinates undergo these reactions with complete retention of the phosphorus stereocenter.[109]



(Eq. 1.29)

The generality of palladium-catalyzed cross-coupling of *H*-phosphinates with C_{sp2}-X and related partners was established by Montchamp et al (Eq. 1.30).[110,111] The effect of the ligand and additives on the catalyst system was investigated and the studies showed that xantphos/ethylene glycol as well as dppf/1,2-dimethoxyethane along with diisopropylethylamine as the base proved

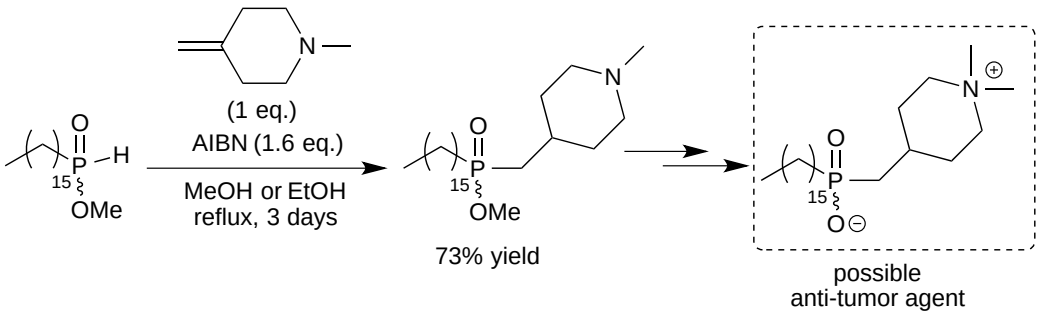
useful for the synthesis of numerous P-C containing compounds. Gratifyingly, even unactivated aryl chlorides worked well under the optimized reaction conditions.



(Eq. 1.30)

1.3.7 Free-radical Reactions

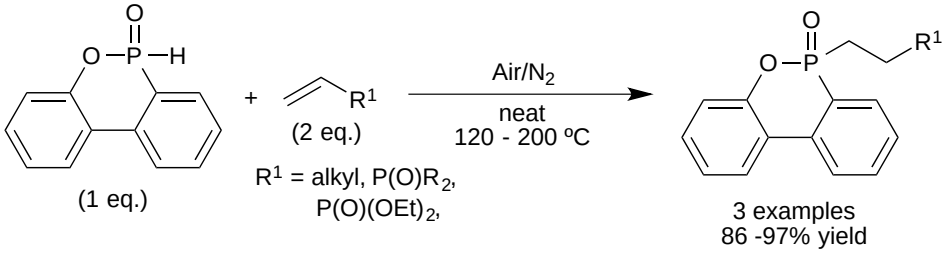
Radical initiators such as benzoyl peroxide and AIBN are known for promoting the addition of *H*-phosphinates to unsaturated substrates. There are a few reports in the literature of this reaction, but in general it is inefficient and often requires specialized radical initiators, very harsh conditions and a large excess of one of the reagents and initiator. Regan, however, was able to utilize the radical reaction between methyl hexadecylphosphinate and 1-methyl-4-methylenpiperidine to prepare phosphinate analogues of anti-tumor agents Perifosine (Eq. 1.31).[112]



(Eq. 1.31)

Han described an air-induced anti-Markovnikov addition of aryl-*H*-phosphinates to alkenes, which requires elevated temperatures (Eq. 1.32).[113] This clearly shows that there is a

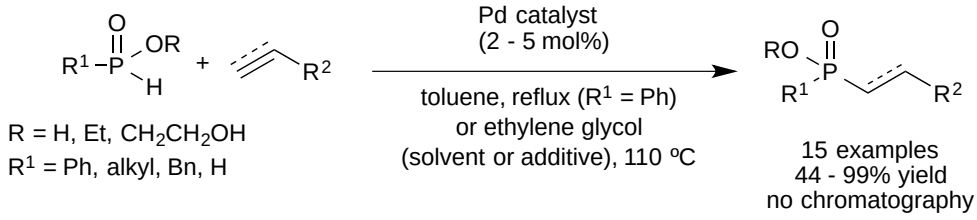
large exception regarding increased reactivities of aryl-*H*-phosphinate alkyl esters that is frequently used in methodology developed by Han, Tanaka and many others in the field.



(Eq. 1.32)

1.3.8 Metal-catalyzed Hydrophosphinylation Reactions

Montchamp reported the first hydrophosphinylation of alkyl-*H*-phosphinic acids with alkenes and alkynes (Eq. 1.33).[114] The inability to conduct this reaction under typical hydrophosphinylation conditions required investigation into alternative methods. After extensive experimentation, it was discovered that the use of ethylene glycol as a solvent or co-solvent aided in the catalysis and afforded products in useful yields.

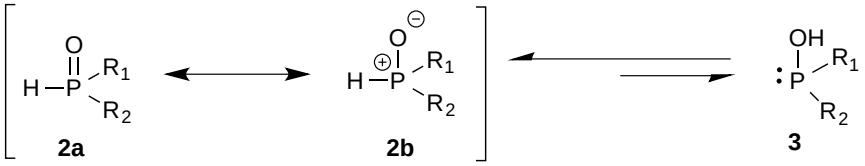


(Eq. 1.33)

Chapter Two: P(V) to P(III) Tautomerization of Phosphinylidene Compounds

2.1 Introduction

Tautomerization is an important class of chemical reaction involving the interconversion of constitutional isomers. Perhaps the best-known example is the hydrogen-transfer ("prototropic") keto-enol tautomerism. The phosphiniylidene P-OH moiety also displays prototropic tautomerism (Eq. 2.1).



(Eq. 2.1)

The phosphinylidene tautomeric equilibrium in Eq. 2.1 is generally dominated by the P(V) form **2a**.[115,116] The P(III) nucleophile **3** appears to be the reactive species in many phosphinylidene reactions making the thermodynamics and kinetics of Eq. 2.1 critical to the applications of phosphinylidene synthons mentioned in Chapter 1. Electron-donating substituents R^1/R^2 stabilize **2a** through the phosphonium **2b**, and electron-withdrawing substituents destabilize **2a,** with phosphinous acid **3** becoming more dominant. A good example of this destabilization is when $R^1 = R^2 = CF_3$ resulting in **3** being major.[117,118] Aryl *H*-phosphinates (R^1=Ar, R^2=OAlk or OAr) also have increased reactivities to form higher proportions of P(III) in equilibrium with P(V) due to resonance stabilization of the P(III) lone pair.[114,119,120] The P(III) form can also be stabilized by coordination to transition metal complexes with molybdenum and ruthenium,[121,122] via silylation or Lewis acidic borane complexed to phosphonites.[53]

The understanding of the tautomerization presented in Eq. 2.1 is essential for explaining the reactivities of phosphinates, *H*-phosphinates, *H*-phosphonates, and phosphine oxides (Chart 1.1). This chapter will describe a combination of computational mechanistic studies and experimental kinetics measurements to investigate this equilibrium in a general yet quantitative

manner. This work summarizes and extends previous experimental and computational investigations reviewed in detail below.

There have been several computational studies of how groups R^1 and R^2 affect the thermodynamics of phosphinylidene tautomerization.[123–126] These studies display the trends as discussed above with electron donor or acceptor groups either destabilizing or stabilizing the P(III) form, respectively. Accurate calculations of tautomerization thermodynamics; however, appear to require complex quantum chemical functions and long computation times to treat the phosphorus hypervalency.[127]

Calculations have unambiguously demonstrated that the tautomerization in Eq. 2.1 requires catalysis. Accurate electronic structure calculations show that uncatalyzed tautomerization of phosphine oxide (R^1=R^2=H) proceeds through a strained three-membered ring with a prohibitively high reaction barrier ~60 kcal mol^{-1}.[123,127,128] Substantially lower tautomerization barriers are predicted when P(V) dimers exchange a pair of protons,[124,125,129] in phosphine oxide complexes with transition metals[8,9] or bicyclic guanidines which provides a transfer of protons.[130] Our initial studies, which will be discussed in more detail in the next section, demonstrate that even single molecules of H_2O can accelerate the tautomerization to experimentally realistic rates.

Previous experimental data also suggest that phosphinylidene tautomerization is important in reactivity. The reaction between dimethyl phosphite and chloroacetone was proposed to proceed through base-catalyzed tautomerization.[131] Chiral BINOL-derived phosphoric acid-catalyzed imine hydrophosphonylation was proposed to involve the catalyst's stabilization of the P(III) phosphite.[132] Montchamp proposed that alkylation of alkyl phosphinates and *H*-phosphinates involved base-catalyzed tautomerization or stabilization of P(III) form.[45,46]

2.2 Results and Discussion

2.2.1 Tautomerization by Water

Figure 2.1 shows B3LYP/6-311++G(3df,3pd) Gibbs free energy surfaces and transition state geometries for phosphine oxide (R^1=R^2=H) tautomerization in the presence of 0-2 water molecules. Uncatalyzed tautomerization has a prohibitively high barrier, consistent with previous work. A single water molecule can catalyze tautomerization by simultaneously accepting a proton from phosphorus and donating one to oxygen, dramatically lowering the barrier from 58 to 36 kcal mol^{-1}. This is qualitatively similar to previous tautomerization mechanisms involving phosphinylidene dimers[124,125,129] or guanidines.[130] Continuum solvents do not capture this effect: the uncatalyzed Gibbs free energy barrier increases to 61 kcal mol^{-1} in continuum water.

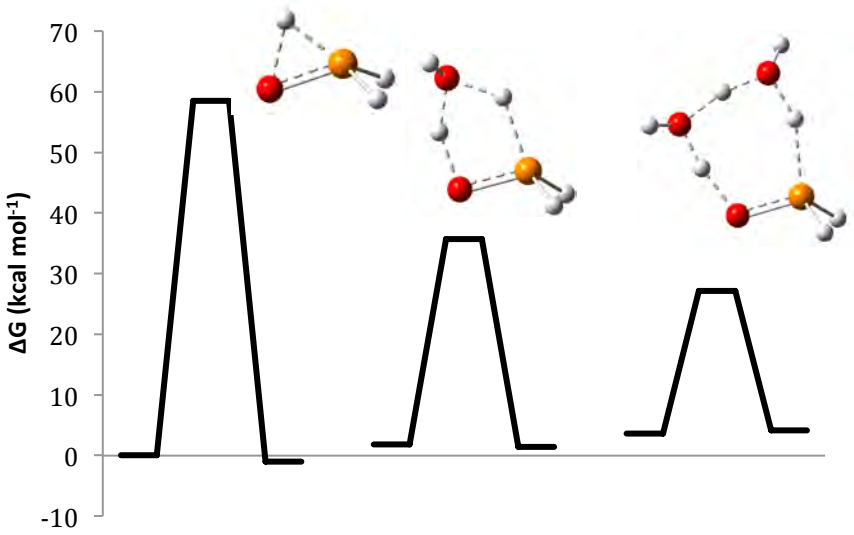


Figure 2.1 Calculated Gibbs free energy surfaces and transition state geometries for H_3PO tautomerization with zero, one, or two water molecules. Free energy surfaces include P(V) reactant, transition state, and P(III) product complexed with water, and are referenced to isolated P(V).

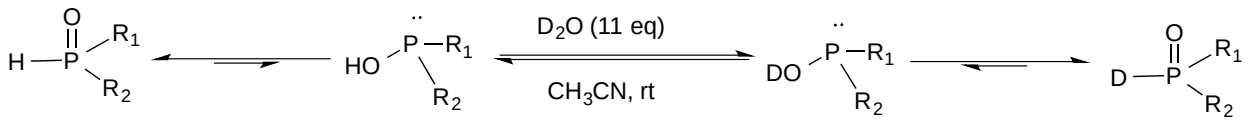
A second water molecule enables a less strained transition state and further lowers the overall barrier despite the entropic penalty to complexation.

2.2.2 Tautomerization and Deuteration

Deuteration of phosphinylidenes in D_2O is directly correlated with tautomerization because it must involve the formation of the P(III) tautomer to work. Figure 2.1 shows that tautomerization catalyzed by 1-2 molecules of D_2O will break a P-H bond and form a P-O-D bond. P(III) phosphinylidenes formed by other methods (uncatalyzed tautomerization, dimerization, etc) will readily exchange the P-O-H proton for deuterium. This is reasonable because direct P(O)H to P(O)D conversion would be extremely energy demanding.

Thus deuteration rates provide a more-or-less direct measure of tautomerization for the formation of P(III) isomer even though this is not directly observed. The experimental design is generalized in Scheme 2.1 and is further detailed in the experimental section. Furthermore, the reaction may be directly observed and quantified over time using ^{1}H coupled ^{31}P NMR spectroscopy as depicted in Figure 2.2. D_2O is used in excess (11 equiv) to ensure that the deuteration follows pseudo first-order reaction kinetics to give the most accurate comparison between substrates.

Scheme 2.1 Deuteration of phosphinylidene compounds using an excess of D_2O.



The deuteration of a variety of phosphinylidene substrates with alkyl, hydroxyl and aryl functional groups was studied and the decay of starting material quantified from the ^{31}P NMR spectra is plotted in Figures 2.3 and 2.4. Table 2.1 summarizes the data obtained from the plots.

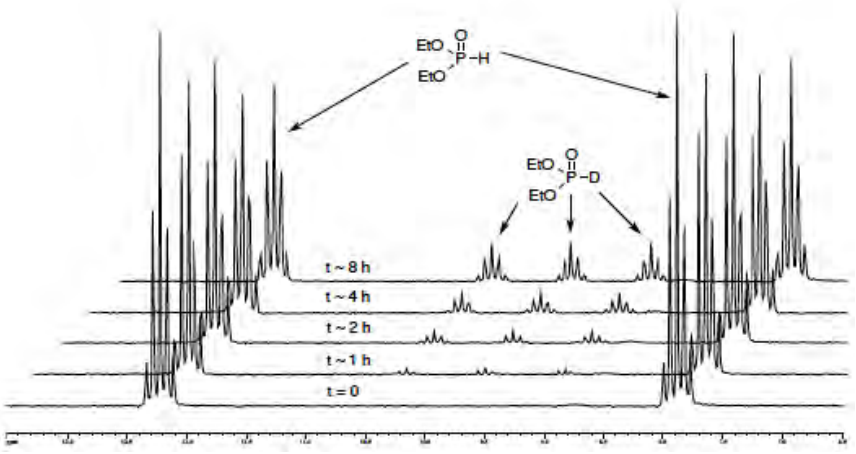


Figure 2.2 Proton coupled ^{31}P NMR spectra obtained during the deuteration of diethyl *H*-phosphonate (1 M in CH_3CN) using D_2O (11 equiv) at room temperature.

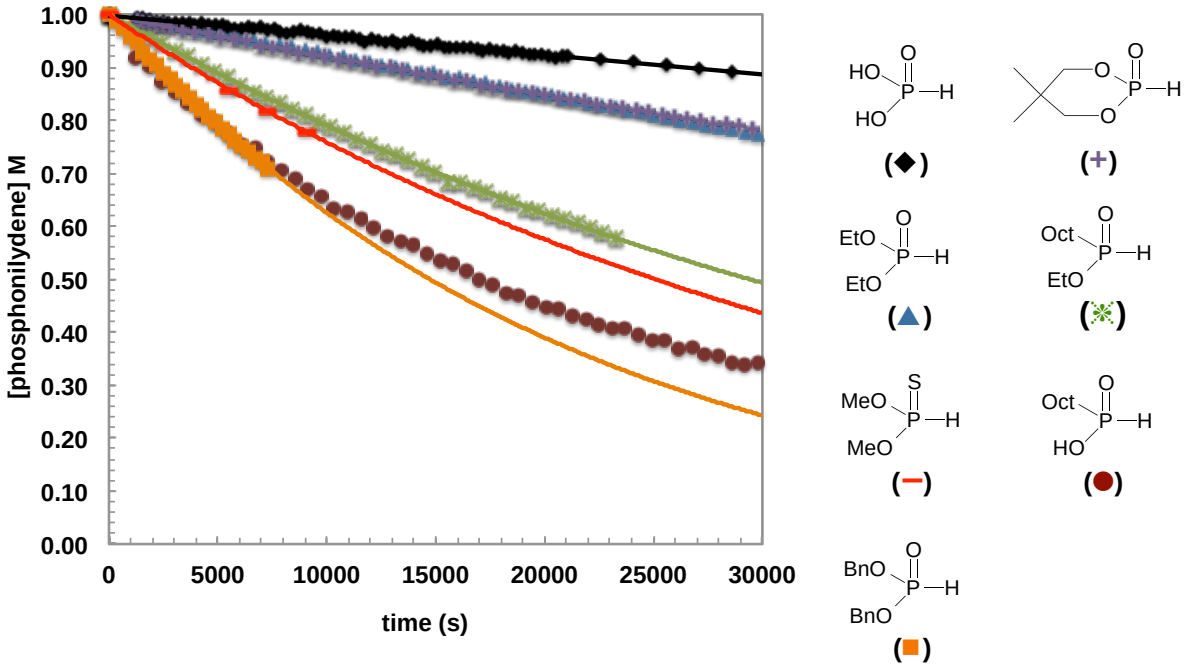


Figure 2.3 Decay of phosphinylidene compounds (1M in CH_3CN) during deuteration with D_2O (half-lives > 3 hours).

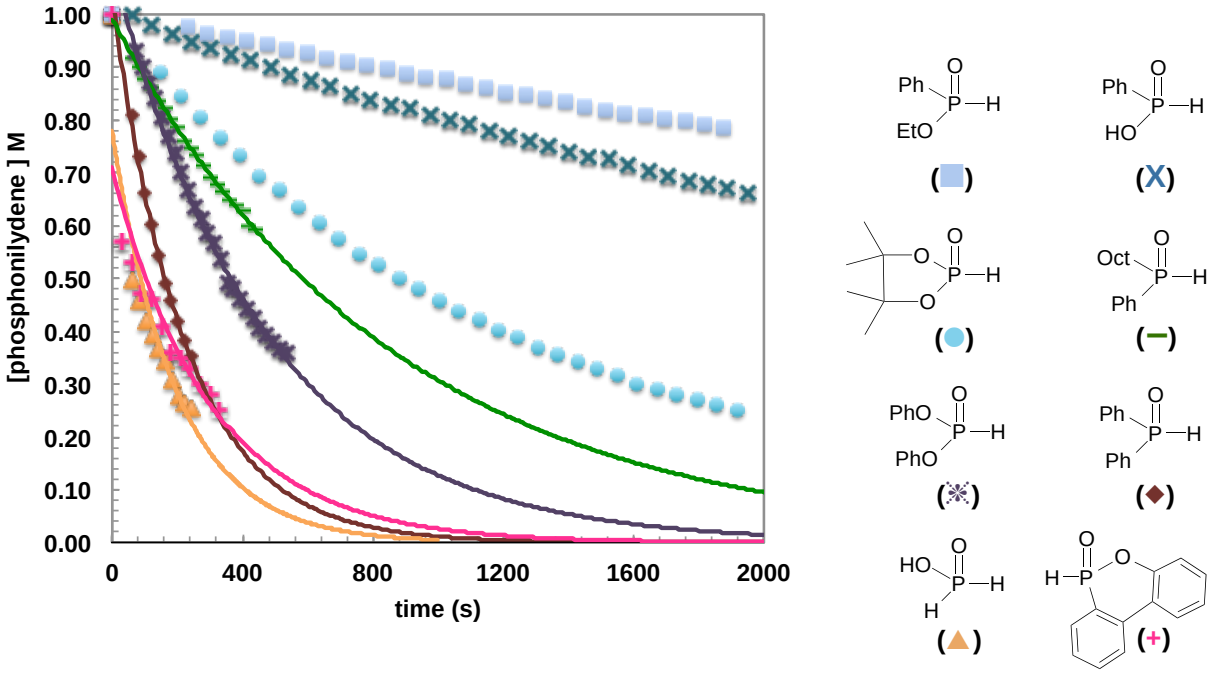


Figure 2.4 Decay of phosphinylidene compounds (1M in CH_3CN) during deuteration with D_2O (half-lives ~1 hour or less).

Of the compounds studied, both NaH_2PO_2 (entry 1) and $Bu_2P(O)H$ (entry 2) do not undergo any observable deuteration under these conditions, even after several days. This might not be surprising considering the electron-donating substituents in these compounds. Phosphorous acid (H_3PO_3, entry 3) has the longest half-life observed at around 37 h. In contrast, hypophosphorous acid (H_3PO_2, entry 16) is over 2000 times (3-orders magnitude) faster for deuteration with a half-life of only 64 s. The difference in reactivity between H_3PO_2 and H_3PO_3 is well established. Also, the 1st pK_a of H_3PO_3 is lower than that of H_3PO_2 (1.8 versus 2.0, respectively) meaning that the phosphorus atom is less positively charged in phosphorous acid at pH 7. The replacement of an –OH group with an *n*-octyl- group increases the rate of reaction by a factor of 9 (entry 8), but even better is the substitution of a Ph-group directly attached to the phosphinylidene making the rate of reaction 45 times faster (entry 11).

Table 2.1 Pseudo first-order kinetics data for the decay of starting phosphinylidene after addition of D_2O.

entry	R1	R2	Rate Constant (Ms^{-1})	Linearity (r^2)	Half -Life (s)
1	H	NaO	-	-	not observed
2	Bu	Bu	-	-	not observed
3	OH	OH	3.693×10^{-6}	0.9955	134687 (37 h)
4	EtO	EtO	7.758×10^{-6}	0.9995	64929 (18 h)
5	$(CH_3)_2C(CH_2O)_2$		9.220×10^{-6}	0.9906	54666 (15 h)
6	EtO	Oct	1.814×10^{-5}	0.9938	26689 (7.4 h)
7[a]	$(MeO)_2P(S)H$		2.354×10^{-5}	0.9968	21019 (5.8 h)
8	OH	Oct	3.259×10^{-5}	0.9807	14508 (4 h)
9	BnO	BnO	4.028×10^{-5}	0.9975	12325 (3.4 h)
10	EtO	Ph	1.146×10^{-4}	0.9857	4030 (67 min)
11	OH	Ph	1.609×10^{-4}	0.9913	2965 (49 min)
12	$[(CH_3)_2(CO)]_2$		7.211×10^{-4}	0.9980	882 (15 min)
13	Ph	Oct	1.001×10^{-3}	0.9960	498 (8.3 min)
14	PhO	PhO	1.336×10^{-3}	0.9998	373 (6.2 min)
15	Ph	Ph	3.159×10^{-3}	0.9938	155 (2.6 min)
16	H	OH	7.833×10^{-3}	0.9999	64
17	DOPO[b]		1.443×10^{-2}	0.9999	35

[a]Dimethyl *H*-thiophosphonate. [b] DOPO = 6*H*-Dibenzo[*c*,*e*][1,2λ^5]oxaphosphinine 6-oxide.

Thus, the special reactivity of aryl-substituted phosphinylidenes over alkyl-substituted ones is clearly confirmed. Compounds with only alkyl or aryl group substituents further increase the rate of reaction by an order of magnitude with the half-life of diphenylphosphine oxide (entry 15) at only 2.6 minutes and octylphenylphosphine oxide is a little slower at 8.3 minutes (entry 13) as expected given that the octyl group is electron donating and the phenyl group is electron withdrawing.

Diethyl *H*-phosphonate (entry 4) had the slowest rate of reaction with a half-life of 18 h; however the half-life decreased slightly to 15 h for the more strained cyclic neopentylene *H*-phosphonate (entry 5). Dibenzyl *H*-phosphonate reacted faster (entry 9), while diphenyl *H*-

phosphonate (entry 14) reacted the fastest. Again, this is expected based on electronic effects, and is confirmed experimentally.[21] Replacement of one ethoxy with a *n*-octyl group, decreases the half-life by 2.4 times (entry 6), a replacement with a phenyl group (entry 10) further increases the rate of deuteration (16 times over diethyl *H*-phosphonate). Dimethyl thio-*H*-phosphonate (entry 7) shows an increase in the deuteration rate consistent with less stabilization of the positive charge at phosphorus by the sulfur atom. Parsons also noted this increase in reactivity and even reported DFT calculations (B3LYP/6-31G(d,p)) of theoretical bond dissociation energies (BDE) for various phosphonates, phosphine oxides, thiophosphonates and phosphine sulfides that showed a similar trend (Figure 2.5).[133]

Pinacol-*H*-phosphonate (entry 12) showed comparable reactivity to many of the aromatic phosphinylidene compounds with a half-live of 15 minutes, which is approximately 75 times faster than $(EtO)_2P(O)H$ (entry 4) and 200 times faster than phosphorous acid (entry 3). Han and Tanaka specifically noted and studied the increased reactivity of the pinacol *H*-phosphinate in the development of their palladium- catalyzed hydrophosphinylation of alkenes[134] and their

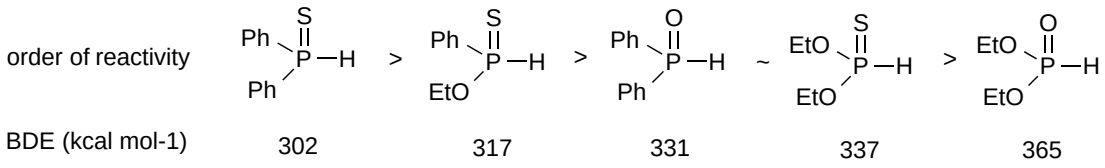


Figure 2.5 Calculated BDE's of various hydrogen-phosphorus compounds.

rhodium-catalyzed hydrophosphinylation of terminal alkynes.[135] Although conjectural at this point, relief of ring strain caused by steric hindrance between the four methyl groups appears to be the driving factor for increased rate of deuteration. In comparison, the less strained neopentyl phosphinate has a half-life closer to diethyl phosphite (entry 5).

Computational studies of the H_2O-catalyzed tautomerization of various phosphinylidenes largely match the trends in experimental deuteration rates.[136] Table 2.2 compares experimental half-lives with calculated energies and barriers for P(V)->P(III) tautomerization. To decrease computational time, a simplified model, MeP(O)(OMe)H, was used for the calculations.

Table 2.2 Experimental deuteration half-life (s) and calculated uncatalyzed and H_2O-catalyzed tautomerization Gibbs free energies and barriers (kcal mol^{-1}) of various phosphinylidenes.

		Uncatalyzed		Water-catalyzed		
R^1,R^2	Half-life	Barrier	Energy	Complexation	Barrier	Energy
Me, Me	-	64.6	7.8	3.0	40.1	11.2
Ph, OH	2960	64.8	9.2		42.3	
EtO,Oct	26689	64.1	10.2	3.7	42.9	12.1
BnO, BnO	12375					
Oct, OH	14508	64.1	9.8		44.2	
EtO,EtO	64929	64.6	10.2	4.7	43.9	10.5
Ph,Oct	498	63.3	7.2	3.6	40.1	9.5
PhO,PhO	373	62.8	8.7	5.5	41.0	7.5
Ph,Ph	155	63.4	6.8	4.3	40.2	7.2
H,ONa	-	62.1	23.3	1.8	37.8	22.6
H,OH	64	64.0	7.0	4.9	41.1	6.4
DOPO	35	59.4	7.4	7.0	39.4	13.5
H,H	-	58.5	-1.1	4.1	34.0	-0.4

For the most part, the calculated uncatalyzed and water-catalyzed tautomerization barriers qualitatively agree with the experimental half-lives. Besides H_3PO_2, Ph- and PhO-groups give relatively short deuteration half-lives and the lowest tautomerization barriers for the series of alkyl- or arylated phosphinylidenes. Figure 2.6 graphically illustrate the good correlation between the calculated barriers and the half-lives of the various phosphinylidene compounds.

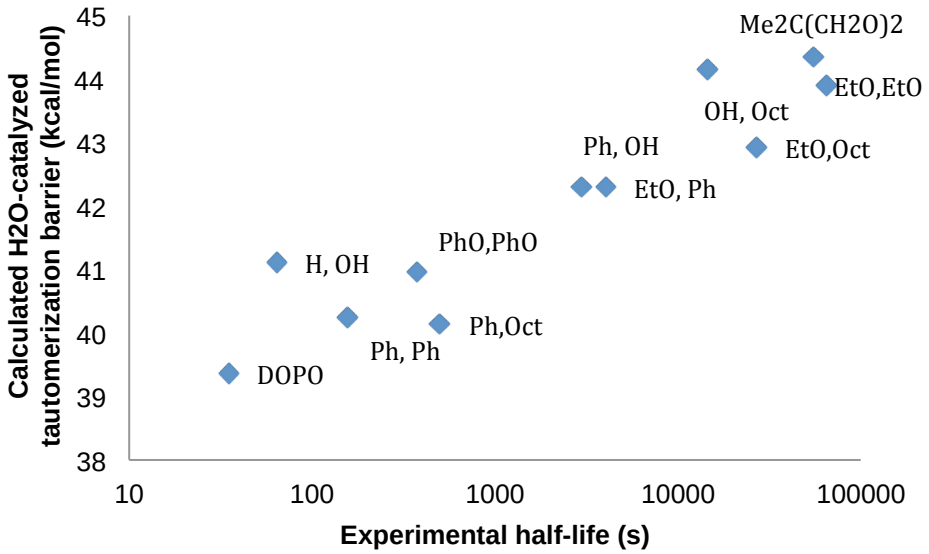
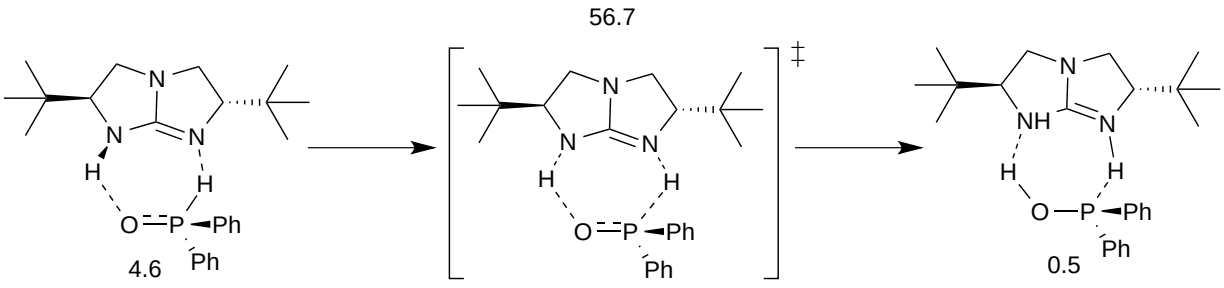


Figure 2.6 Calculated catalyzed (by one molecule of water) barriers vs. experimental half-lives

2.2.3 Influence of Organic Catalysts on Tautomerization

As noted previously, Brønsted acids and bases have been utilized to stabilize the P(III) tautomer and thereby increase the reactivity of the phosphinylidene for the target reaction. In a recent computational study, Wong et al. showed the stabilization of the P(III) tautomer for diphenylphosphine oxide using a chiral bicyclic guanidine catalyst as applied to an asymmetric phospha-Michael reaction (Scheme 2.2). To note, the guanidine acts as both a Brønsted acid and

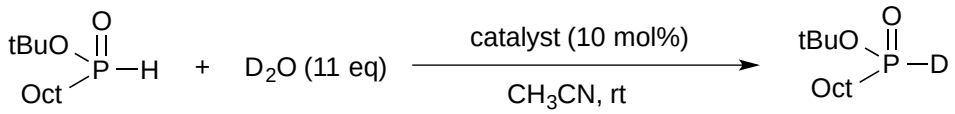
Scheme 2.2 Tautomerization pathway as influenced by bicyclic guanidine catalyst. Gibbs free energy values (233 K) reported in kcal mol^{-1}.



base in this example.[130]

In the same regards, a variety of different organic acids and bases were tested to understand their influence on the rate P(V) to P(III) tautomerization with the deuteration of an alkyl *H*-phosphinate or *H*-phosphonate as the model reaction (Scheme 2.3).

Scheme 2.3 Deuteration of *tert*-butyl octylphosphinate using an excess of D_2O and 10 mol% catalyst.



For the catalyst studies, *tert*-butyl octylphosphinate was also chosen as the model compound due to its desirable half-life of ~8 hours (no additive) reducing amount of instrument time needed. The *tert*-butyl ester was chosen to protect the compound against de-alkylation that is typically observed when using strong bases. Data collected from the ^{31}P NMR kinetics experiments are presented in Figure 2.7 and summarized in Table 2.3. Bicyclic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was one of the first catalysts tested and a highly accelerated rate of deuteration was observed with the half-life calculated at only 32 seconds or 861 times faster than the control experiment with no additive (entry 13). Tetramethylguanidine (TMG) showed a slower rate of deuteration at 8.8 minutes, but this is still very fast when comparing the 39-fold increase in reaction rate with the control (entry 12). Next, neutral thiosaccharin (TS) increased the rate of reaction approximately 10 times over the control with half-life measured at 41 minutes (entry 11). As a basis of comparison, saccharin (SC) was also screened and the reaction was five times less reactive than thiosaccharin at 4.1 hours (entry 3). More computational studies are needed, though, to understand how the interraction between the thiosaccharin and the phosphinylidene

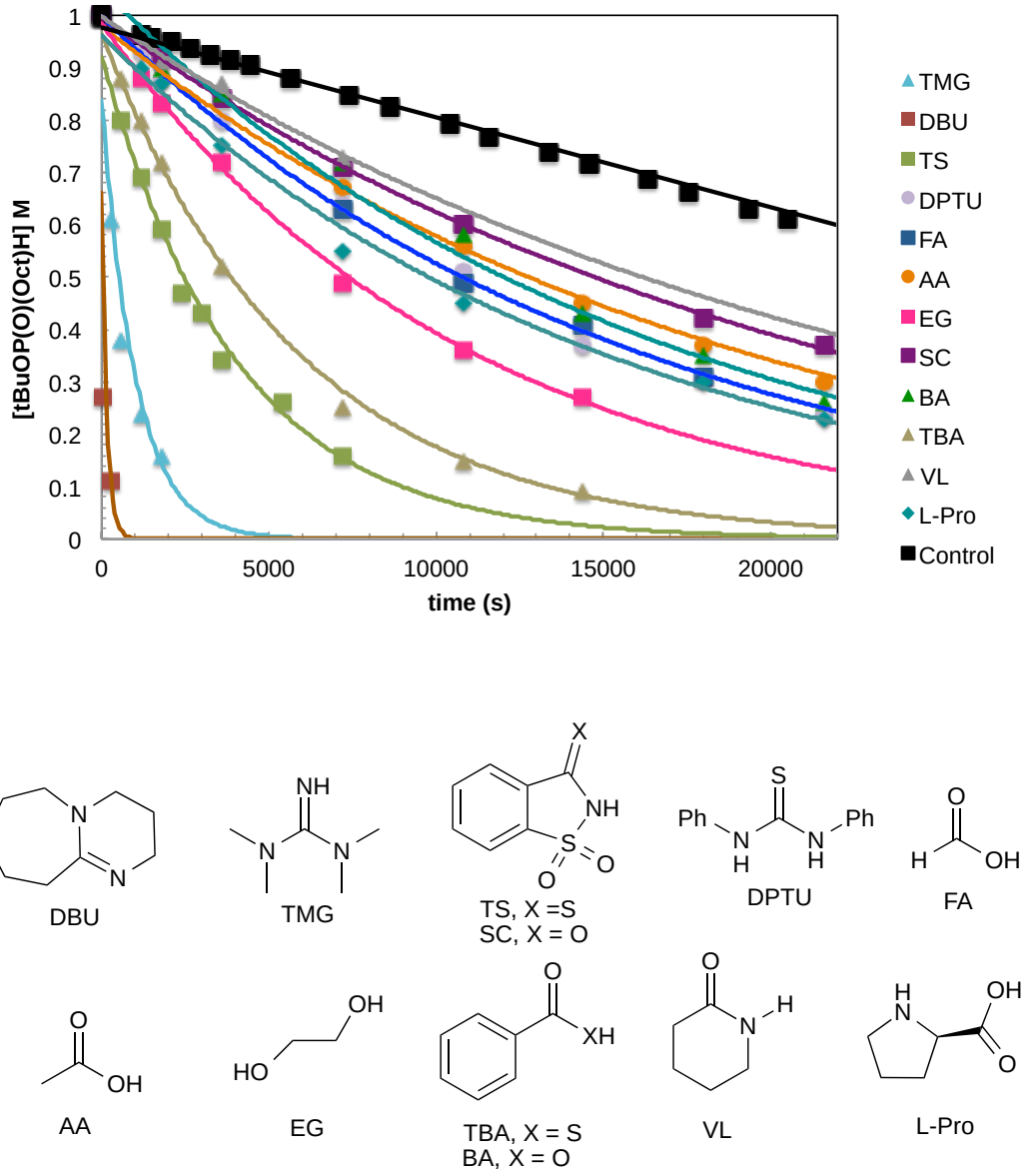


Figure 2.7 Decay of *tert*-butyl octylphosphinate (1M in CH_3CN) during deuteration with D_2O catalyzed by various organic compounds. No additive was used in the control experiment.

stabilizes the P(III) tautomer. The reaction rates between thiobenzoic acid (TBA, entry 10) and benzoic acid (BA, entry 5) showed similar differences in reaction rates with the half-life of decay 1.1 hours for thiobenzoic acid and 3.3 hours for benzoic acid. Using ethylene glycol (EG) resulted in a calculated half-life of 2.1 hours (entry 9), and an increase in reactivity of *H*-phosphinates using ethylene glycol has already been noted in our previous work with palladium-

catalyzed cross coupling and hydrophosphinylation reactions (See Chapter 1, Eqs. 1.30 and 1.33).[111,114] Formic acid (FA), diphenylthiourea (DPTU) and L-proline (L-pro) all showed very close rates of reactions with half-lives ranging from 2.7 to 3 hours or approximately 2.5 times faster than the control experiment (entries 6-8).

Table 2.3 Kinetics data for decay of *tert*-butyl octylphosphinate after addition of D_2O using various catalysts.

entry	Catalyst[a]	Rate Constant (Ms^{-1})	Linearity (r^2)	Half -Life (s)	Rate factor[b]
1	none (control)	2.533×10^{-5}	0.9977	27922 (7.8 h)	-
2	VL	4.268×10^{-5}	0.9896	16179 (4.5 h)	1.7
3	SC	4.678×10^{-5}	0.9990	14738 (4.1 h)	1.8
4	AA	5.266×10^{-5}	0.9968	12771 (3.6 h)	2.1
5	BA	6.173×10^{-5}	0.9891	12030 (3.3 h)	2.4
6	FA	6.418×10^{-5}	0.9978	10789 (3.0 h)	2.5
7	DPTU	6.627×10^{-5}	0.9979	10583 (2.9 h)	2.6
8	L-Pro	6.679×10^{-5}	0.9946	9790 (2.7 h)	2.6
9	EG	9.168×10^{-5}	0.9980	7387 (2.1 h)	3.6
10	TBA	1.702×10^{-4}	0.9958	3862 (1.1 h)	6.7
11	TS	2.473×10^{-4}	0.9885	2466 (41 min)	9.8
12	TMG	9.852×10^{-4}	0.9575	525 (8.8 min)	39
13	DBU	2.182×10^{-2}	0.9999	32	861

[a]VL = δ-valerolactam; SC = saccharin; AA = acetic acid; BA = benzoic acid; FA = formic acid; DPTU= diphenylthiourea; L-pro = L-proline; EG = ethylene glycol; TBA = thiobenzoic acid; TS = thiosaccharin; TMG = tetramethylguanidine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] The rate factor is defined as rate constant (catalyst)/ rate constant (control).

Even simple acetic acid (AA) increased the rate of deuteration with a half-live of 3.6 hours (entry 4). Using δ-valerolactam (VL) as an additive resulted in a half-life of 4.5 hours (entry 2) similar to the result with saccharin, which is also a cyclic amide. The slight decrease in reaction rate for saccharin suggests that a locked conformation using a fixed ring system and

smaller ring size help the bonding between the additive and the phosphinylidene compound that ultimately increases the efficiency of the P(V) to P(III) tautomerization.

Preliminary DFT calculations for several of the catalysts have been completed by a collaborator and are reported in Table 2.4. The logarithm of the half-life is also reported in the table as an estimate of the barrier heights according to Arrhenius theory. The computations show a good correlation between the half-life and energy barriers with two outliers: thiosaccharin and tetramethylguanidine. In these cases, multiple mechanisms may be involved in the catalysis of tautomerization due to the compounds' dual acid/base functionality. The calculation for thioformic acid (ThFA) reveal the lowest energy barrier and is included as basis of comparison with other catalysts that have tautomeric forms such as thiosaccharin (HN-C=S to N-C-SH) and thiobenzoic acid (HO-C=S to O=C-SH).

Table 2.4 Experimental deuteration half-life (s) in comparison to calculated energy barriers (kcal mol-[1]) of various organic catalysts.

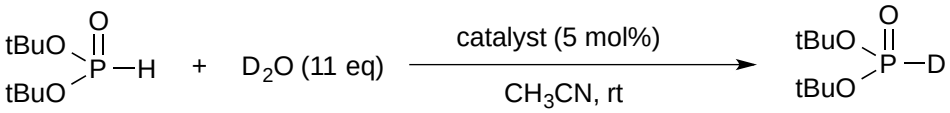
Catalyst[a]	Half-life (s)	ln (Half-Life)	$\Delta E^{\ddagger}$(C)
H_2O (control)	27922	10	39.6
VL	16179	9.7	23.7
SC	14738	9.6	21.7
BA	12030	9.4	21.5
FA	10789	9.3	20.8
TBA	3862	8.3	19.0
ThFA	-	-	17.9
TS	2466	7.8	21.5
TMG	525	6.3	29.1

[a]VL = δ-valerolactam; SC = saccharin; BA = benzoic acid; FA = formic acid; TBA = thiobenzoic acid; ThFA = thioformic acid; TS = thiosaccharin; TMG = tetramethylguanidine.

Unfortunately, thioformic acid is a thermally unstable compound at room temperature[137] and the acquisition of kinetic data could not be obtained experimentally for this additive.

To determine if the trend of catalyst performance remains the same with a different phosphinylidene substrate, deuteration of di-*tert*-butyl phosphite was investigated using the most active catalysts studied with *tert*-butyl octylphosphinate (Table 2.4). In this set of experiments, an excess of D_2O was used but the catalyst amount was reduced to 5 mol% (Scheme 2.5). Figure 2.8 shows the plotted data of the experiments run and Table 2.6 summarizes the kinetics data. The first observation was that the di-*tert*-butylphosphite has a faster rate of deuteration of a half-life of 14 hours with no additive (Table 2.5, entry 1) compared with diethyl phosphite at 18 hours (Table 2.1, entry 4). Because the *tert*-butyl group is more electron donating, a longer half-life was expected. The steric strain relief to P(III) may contribute to the approximately 1.5 times acceleration in the reaction, but this needs to be investigated further. Not surprisingly, DBU provided the fastest rate of deuteration with a half-life of 64 s or approximately 700 times faster than the control (entry 5).

Scheme 2.5 Deuteration of di-*tert*-butyl phosphite using an excess of D_2O and 5 mol% catalyst.



Tetramethylguanidine also catalyzed the rate of deuteration rapidly with a 2.7 minutes half-life. Notably, the rate factor is much higher at 279 times increase in rate compared with tert-butyl octylphosphinate (Table 2.3, entry 12), but that substrate also has a shorter baseline half-life with no additive. Thiosaccharin was slower as a catalyst with only a 5.6 hour half-life (entry 3). Although the increase in the rate of reaction does not appear to be substantial, this experiment shows that thiosaccharin could be a good mild base to use in reactions that use phosphinates with ester groups that react with strong bases such as DBU and tetramethylguanidine. The use of

ethylene glycol did not increase the rate of reaction significantly with a half-life of only 12 hours (entry 2).

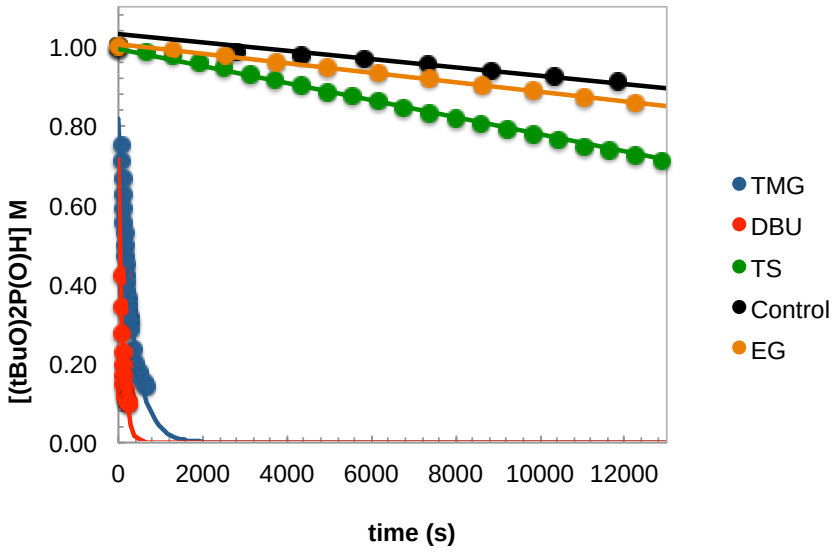


Figure 2.8 Decay of di-*tert*-butyl phosphite (1M in CH_3CN) during deuteration with D_2O catalyzed by various organic compounds.

Table 2.5 Kinetics data for decay of Di *tert*-butyl phosphite after addition of D_2O using various catalysts.

entry	Catalyst	Rate Constant (Ms^{-1})	Linearity (r^2)	Half -Life (s)	Rate factor[b]
1	none (control)	1.052×10^{-5}	0.9955	50485 (14 h)	-
2	EG	1.203×10^{-5}	0.9994	42028 (12 h)	1.1
3	TS	2.401×10^{-4}	0.9954	20162 (5.6 h)	23
4	TMG	2.937×10^{-3}	0.9914	163 (2.7 min)	279
5	DBU	7.511×10^{-3}	0.9903	64	714

[a]EG = ethylene glycol; TS = thiosaccharin; TMG = tetramethylguanidine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b]The rate factor is defined as rate constant (catalyst)/ rate constant (control).

Given the promising result with the initial phosphinate substrate (Table 2.4, entry 9), it is speculated that the steric bulkiness of *tert*-butyl phosphite may also cause less efficient binding to the catalyst.

2.2.4 Bonding of the Catalysts with the Phosphinylidene

Understanding the lowering of tautomer transition state energies between the phosphinylidene compound and the catalyst is necessary to understand what makes the catalyst efficient. Furthermore, hard/soft acid/base interactions between phosphinylidene tautomers and catalyst are also important to consider. Figure 2.9 shows the binding motifs for top five catalysts that increased the rate of deuteration significantly. DBU appears to stabilize the direct transfer of proton from the phosphorus to oxygen being very basic.

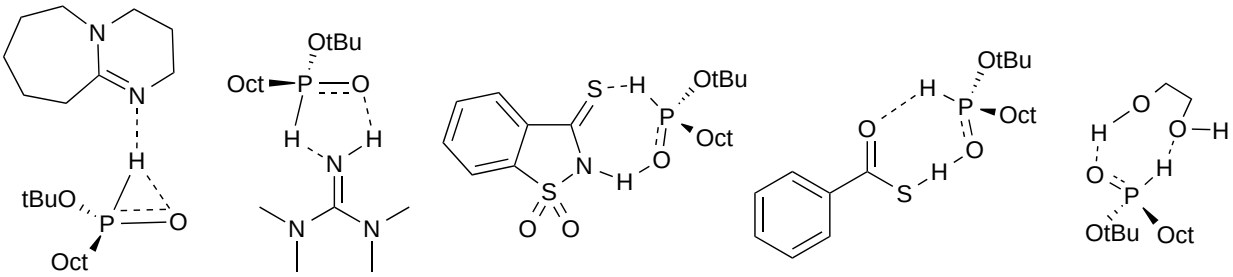


Figure 2.9 Binding motifs between *tert*-butyl octylphosphinate and several catalysts.

A computational model using the analogous base trimethylamine and structurally simplified methyl methylphosphinate supports this hypothesis with the barrier energy lowered from 60 kcal mol^{-1} with no additive to 27 kcal mol^{-1} with the base. With the use of D_2O as a deuterating agent, water also continues to act as a catalyst in the tautomerization reaction lowering the barrier to 33 kcal mol^{-1}, but it is unknown whether water works in coordination with the other catalysts. For the remaining catalysts, each have protons that can bind to the P=O bond and allow the hard or

soft base in the molecule to bind to the proton transferring from the phosphorus to the oxygen. Tetramethylguanidine is a strong Brønsted base like DBU and its lone pair of electrons readily facilitate a transfer of hydrogen from the phosphorus to the oxygen. Thiosaccharin also appears to form a nice complex with the phosphinate, although two possible tautomer structures are possible for the catalyst (Figure 2.10). In rationalizing the good performance as a catalyst, the tautomeric binding structure appears to be the more plausible as the lone pair of electrons on the amine would make it a harder base and more capable of stabilizing the transferring P-H hydrogen. Similarly, thiobenzoic acid provides two binding motifs with the top structure (Figure 2.11) the most likely complex since that compound is more stable with the acidic hydrogen on the sulfur versus the oxygen, and this is well documented.[138] Ethylene glycol appears to work as a decent catalyst because its hydroxyl groups have dual functionality: One hydroxyl group binds to the P=O bond and the second hydroxyl H-group acts as a weak base to facilitate the P(V) to P(III) tautomerization.

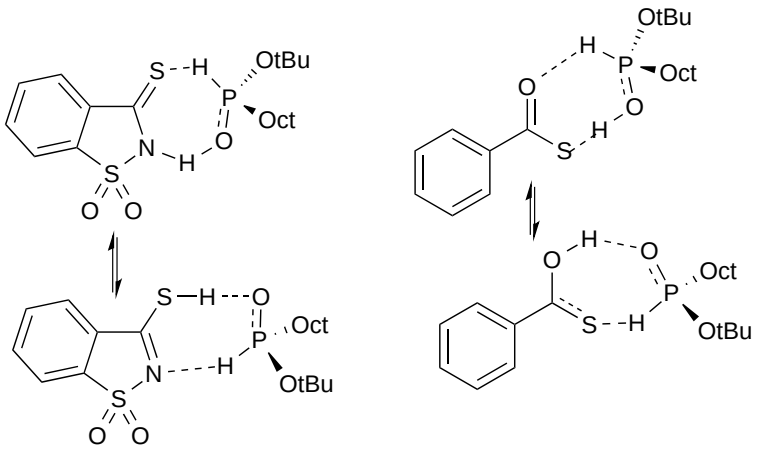


Figure 2.10 Phosphinate binding to tautomeric structures of thiosaccharin and thiobenzoic acid.

A computational study was also completed through a collaboration to understand the hard/soft acid and base interactions using H_3PO and H_3PS as simplified phosphinylidene models to give a

better idea of the type of functionalities that make an optimal tautomerization catalyst. Table 2.6 summarizes the data for the energies of binding (ΔE_b), reaction (ΔE_r), barrier relative to the most stable complex ($\Delta E^{\ddagger}(C)$), dissociated reactants ($\Delta E^{\ddagger}(DR)$) and the overall barrier ($\Delta E^{\ddagger}(DR) = \Delta E^{\ddagger}(C) - \Delta E_b$) as obtained from gas-phase DFT calculations.

First to note is the difference in overall barrier energies $\Delta E^{\ddagger}(DR)$ between H_3PO and H_3PS (28.2 vs. 24.9 kcal mol^{-1}) are in agreement with the kinetics results presented in Table 2.2 for analogous compounds $(EtO)_2P(O)H$ and $(MeO)_2P(S)H$ and the calculated BDE's in Figure 2.5. The calculations are completed for the P(V) tautomer-catalyst interaction of H_3PO which has a soft acid (P-H) and hard base (P=O). In comparing the catalyst with soft base and hard acid compound HC(=S)OH (entry 4) has the lowest calculated $\Delta E^{\ddagger}(DR)$ at 4.4 kcal mol^{-1}. For H_3PS that contains a soft acid (P-H) and soft base (P=S), but hard acid/hard base HCOOH (entry 9) has the lowest calculated $\Delta E^{\ddagger}(DR)$ at 9.7 kcal mol^{-1}.

Table 2.6 Calculated catalyst-P(V) Energies (kcal mol-1).

Molecule	**entry**	**Catalyst**	**ΔE_b**	**$\Delta E^{\ddagger}$ (C)**	**$\Delta E^{\ddagger}$ (DR)**	**ΔE_r**	**Acidity/Basicity[a]**
H_3PO	1	None	-	62.3	-	-0.3	-
	2	H_2O	-6.2	34.5	28.2	-0.1	-
	3	HCOOH	-12.8	17.5	4.7	2.9	HA/HB
	4	HC(=S)OH	-10.3	14.7	4.4	3.2	HA/SB
	5	HC(=O)SH	-7.3	14.6	7.3	0.7	SA/HB
	6	HCSSH	-6.6	12.9	6.3	0.6	SA/SB
H_3PS	7	None	-	47.0	-	-3.7	-
	8	H_2O	-4.5	29.3	24.9	-1.7	-
	9	HCOOH	-8.2	17.9	9.7	-0.4	HA/HB
	10	HC(=S)OH	-4.9	16.9	12.0	-1.6	HA/SB
	11	HC(=O)SH	-5.0	16.7	11.7	-1.0	SA/HB
	12	HCSSH	-4.0	15.9	11.9	-2.0	SA/SB

[a] HA = hard acid; HB = hard base; SA = soft acid; SB = soft base

To note, the calculations do not necessarily follow the trends that are expect with H_3PO the energy barrier height would follow: HC(=O)SH > HCOOH ~ HCSSH > HC(=S)OH. For H_3PS, the expected energy barrier height would follow: HCOOH > HC(=O)SH ~ HC(=S)OH > HCSSH.

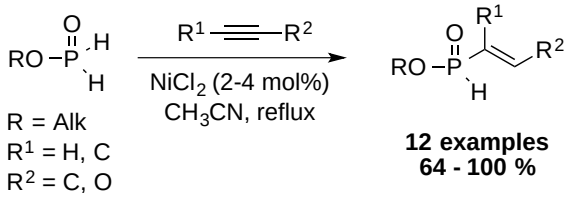
2.3 Conclusion

The present chapter was used to highlight the synergistic computational and experimental studies used to understand P(V) to P(III) tautomerizaton. Gratifyingly, the computational energy barrier data mostly followed the same trend as the half-lives acquired by ^{31}P NMR. In the first part, the data unequivocally demonstrated special and accelerated reactivities for phosphonylidenes containing phenyl groups and strained sterically bulky rings. The second half of this chapter was used to demonstrate how computational chemistry, in collaboration with an expert in the field, may be used to help understand and develop efficient tautomerization catalysts via calculating the transition state energies of phosphinylidene-catalyst complexes. Strong bases such as DBU and tetramethylguanidine provide the most accelerated reactions, but cannot be used broadly with phosphorus compounds with base-labile groups. The computational studies showed that neutral thiosaccharin and related thioamide compounds are promising as mild tautomerization catalysts because of their favorable acid/base interactions with the phosphorus tautomers. Expanded experimental and computational investigations are needed to understand how ethylene glycol works as a decent catalyst. Based on the initial calculations, analogues of ethylene glycol containing a longer spacing alkyl chain and a Lewis base should work well. The study of chiral additives for asymmetric catalysis of phosphinylidenes is also of interest.

Chapter Three: Nickel-catalyzed Hydrophosphinylation of Alkenes

3.1 Introduction

As summarized in Chapter 1, extensive studies of palladium-catalyzed hydrophosphinylation of unsaturated hydrocarbons with hypophosphorous acid derivatives were completed.[79,80] Although the methodology developed was very efficient and used catalyst loading ≤ 2 mol%, a catalyst system using cheaper nickel salts was desired. In 2005, an inexpensive and straightforward nickel chloride-catalyzed addition of phosphinates to terminal and internal alkynes was reported (Eq. 3.1).[139] In this reaction $ROP(O)H_2$ plays several roles: a) reagent, b) reducing agent to activate the nickel pre-catalyst, c) ligand to stabilize the Ni(0) catalyst, and d) as a drying agent when $NiCl_2$-hydrate or moisture is present.[139]



(Eq. 3.1)

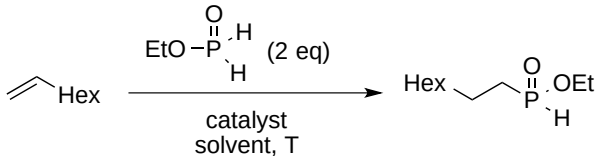
Unfortunately, hydrophosphinylation of alkenes under similar conditions was not very successful (^{31}P-NMR yield < 70%) and not competitive with the palladium-catalyzed version developed.[79,139] Often in nickel catalysis, $Ni(cod)_2$ is the precursor, but it is an expensive ($Ni(cod)_2$ =$8761/mol; $PdCl_2$=$5267/mol based on current costs from Sigma-Aldrich) and a highly air-sensitive species requiring a glove box and related stringent inert atmosphere techniques. On the other hand, nickel chloride (anhydrous salt, $80/mol, Sigma-Aldrich) is cheaper than palladium salts and its complexes by two orders of magnitude. The following chapter will summarize the progress with nickel-catalyzed hydrophosphinylation and the successful addition of phosphinates to unactivated alkenes catalyzed by nickel chloride, in the presence of an external phosphine ligand.

3.2 Results and Discussion

3.2.1 Reaction Optimization

For the study of $NiCl_2$-catalyzed hydrophosphinylation of alkenes, the model substrate chosen for an unactivated olefin was 1-octene. Ethyl phosphinate was prepared via our alkoxysilane method and used as a 0.5 M stock solution.[18] Various conditions and catalysts were investigated as shown in Table 3.1. As previously reported,[139] $NiCl_2$ alone does not work well with 1-octene (entry 1), but under similar conditions $Cl_2Ni(PPh_3)_2$ is more successful (entry 5),

Table 3.1 Nickel catalysis in the hydrophosphinylation of 1-octene with $EtOP(O)H_2$.



Entry	Solvent, T	Catalyst	^{31}P-NMR yield %[a]
1	$PhCH_3$, rt	$NiCl_2$ (3 mol %)	25
2	CH_3CN, reflux	$Cl_2Ni(PPh_3)_2$ (4 mol %)	30
3	THF, reflux	$Cl_2Ni(PPh_3)_2$ (5 mol %)	47
4	$PhCH_3$, reflux	$Cl_2Ni(PPh_3)_2$ (4 mol %)	45
5	$PhCH_3$, rt	$Cl_2Ni(PPh_3)_2$ (4 mol %)	65
6	$PhCH_3$, rt	$NiCl_2$ (5 mol %) PPh_3 (20 mol %)	61
7	$PhCH_3$, rt	$Ni(PPh_3)_4$ (3 mol %)	0
8	$PhCH_3$, reflux	Cl_2Ni(dppp) (4 mol %)	20
9	$PhCH_3$, rt	Cl_2Ni(dppp) (4 mol %)	69
10	$PhCH_3$, rt	Cl_2Ni(dppe) (5 mol %)	96
11	$PhCH_3$, rt	$NiCl_2$ (3 mol %) dppe (3.3 mol %)	87
12	$PhCH_3$, rt	$NiCl_2$ (3 mol %) dppe (5 mol %)	93

[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

whereas heating in various solvents gives poorer results (entries 2-4). Addition of triphenylphosphine to $NiCl_2$ gives roughly similar results (entry 6), but the use of preformed $Ni(PPh_3)_4$ does not give any addition product (entry 7). As before, the reaction at room temperature is superior (entry 9 versus 8), but dppp (1, 3-bis(diphenylphosphino)propane) does not result in a very significant improvement over PPh_3. On the other hand, dppe gives much improved results (entries 10-12). Analysis of the reaction mixtures by gas chromatography usually indicated the complete disappearance of 1-octene with concomitant formation of octane and octene isomers as by-products, especially pronounced at higher temperatures.

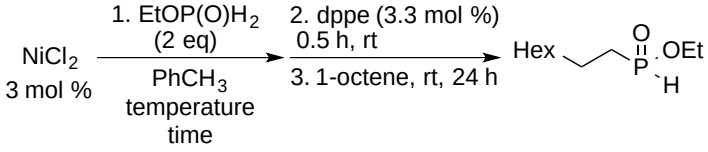
Expectedly, this indicated that transfer hydrogenation[140–148] is one of the significant competing pathways. Because alkynes are more reactive than alkenes, competing pathways in hydrophosphinylation are less of a problem, and plain $NiCl_2$ is successful.[139] The results in Table 1 also allowed for a few working hypotheses: a) toluene is a good solvent and room temperature is a requirement to maximize the yields; b) the presence of a ligand has a significant influence on alkene hydrophosphinylation, and dppe appears to be the best choice. Fortunately, dppe is also the cheapest of the bidentate phosphine ligand family ($1036/mol, Strem). Furthermore, based on our prior work with alkynes and the identification of a preactivation process,[139] we knew that the reaction of $NiCl_2$ with an alkyl phosphinate, either at room temperature or with heating, results in the formation of a nickel(0) species corresponding to $Ni[(RO)P(OH)H]_4$ (^{31}P-NMR d ~170 ppm (d, $J_{P\text{-}H}$ = 341 Hz)) in the absence of other ligands. This is not surprising since the reduction of nickel salts with phosphinates is the basis of the electroless plating process (Kanigen® process), which is responsible for the major industrial consumption of phosphinates.[149,150]

For this reason, a different experimental protocol was investigated in which the nickel catalyst precursor is first pre-reacted with the phosphinate at room temperature for 2 hours,

before the addition of 1-octene, with or without dppe as an external ligand. Results are summarized in Table 3.2. This protocol results in clear improvements over the conditions of Table 3.1 (entries 1-9), but follows up on the excellent results in Table 3.1 (entries 10–12).

Even $NiCl_2$ gives an almost 3-fold increase, though it remains a moderate yield (Table 3.2, entry 2). Preactivation of $NiCl_2$ at room temperature for 2 hours before the addition of dppe was ideal (entry 1) and the process gives comparable results when preformed $Cl_2Ni(dppe)$ is used (entry 4).

Table 3.2 Optimization of the hydrophosphinylation of 1-octene with $EtOP(O)H_2$ through preactivation.



entry	time	temp	^{31}P NMR Yield (%)[a]
1	2h	rt	100
2[b]	2 h	rt	61
3[c]	2 h	rt	57
4[d]	2 h	rt	98
5	8 h	rt	87
6	30 min	rt	59
7	2 h	85 °C	24
8	10 min	reflux	89

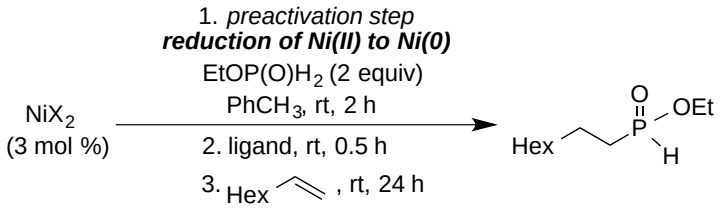
[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra. [b] Without dppe. [c] Under air. [d] $Cl_2Ni(dppe)$ was used.

Not surprisingly, when oxygen is present, the yield drops significantly as nickel (0) is air sensitive (entry 3). Longer preactivation at room temperature resulted in a small drop in yield (entry 5), but a larger one at the shorter 30 min time interval (entry 6).

Consistent with Ni(0) decomposition, this was worse when heating was applied (entry 7), however a short period of heating gave good results (entry 8).

To obtain a comparison of reactivities, other nickel catalysts and ligands were tested but failed to give better results (Table 3.3).

Table 3.3 Hydrophosphinylation of 1-octene with $EtOP(O)H_2$ through preactivation of various nickel halide catalysts and ligands.



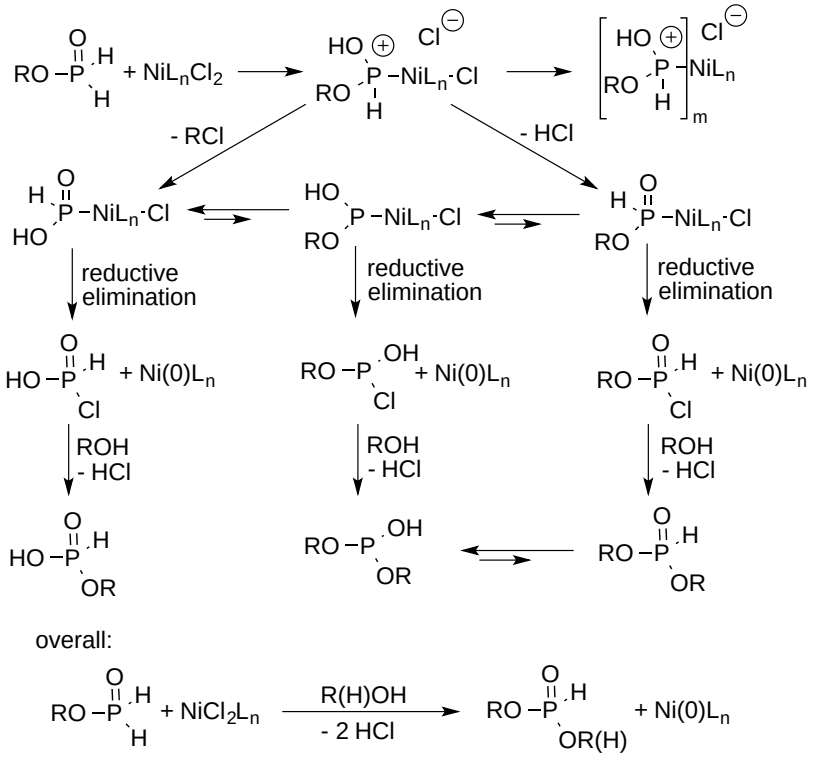
entry	catalyst[a]	^{31}PNMR Yield (%)[c]
1	$Cl_2Ni(PPh_3)_2$	17
2	$NiCl_2$ + PPh_3 (6.6 mol%)	66
3	$NiCl_2$ + PPh_3 (12 mol %)	39
4	$NiCl_2$•$6H_2O$ + dppe	72
5	$NiBr_2$ + dppe	75
6	NiI_2 + dppe	57
7	Ni on SiO_2/Al_2O_3[b] + dppe	NR
8	Cl_2Ni(dppp)	87
9	$NiCl_2$ + dppp	85
10	Cl_2Ni(dppf)	48
11	$NiCl_2$ + dppf	42

[a] 3.3 mol % of ligand used if not already pre-complexed with $NiCl_2$. [b] 65 wt % Ni. [c] NMR yields are determined by integration of all resonances in the ^{31}P NMR spectra.

3.2.2 Mechanistic Considerations

Scheme 3.1 shows possible mechanistic pathways for the reduction of the nickel(II) precursor into catalytically active Ni(0). Some alcohol (ROH) is typically present as a result of phosphinate synthesis.[18] The formation of *H*-phosphonates is always observed in the process. It should be noted that the hydrophosphonylation of alkenes that could result from their presence is not observed, even though various hydrophosphonylation processes have been described in the literature.[151,152] After intial addition of the phosphinate to the Ni(II) species, an abstraction of

Scheme 3.1 Mechanistic pathways in the formation of nickel(0) from nickel(II) species using alkyl phosphinates.



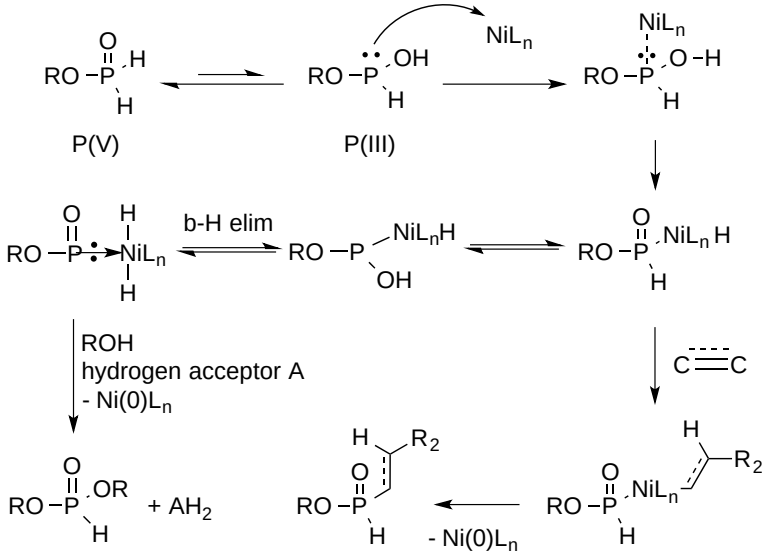
chlorine may occur either as and alkyl chloride (RCl) or hydrochloric acid (HCl). As mentioned in Chapter 2, metals stabilize the formation of the P(III) tautomer, and as mentioned previously

this is sometimes observed via downfield shift of the phosphinite in the ^{31}P NMR spectra. Because of this P(III) tautomerization, three different reductive elimination pathways of Ni(0) are possible that result in the formation of a P-Cl bond with either the P(V) phosphinate or P(III) phosphinate. The P-Cl compounds readily react with the excess alcohol in solution to form the *H*-phosphonate. The formed HCl then can re-oxidize the Ni(0) back to Ni(II) and the reaction cycle starts over.

Only alkyl phosphinates ($ROP(O)H_2$) gave good results in this reaction, as was the case with alkynes. Hypophosphorous acid or its salts did not provide any significant yield of hydrophosphinylation (results not shown). This might be due to either increased transfer hydrogenation or less efficient formation of a nickel(0) species, the former being most likely.[153]

A plausible mechanism for the nickel-catalyzed hydrophosphinylation reaction is shown in Scheme 3.2.

Scheme 3.2 Possible mechanism for the nickel-catalyzed hydrophosphinylation reaction.



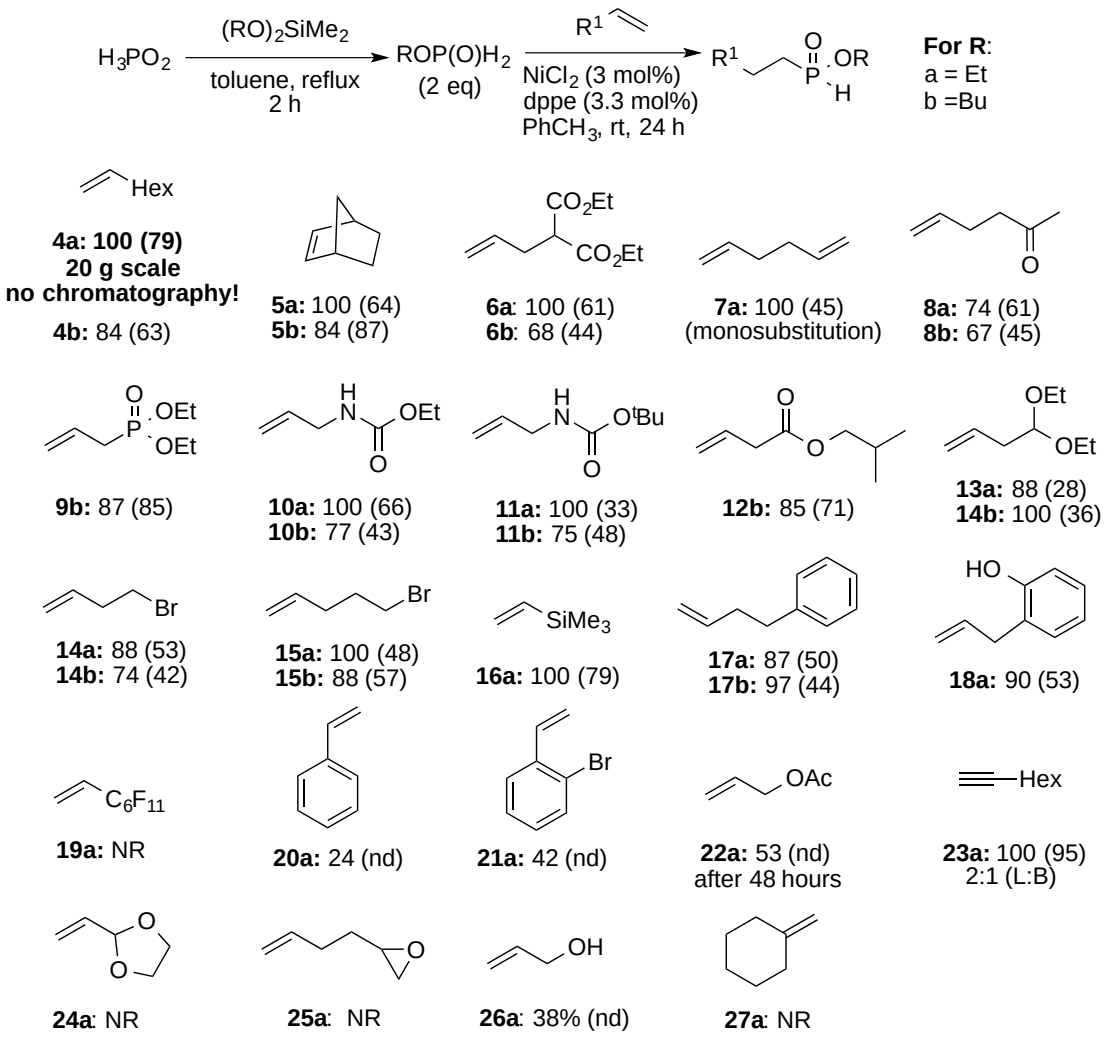
Complexation of nickel(0) to the P(III) phosphinate tautomer gives an intermediate which can either decompose to a complexed dihydride leading to transfer hydrogenation, [140–148] or a monohydride that can add to unsaturated hydrocarbons. Although an experiment using a radical

quencher was not completed, the lack of reactivity with internal alkenes such as cyclohexene rule out a free radical-based mechanism. The role of the ancillary ligand (for example dppe) would be to stabilize the Ni(0) species and prevent/slow down the formation of the dihydride through β-hydrogen elimination leading to transfer hydrogenation. Furthermore, phosphines are better at stabilizing the Ni(0) as they are better ligands than phosphinites. When alkynes are employed, a faster reaction rate allows hydrophosphinylation to take place under "ligandless" conditions.

3.2.3 Scope of the Optimized Reaction

With the above results in hand, a study of reaction scope was the logical next step. Thus, various terminal alkenes and a terminal alkyne were explored as hydrophosphinylation substrates. Scheme 3.3 summarizes the results. Ethyl phosphinate was prepared using (diethoxy)dimethylsilane, and butyl phosphinate either through the analogous alkoxysilane method, or the Dean-Stark esterification of H_3PO_2, as reported previously.[18] Reactions following the conditions of Table 2 (entry 1) were then applied. Consistently high NMR yields were observed, however, isolated yields varied significantly, due in large part to the hydrolytic sensitivity of *H*-phosphinate esters and substrate polarity during chromatographic purification on silica gel.[139] In general, the isolated yields were better for the more non-polar substrates as they have less affinity for to get adsorbed onto the acidic silica gel. Nonetheless, the present nickel-catalyzed alkene hydrophosphinylation reaction generally proceeded satisfactorily in yields often similar to our previously reported palladium-catalyzed methodology.[79] For example, hydrophosphinylation of 1-octene (**4**) was conducted on a 20-g scale, and the product was

Scheme 3.3 [a] Preliminary scope of the nickel-catalyzed hydrophosphinylation reaction.



[a] ^{31}P NMR yield (isolated yield); NR = no reaction; n.d. = not determined; L:B = linear to branched.

obtained in 79 % yield, *without any chromatography*. This was achieved by partitioning the product between acetonitrile and several washes of hexanes to remove the non-polar silicate. The only internal alkene to work with this methodology was norbornylene (**5**), but this substrate contains a strained ring system making the alkene more reactive.

Several substrates reacted poorly (<40% NMR yield) or not at all such as allyl chloride and allyl alcohol (**26**), which have more than site of reactivity and can also form π-allyl

complexes with nickel. 1*H*,1*H*,2*H*-Perfluoro-1-octene (**19**) is less reactive due to electronegative perfluorinated alkyl chain pulling electron density away from the alkene. Vinyl compounds such as styrene (**20**), 2-vinyl-1,3-dioxolane (**24**), and methylenecyclohexane (**27**) are also not reactive, although *o*-bromostyrene (**21**) shows some product formation at 42% NMR yield. Significant differences between Pd- and Ni-catalyzed reactions of phosphinates have been noticed previously.[63]

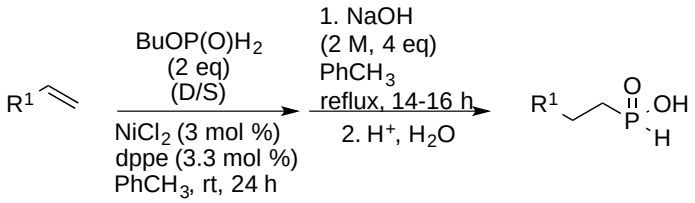
Later on it was discovered that the nickel catalyst also lowers the isolated yield through oxidation of the *H*-phosphinate product into the corresponding phosphonate monoester $R^1P(O)(OR)(OH)$. At this point, it was found that an extractive work-up using dimethylglyoxime ($C_4H_8N_2O_2$, a known nickel complexant) prior to purification helped improved the isolated yield.

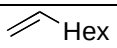
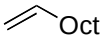
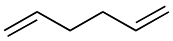
3.2.4 Nickel-catalyzed Hydrophosphinylation followed by Hydrolysis

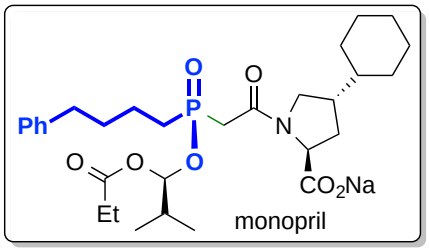
Because of the remaining occasional discrepancies between NMR yields and isolated yields in Scheme 3.3, a different protocol was investigated next for the synthesis of more stable *H*-phosphinic acids. The idea was to prepare *H*-phosphinic acids through saponification of the crude hydrophosphinylation mixture, and purification through simple acidification/extraction therefore avoiding all chromatography and associated hydrolysis of the H-phosphinate esters. The results of this study are summarized in Table 3.4.

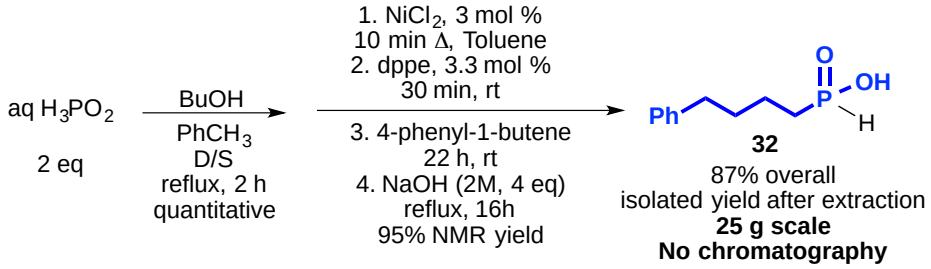
As predicted, this process not only allows for increased isolated yields but it also avoids chromatographic purification altogether. Based on the conditions shown in Table 3.4, our nickel-catalyzed hydrophosphinylation/hydrolysis sequence was investigated with 4-phenyl-1-butene as the substrate (Eq. 3.2).

Table 3.4 Nickel-catalyzed hydrophosphinylation/hydrolysis.



Compound	Alkene	^{31}P NMR yield	Isolated yield (no chromatography)
28		(90 %)	82 % (7 g scale)
29		(93 %)	70 %
30		(100 %)	87 %
31		(100 %)	81 %





(Eq. 3.2)

Monopril (fosinopril) is a (pro)drug used in the treatment of congestive heart failure (angiotensin converting enzyme (ACE) inhibitor).[154,155] Its current synthesis involves the AIBN-initiated free radical hydrophosphinylation of 4-phenyl-1-butene with H_3PO_2, but a few percent of a regioisomeric impurity (formation of the branched isomer) complicate the manufacture.[154] With the nickel-catalyzed reaction, excellent yield of product was obtained with little or no formation of regioisomer (< 0.5 % as determined by ^{31}P-NMR) on a relatively large laboratory

scale, and again without any chromatography. The bench-stable product (**32**) eventually formed crystals upon standing over time, and the first recorded X-ray structure of the compound was solved (Figure 3.1).

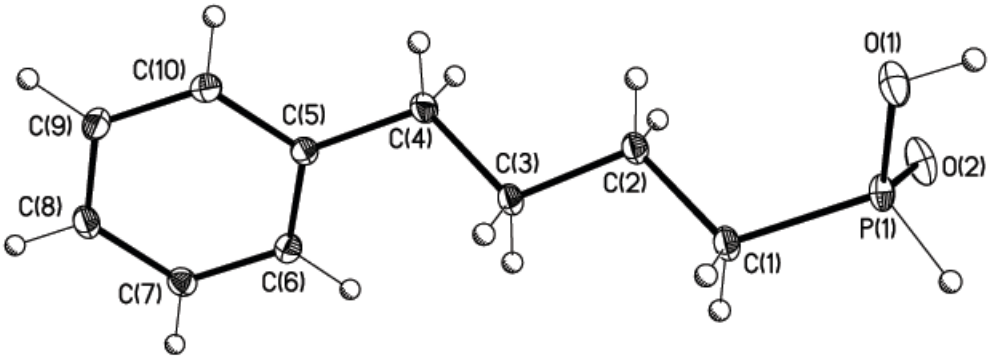


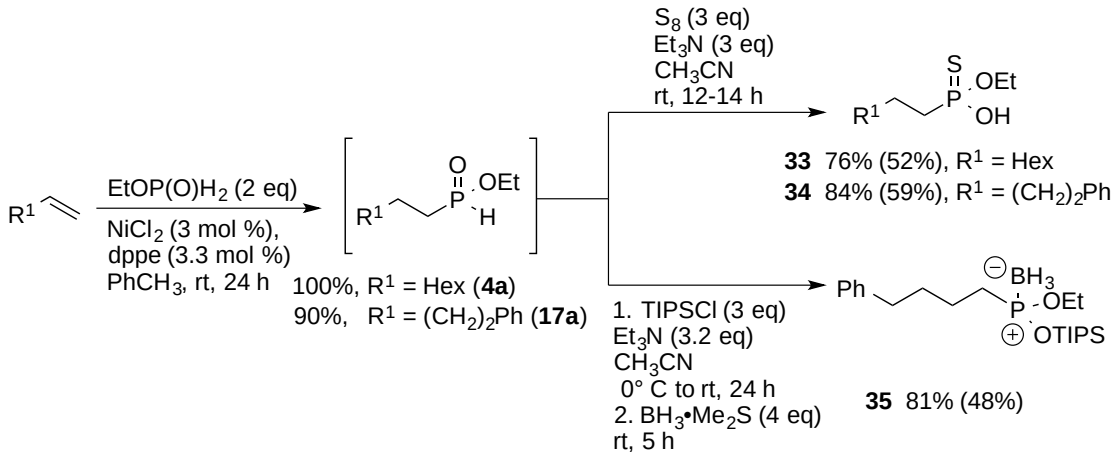
Figure 3.1 X-ray structure of 4-(phenylbutyl)-*H*-phosphinic acid (**32**).

3.2.5 Tandem Reactions

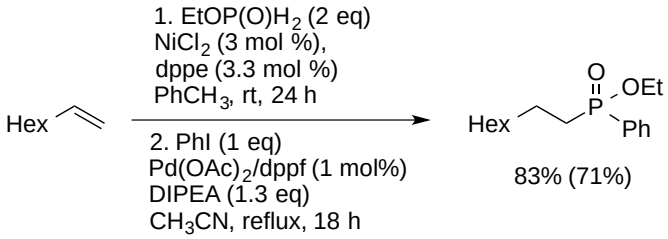
Based on the same idea, the direct conversion of crude *H*-phosphinate esters into other important organophosphorus compounds was examined next since the crude mixtures contained high yields of product. Scheme 3.4 summarizes these results. The standard nickel-catalyzed hydrophosphinylation for 1-octene (**4a**) and 4-phenyl-1-butene (**17a**) was completed and both crude products showed >90% NMR yields. Oxidative thiolation of both substrates occurred readily with elemental sulfur at room temperature under base conditions to produce the expected phosphothioic acid products in 52% isolated yield for compound **33** and 59% isolated yield for compound **34** after two steps. Tandem complexation with borane was completed on ethyl phenylbutyl-*H*-phosphinate (**17a**) using previous established procedure[53] to produce compound **35** in 48% isolated yield after two steps. Another one-pot process of interest is the cross-coupling of the intermediate *H*-phosphinate (Eq. 3.3). Various literature conditions related to the cross-

coupling of *H*-phosphinate with aryl halides have been reported.[110,111] However, in Eq. 3.3, Hirao cross-coupling conditions previously expanded by our group were employed since reactive iodobenzene was the coupling partner.[139,156]

Scheme 3.4[a] Nickel-catalyzed hydrophosphinylation/complexation sequence.



[a] ^{31}P-NMR yield (isolated yield).



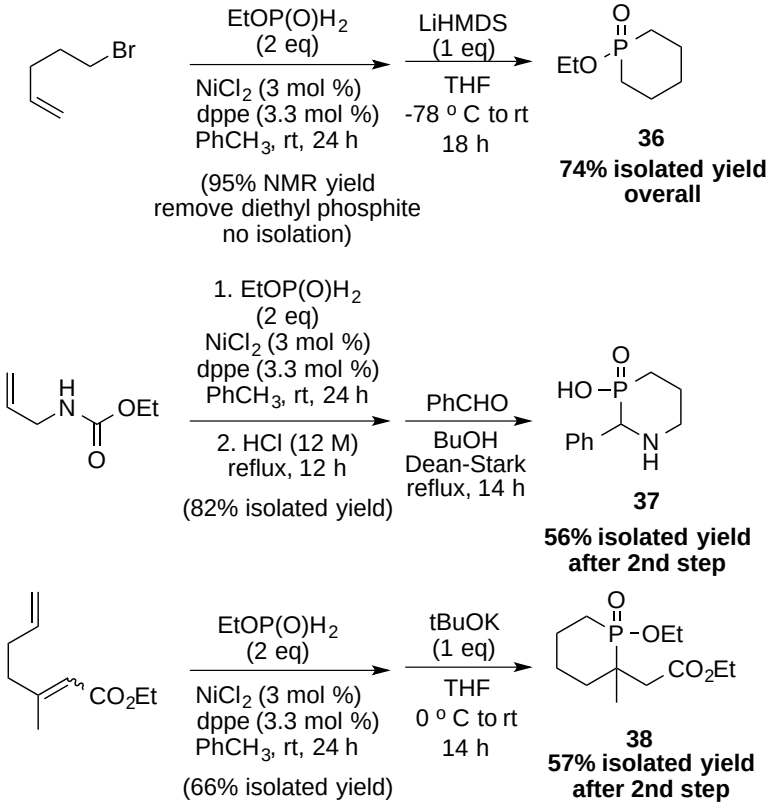
(Eq. 3.3)

Additionally, the present nickel-catalyzed hydrophosphinylation of alkenes can be employed instead of our palladium version in order to prepare various compounds more cheaply. Scheme 3.5 shows three such examples and their application to the synthesis of *P*-heterocycles.[157] Hydrophosphinylation of 5-bromo-1-pentene gives the desired addition product (**15a**) contaminated with $(EtO)_2P(O)H$, which was removed in vacuo. Addition of THF and

LiHMDS[95] to the resulting crude mixture formed the corresponding 1-ethoxyphosphorinane 1-oxide heterocycle (**36**) in good isolated yield. Addition of ethyl phosphinate to allyl carbamate followed by acid hydrolysis gives the intermediate *H*-phosphinic acid in excellent yield (actually higher than with the palladium-catalyzed methodology).[158] Heterocyclization using the Kabachnick-Fields protocol[158,159] gave the corresponding *P*,*N*-heterocycle (**37**) uneventfully, as we reported previously.[158] Finally, hydrophosphinylation of the terminal alkene of methyl (*E*)-3-methyl-2,6-heptadienoate,[160] followed by cyclization through conjugate addition delivered the substituted phosphorinanic ester (**38**) as a mixture of diastereoisomers

.

Scheme 3.5 Nickel-catalyzed hydrophosphinylation applied to the preparation of *P*-heterocycles.



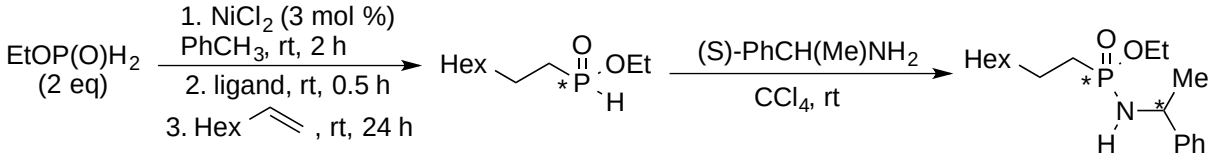
3.2.6 Nickel-catalyzed Desymmetrization of $ROP(O)H_2$

The potential for the desymmetrization of $ROP(O)H_2$ using a chiral phosphine ligand was briefly investigated (Table 3.5).

Although a number of other chiral ligands were screened, results were unsatisfactory because the P-C bond-forming step gave low or no yield.

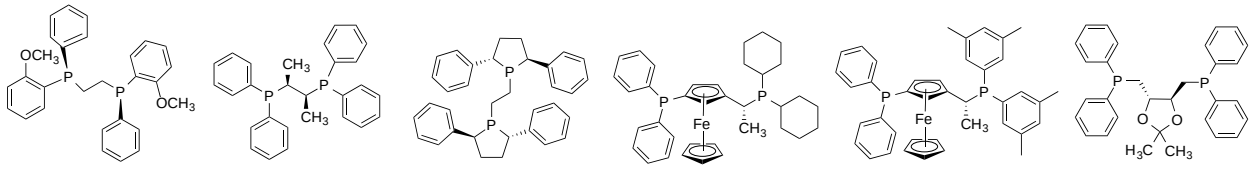
As expected, dppe-like ligands provided good reactivity (entries 1 and 2). One Josiphos-type ligand displayed good reactivity (entry 4) while others simply did not give any hydrophosphinylation. Correlation of enantiomeric excesses (ee) were determined by derivitizing

Table 3.5 Desymmetrization of $EtOP(O)H_2$ through hydrophosphinylation using a chiral ligand.



Entry	ligand[a]	^{31}P-NMR yield %[b]	de %[c]
1	(*R, R*)-DIPAMP	90	12
2	(*S, S*)-Chiraphos	89	18
3	(*S, S*)-Ph-BPE	69	16
4	JosiPhos-(*R*)-(*S*)-PDF-$Pxyl_2$	96	17
5	JosiPhos-(*R*)-(*S*)-$PPFPCy_2$	0	-
6	(*S, S*)-DIOP	0	-

[a] 3.3 mol %. [b] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra. [c] ee determination was conducted as in ref 28 using (*S*)-methyl-benzylamine and CCl_4.



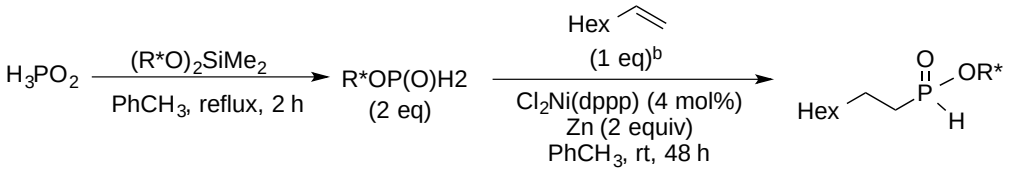
the crude *H*-phosphinates with (S)-(–)-methylbenzylamine and CCl_4 using the Atherton-Todd reaction. The diasteriomers can then be differentiated by ^{31}P NMR to calculate the de's (de = ee). This method was validated by chiral HPLC analysis, and the de values obtained by ^{31}P NMR were accurate.[20]

Desymmetrization via preparation of chiral alkyl phosphinates was also quickly examined.

Because the alkylsiloxane reagents for (-)-menthol and (-)-8-phenylmenthol are not commercially available, these were synthesized using the corresponding alcohols and dichlorosilane.

Furthermore, the bulkiness of the alkyl group severely restricted the ability of the phosphinate to preactivate and reduce $NiCl_2$ on its own. Scheme 3.6 summarizes the reaction of (-)-menthyl phosphinate (**39**) with 1-octene using pre-complexed $NiCl_2$(dppp) and activated zinc powder as a reducing agent to generate the active Ni catalyst. Although the reactivity was moderate, the desymmetrization was inefficient.

Scheme 3.6[a] Desymmetrization of Phosphorus using (-)-Menthol as Chiral Auxillary.



39: 63% (41%) R* = (-)-menthyl
d.e. = 37%
40: 21% (nd) R* = (-)-8-phenylmenthyl
d.e. = 72%

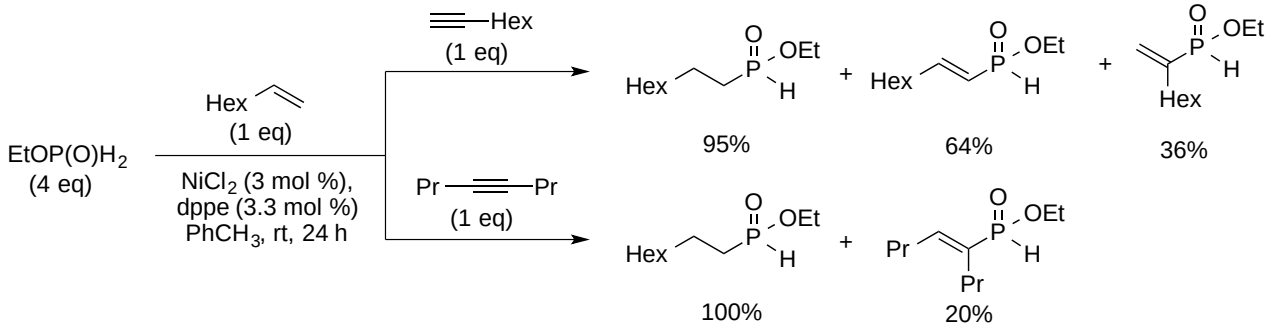
[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.
[b] Extra equivalent of 1-octene used in reaction with (-)-8-phenylmenthyl phosphinate (**40**).

The bulkier 8-phenylmenthol phosphinate (**40**) was reacted under similar conditions and the d.e. was competitive with the previously reported asymmetric palladium-catalyzed hydrophosphinylation.[20] However, reactivity was significantly lower.

3.2.7 Relative Reactivities between Alkenes and Alkynes

Finally, a competition study of nickel-catalyzed hydrophosphinylation at room temperature for 24 hours was conducted to understand the reactivities of the optimized reaction between alkenes and alkynes (Scheme 3.7). The formation of phosphinate products was equivalent between the reaction with 1-octene and 1-octyne. Not surprisingly, the reaction with 4-octyne was slower with a 5:1 ratio of alkene to alkyne products.

Scheme 3.7 [a] Hydrophosphinylation Competition Studies with 1-octene and 1- and 4-octyne.



[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

3.3 Conclusion

The following chapter describes the successful development of nickel-catalyzed hydrophosphinylation of unactivated alkenes, which was not fully realized in the initial studies with alkynes. Furthermore, this new methodology provides a cheap alternative to palladium-

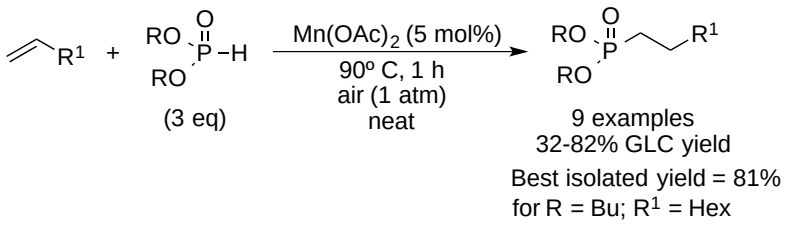
catalyzed hydrophosphinylation that was previously developed. The reaction was optimized by first reducing the nickel chloride with alkyl phosphinate and further stabilizing it with the cheap bisphosphine ligand, dppe. Experimental observations like the concurrent formation of dialkyl phosphites appear to affirm the reaction mechanisms proposed. The optimized reaction was functional group tolerant for a variety of different alkenes and can be utilized in tandem with a variety of different P-H bond manipulations like cross-coupling with aryl halides or intramolecular cyclizations.

Large scale synthesis of alkyl-*H*-phosphinates may be achieved with this method, and has become standard for preparing intermediates for further development of P-C and P-O bond-forming methodology. Continued work is required for a robust asymmetric version of nickel-catalyzed hydrophosphinylation.

Chapter Four: Manganese-catalyzed Addition of *H*-Phosphinates to Alkenes and Alkynes

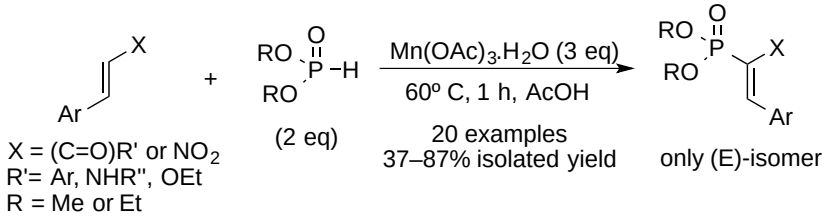
4.1 Introduction

Manganese-promoted free-radical reactions have become a staple of organic synthesis.[161] Besides their low toxicity, manganese compounds are inexpensive over a broad range of oxidation states (anhydrous $MnCl_2$, 98% = \$4.3/mol; anhydrous $Mn(OAc)_2$, 98% is \$76/mol; based on current costing from Alfa Aesar). Ishii and coworkers pioneered the reactions of *H*-phosphonate diesters for elegant P-C bond formation using catalytic manganese(II) acetate under aerobic conditions, but only a few isolated yields were determined (Eq. 4.1).[162]



(Eq. 4.1)

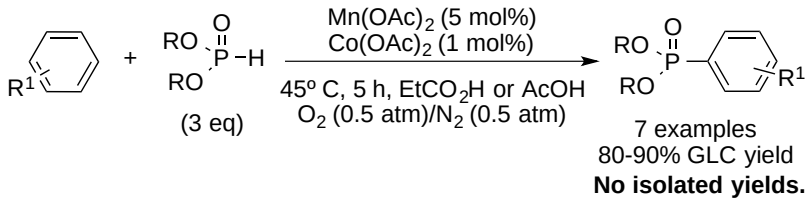
Building on Ishii's work, Zhang reported the manganese(III)-mediated phosphonation of α, β-unsaturated arylketones to prepare alkenylphosphonates (Eq. 4.2). Using stoichiometric manganese(III) acetate, isolated yields for the conjugated alkene substrates tried ranged from 37 to 87% with the least reactive compounds containing an ethyl ester group (X = (C=O)OEt).[163] To note, the reaction is regioselective for only the (E)-alkenylphosphonate.



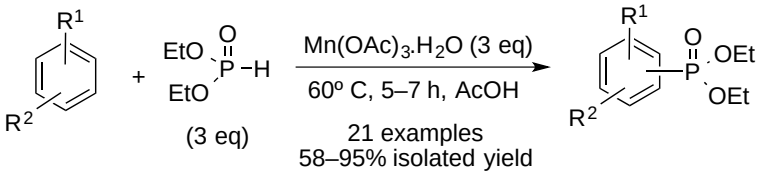
(Eq. 4.2)

The direct arylation of H-phosphonate diesters has been investigated intensely.[164] Ishii also reported the phosphonation of arenes using a catalytic $Mn(OAc)_2/Co(OAc)_2/O_2$ redox

system with 80 to 90% GLC yield of several arenes studied. No isolated yields were reported, so the true efficiency of the system is unknown (Eq. 4.3).[164] Zhang also applied the same stoichiometric $Mn(OAc)_3$ system used with the alkenyl arylketones to the arylation of substituted arenes (Eq. 4.4).[165] Decent yields for aryl substrates with a variety of electron-donating and withdrawing groups were obtained, although many of these products were mixtures of regioisomers.



(Eq. 4.3)



(Eq. 4.4)

For what is known, similar manganese-catalyzed additions of alkenes, alkynes and arenes with *H*-phosphinates have not been studied previously.

Continuing the interest in *H*-phosphinate reactivity in both free radical and metal-catalyzed processes,[2] exploration of the reactions with *H*-phosphinates using manganese acetate (II or III) and various unsaturated partners was initiated. This chapter summarizes the findings. The reaction of *H*-phosphinates with alkenes and alkynes to form disubstituted phosphinates is in general a difficult process even under free radical conditions, especially with alkyl *H*-phosphinate esters.[114,166] Since the current methodologies from this laboratory can provide many different *H*-phosphinates,[2] it was determined that Ishii's reaction should be studied on these

substrates. In the Ishii process,[162] $(RO)_2P(O)H$ is used under neat conditions and in excess (3 equivalents),[167] which is quite wasteful although those compounds are inexpensive. For a practical reaction, decreasing this to stoichiometric (or as nearly stoichiometric as possible) conditions would be much more desirable, especially if more valuable *H*-phosphinates $R^1P(O)(OR)H$ are to be employed.

4.2 Results and Discussion

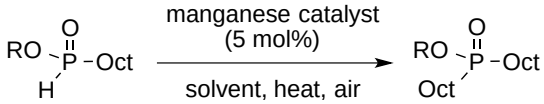
4.2.1 Optimization of the Reaction Conditions

This investigation started by looking at relatively challenging octyl-*H*-phosphinate esters OctP(O)(OR)H as the model compounds. Table 1 shows the results. Under oxidative conditions, it is clear that a competitive pathway leading to OctP(O)(OR)OH will be operating (responsible for most of the lost mass). Ishii's conditions used an excess of the $(RO)_2P(O)H$ reagent because of this oxidative side reaction.[162] On the other hand, using an excess of alkene/alkyne will increase oligomerization especially under neat conditions. Moderate to high isolated yields were obtained under a variety of conditions, including neat or in solution.

Reaction of the ethyl ester produced the disubstituted product in 71% yield (entry 1). However, the same reaction at room temperature did not give any product after 48 h. Similarly, no product formed in the absence of catalyst. With the butyl ester, various manganese catalysts could be employed, but generally larger amounts of 1-octene gave slightly better results (for example: entry 4 versus 2). Reactions in solution using C_6H_{12} or DMSO also furnished reasonably good results (entries 6, 8–9), but ethanol and acetic acid (entry 7) produced no desired product. The 1.2:1 molar ratio of reagents under neat conditions produced slightly better results. Interestingly, the Jacobsen (R, R)-salen catalyst could be employed provided sodium acetate is added, presumably to form the catalytically active Mn(III) species *in situ* (entry 10).

Using an excess of *H*-phosphinate gave a higher yield than using an excess of 1-octene (entries 10b versus 10a). Because reagents ratios closer to one are preferable, reactions with a slight excess of *H*-phosphinate (1.2 equivalents) were conducted (entries 11-16). A switch to the cyclohexyl ester of octylphosphinate reduces the amount of dealkylating side reactions that are commonly observed using these substrates (lability of alkyl esters are 1º >2º >3º).

Table 4.1 Reaction conditions for manganese-catalyzed additon to alkenes.[a]



Entry	R (equiv)	Equiv 1-octene	Manganese catalyst	Solvent	Isolated Yield (%)
1	Et (1)	2.5	$Mn(OAc)_2$	neat	71
2	Bu (1)	1	$Mn(OAc)_2$	neat	52
3	Bu (1)	1.5	$Mn(O_2C_8H_{15})_2$ [b]	neat	64
4	Bu (1)	2.5	$Mn(OAc)_2$	neat	81
5	Bu (1)	2.5	$Mn(OAc)_3 \cdot 2H_2O$	neat	85
6	Bu (1)	2.5	$Mn(OAc)_2$	C_6H_{12}	74
7	Bu (1)	2.5	$Mn(OAc)_2$	AcOH	nr
8	Bu (1)	2.5	$Mn(OAc)_2$	DMSO	71
9	Bu (1)	2.5	$Mn(O_2C_8H_{15})_2$ [b]	DMSO	78
10a	Bu (1)	2.5	(*R*,*R*)- Jacobsen NaOAc (20 mol%)	neat	60
10b	Bu (2)	1			83
11	Et (1.2)	1	$Mn(OAc)_2$	neat	77
12	Bu (1.2)	1	$Mn(O_2C_8H_{15})_2$	neat	75
13	Bu (1.2)	1	$Mn(OAc)_2$	neat	89
14	Cy (1.2)	1	$Mn(OAc)_2$	DMSO	97 [c]
15	Cy (1.2)	1	MnO_2	neat	39
16a	Cy (1.2)	1	Mn on Si[d]	neat	71
16b	Cy (1.2)	1	Mn on Si[d,e]	neat	42

a.) All reactions were conducted in air at 100 °C, except in cyclohexane (reflux). All reaction times were 3 h, except for DMSO (18 h). In general, octene dimerization was less than 5%, so simple extraction gave the products >95% pure. b.) Manganese(II) 2-ethylhexanoate. c.) Only 42 % isolated yield after 3 h. d.) Manganese(II) ethyl/butyl phosphonate Silica, 25 mol% used based on loading. e.) Catalyst recycled from entry 16a.

Results were generally comparable (slightly lower or higher) to other stoichiometries under neat conditions but clearly superior in DMSO with the cyclohexyl ester (entry 14).

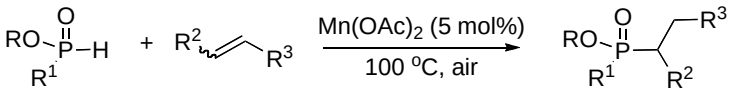
Although $Mn(OAc)_2$ is a relatively inexpensive catalyst itself, activated manganese oxide (MnO_2, $ 3.86/mol, Sigma-Aldrich) was tried as a catalyst, but only gave an isolated yield of 39% (entry 15). With possibilities to recycle and reuse the catalyst, manganese(II) ethyl/butyl phosphonate coated on silica gel was attempted. The reaction produced a lower isolated yield at 71% (entry 16a), and using a recycled catalyst gave only a 42% isolated yield (entry 16b).

A competition experiment was completed between ethyl octylphosphinate and $(EtO)_2P(O)H$ (1.2 equiv) using the conditions presented in Table 1 entry 11. A 2.8:1 phosphinate/phosphonate product ratio was obtained, showing that ethyl octylphosphinate is more reactive. Similarly, diethyl *H*-phosphonate (1.2 equiv) alone gave only a 42% isolated yield of diethyl octylphosphonate, reinforcing the idea that excess reagent (3 equiv) is necessary in Ishii's hydrophosphonylation reaction.[162] Finally, when entry 14 was repeated in the absence of 1-octene, cyclohexyl octylphosphonate monoester was obtained in 82% isolated yield.

4.2.2 Scope of the Optimized Reaction

Once the conditions had been optimized, the scope with various *H*-phosphinate/alkene combinations was further investigated (Table 4.2). Isolated yields ranged from 46 to 90% with alkenes. With cyclooctene some variations in yields were observed depending on the ester chosen (entry 1). The methodology was primarily developed with the reaction vessel opened directly to the air. It was later realized that the use of a drying tube may increase the yield of the reaction by reducing the amount of moisture entering the system.

Table 4.2 Scope of the manganese-catalyzed hydrophosphinylation reaction.[a]



Entry	*H*-phosphinate	R	alkene	solvent	Time (h)	product	Isolated yield (%)
1a		Et			3		65
1b		Bu	cyclooctene	none	3		58
1c		Cy			18		53
1d		Cy			18		92[b]
2		Cy	vinyl pivalate		18		61[c]
3		Et	$NHCO_2Et$	none	3		55
4		Bu	CO_2Et CO_2Et	none	3		72
5		Cy	cyclohexene	none	18		73
6		Cy	Br	none	18		54
7		Cy	Ph	none	18		46
8a		Cy	1-octene	none	18		52
8b				DMSO			89
9		Cy	1-octene	DMSO	24		48
10	(95% de)	Men	1-octene	none	16	(95% de)	79
11	(97% de)	Men	1-octene	DMSO	16	(94% de)	55
12		H	1-octene	DMSO	24		87
13		H	1-octene	DMSO	24		90
14		*i*-Pr	1-octene (3 equiv)	neat	18		69[d]
15		Cy	1-hexyne (0.5 equiv)	none	18		51
16		*i*-Pr	1-hexyne (1 equiv)	DMSO	18		40
17		Et	1-octene	none			NR
18		Et	1-octene	none	18		< 10

[a] Product purity > 95%; [b] With drying tube.; [c] Mixture of branched and linear isomers (1.4: 1 L:B); [d] After hydrolysis (conc. aq. HCl, toluene, reflux, 18 h).

Indeed this was the case and the isolated yield increased to 92% for the cyclohexyl ester (entry 1d). Other alkenes reacted successfully with various cyclohexyl *H*-phosphinate esters (entries 2-9) typically in yields around 50%.

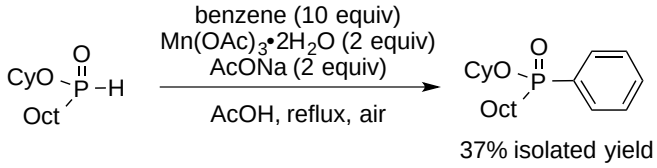
Several vinyl substrates were tried, but only vinyl pivalate produced the product in a decent isolated yield of 61% (entry 2).

Interestingly, *P*-stereogenic menthyl *H*- phosphinates[168] reacted with excellent stereoselectivity to produce the corresponding disubstituted products (entries 9 and 10). Entry 10 constitutes the first example of hydrophosphinylation with *P*-stereogenic *H*-phosphinate that is not substituted with an aryl group.[166] As discussed previously in Chapter 2, aryl substituted *H*-phosphinates have special reactivity.[110,166] In fact, the reaction of menthyl phenyl-*H*-phosphinate with 1-octene using our Et_3B/air system[75] instead of $Mn(OAc)_2$ gave the product in entry 9 in 73% isolated yield and 95% de.

The reaction is not limited to *H*-phosphinate esters as acids also react successfully (entries 12-13). A 1,1-bis-*H*-phosphinate[77] ester could be employed (entry 14) and the corresponding acid was obtained after hydrolysis to both simplify the purification and the ^{31}P NMR spectra. The reaction with 1-hexyne was briefly investigated (entries 15-16). With an excess of *H*-phosphinate the corresponding 1,2-bis-phosphinate was obtained in 51% isolated yield (entry 15). In entry 16, heterocyclization was also achieved using a 1,1-bisphosphinate and 1-hexyne. Ethyl cinnamyl phosphinate (entry 17) and trityl phosphinic acid (entry 18) were highly unreactive with this methodology. Both of these compounds can form highly stable radicals, and this may have deleterious effects on the manganese to form a phosphinate radical by abstraction of the P-H bond.

4.2.3 Manganese-promoted Arylations

We then turned our attention to Mn(III)-promoted reactions based on various literature precedents with *H*-phosphonates.[164] The direct intermolecular arylation of cyclohexyl octyl-*H*-phosphinate ester with benzene gave the corresponsing cyclohexyl octyl-phenylphosphinate in 37% yield (Eq 4.5). Whereas the yield is mediocre, it is comparable to the 48 % yield that was reported with benzene (1 equiv), $(EtO)_2P(O)H$ (2 equiv), $AgNO_3$ (20 mol%), and $Na_2S_2O_8$ (5 equiv).[169]



(Eq. 4.5)

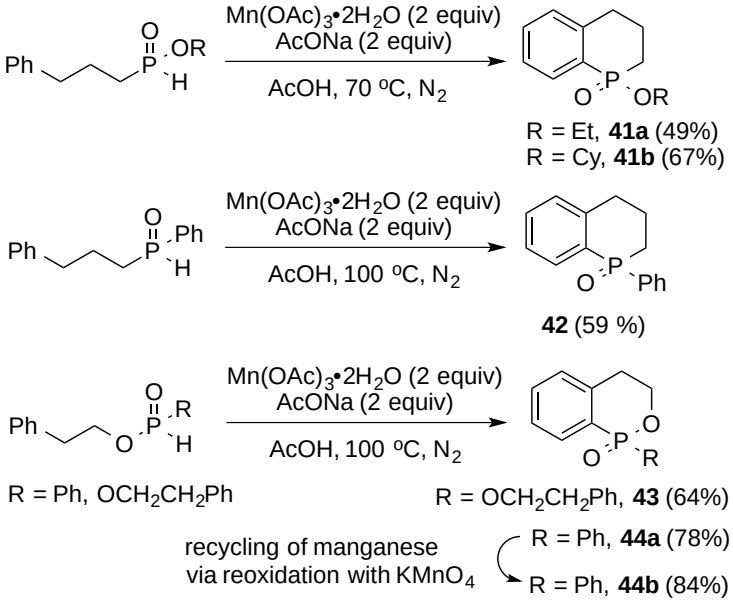
On the other hand, *H*-phosphinates offer possibilities for heterocyclization via intramolecular arylation, which was briefly investigated and the results are shown in Scheme 4.1. 3-Phenylpropyl-*H*-phosphinate esters were cyclized using 2 equivalents of $Mn(OAc)_3$/AcONa. The ethyl ester (**41a**) gave a lower yield (49%) presumably because some cleavage takes place in acetic acid compared with the more resistant cyclohexyl ester (**41b**, 67%).

The reaction was not limited to *H*-phosphinates as shown by the successful cyclization of a related secondary phosphine oxide (**42**, 59%) and an *H*-phosphonate diester (**43**, 64%). Similarly, phenethyl phenyl-*H*-phosphinate ester (**44a**) was cyclized in excellent yield (78%). After this run, the manganese was recovered and converted back to $Mn(OAc)_3$ using $KMnO_4$.[170] A subsequent reaction with the regenerated $Mn(OAc)_3$ gave the same product (**44b**) in 84% yield.

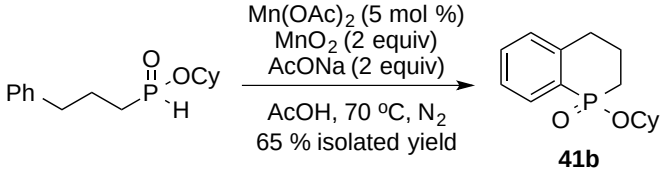
Clearly, this heterocyclization method is competitive with alternative approaches such as metal-catalyzed cross-coupling since the starting materials are readily available and the cost

remains low. It should be noted that attempts at using manganese(II) or (III) catalytically were unsuccessful. However, in the process of developing an improved and more cost effective catalyst system ($Mn(OAc)_3.2H_2O$ is $1103/mol, Sigma-Aldrich), it was discovered that $Mn(OAc)_2$ (5 mol %)/MnO_2 (2 equiv) in combination proved to be comparable to stoichiometric Mn(III) (Eq. 4.6).

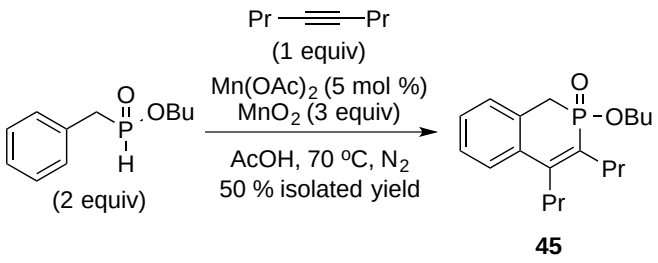
Scheme 4.1 $Mn(OAc)_3$-promoted heterocyclization via intramolecular radical arylation.



Notably, MnO_2 alone gave low conversion, and it was also observed that sodium acetate (NaOAc) was needed or the reaction resulted in lower yields. An additional example of the MnO_2-promoted reaction is shown in Eq. 4.7 for an alkyne-arene annulation.[171]



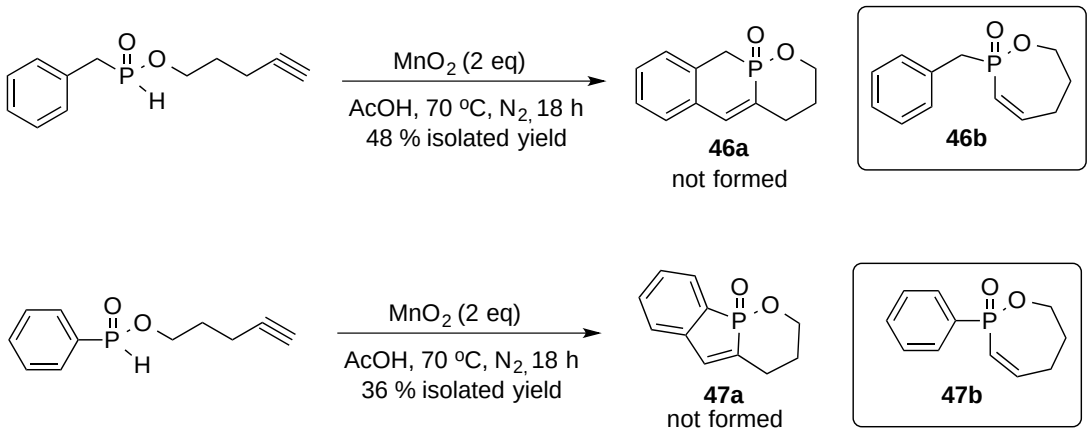
(Eq. 4.6)



(Eq. 4.7)

Other intramolecular reactions were attempted using 4-pentynyl esters of benzyl- and phenylphosphinate to form possible three-membered heterocyclic compounds (Scheme 4.2). Only MnO_2 was used as the catalyst in glacial acetic acid, and as mentioned previously the conversion of starting material is low. Using Baldwin's rules for ring closure of alkynes,[172] it was expected that the exo-dig five- and six-membered cyclic geminal alkenes, respectively, would form as an intermediate and subsequently arylate to obtain the desired products (**46a** and **47a**). Surprisingly, it was observed by ^{1}H NMR that the seven-membered heterocycle (**46b** and **47b**) formed for both phosphinate esters studied and thus preventing any further cyclization to occur.

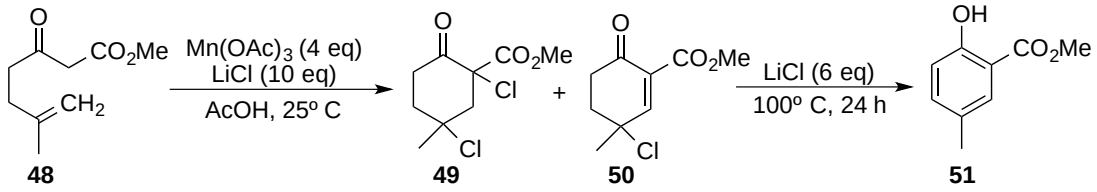
Scheme 4.2 Manganese-mediated cyclization of pentynyl arylphosphinates



4.2.4 Manganese-promoted Addition/Halogenation Reactions

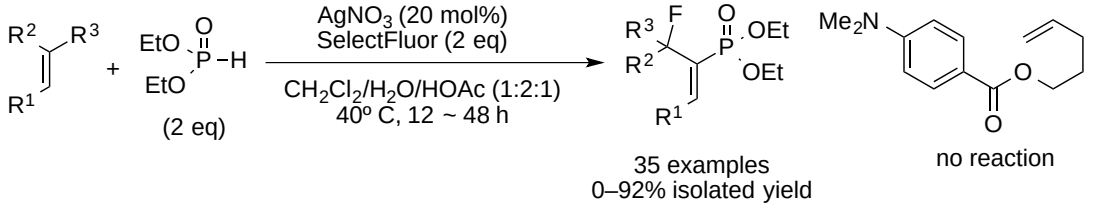
The preparation of β -halogenated phosphinates was inspired by reactions developed with the related carbon analogs β-keto esters. Manganese-promoted addition of β-keto esters to alkenes and subsequent chlorination using lithium chloride (LiCl) was first reported by Vinogradov and Nikishin.[173,174] Snider et al. utilized similar conditions to prepare salicylate derivatives by chlorination of the α-carbon on compound **48** which concomitantly cyclizes to form the dichloride compound **49** and some elimination product **50** (Scheme 4.3).[175–178] The addition of extra LiCl and heating over a 24 hour period provides the salicylate **51** via E_2C elimination in 70% isolated yield.[176]

Scheme 4.3 Intromolecular Oxidative Additon and Chlorination of an alkenyl β-keto ester.



48 **49** **50** **51**

Li et al. recently described the phosphonofluorination of alkenes using $AgNO_3$ as the catalyst and SelectFluor as the fluorinating agent (Eq. 4.8).[179] This method places the halogen in

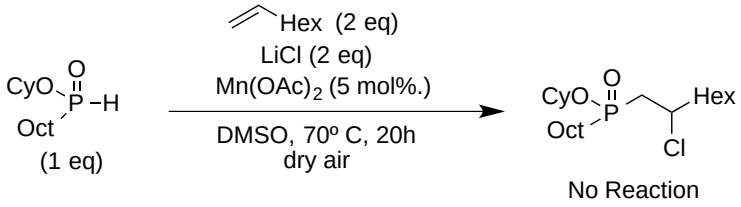


(Eq. 4.8)

the β-carbon position from the phosphonate. All isolated yields were moderate with >44% isolated yield for most alkenes except pent-4-en-1-yl-4-(dimethylamino)benzoate. As previously

mentioned during the discussion about the arylation reaction, $AgNO_3$ also works via a radical method but is expensive. Therefore, $Mn(OAc)_2$ should be just as effective as a catalyst for this particular reaction as well.

An optimization study of the halogenation reaction was conducted and the initial experiment was completed catalytically as presented in Eq. 4.9. No desired product was isolated with these conditions. A switch to 2 equivalents of $Mn(OAc)_3$ under nitrogen atmosphere showed a 20% product conversion as measured by ^{31}P NMR after a $Na_2S_2O_4$ work-up to remove the paramagnetic and NMR silent catalyst. Switching to the catalytic $Mn(OAc)_2$ and MnO_2/NaOAc oxidant/additive system as utilized for inter- and intramolecular arylation reactions presented in equations 4.6 and 4.7 showed further increase in product formation. Therefore, a larger optimization study was conducted and summarized in Table 4.3.

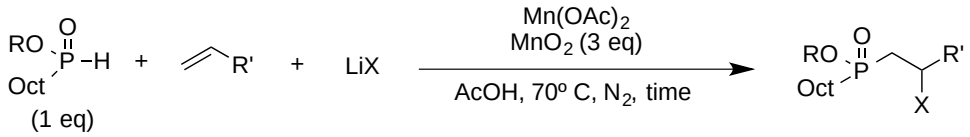


(Eq. 4.9)

Starting with ethyl-octyl-*H*-phosphinate as the model substrate and using an excess of 1-octene and 5 equivalents of LiCl produced desired product in 30% isolated yield (entry 1). Switching to the cyclohexyl ester, increasing the amount of 1-octene and completing the addition of the *H*-phosphinate slowly over 2 hours also did not increase the amount of product formed (entry 2).

Overnight reactions with 2 and 5 equivalents of 1-octene produced the same amount of product (entries 3 and 4).

Table 4.3 Optimization of the Manganese-promoted Addition/Halogenation Reaction.



Entry	R	time (h)	Equiv alkene	$Mn(OAc)_2$ (mol %)	Equiv LiX	Equiv NaOAc	Isolated Yield % (% conversion)[a]
1	Et	18	1-octene 2	5	LiCl 5	3	30
2	Cy	2[b] + 2	1-octene 5	5	LiCl 5	3	(29)
3	Cy	18	1-octene 5	5	LiCl 5	3	52
4	Cy	18	1-octene 2	5	LiCl 5	3	52
5	Cy	18	1-octene 5	5	LiCl 3	-	72
6	Cy	18	1-octene 2	5	LiCl 3	-	(58)
7	Cy	18	styrene 2	5	LiCl 3	-	67
8	Cy	18[b]	1-octene 2	5	LiCl 5	-	(16)
9	Cy	18	1-octene 2	5	LiCl 5	-	(70)
10	Cy	18	1-octene 3	5	LiCl 4.5	-	36 (70)
11	Cy	24	1-octene 5	10	LiCl 5	-	90
12	Cy	24	styrene 5	10	LiCl 5	-	67 (89)
13	Cy	24	1-octene 5	10	LiBr 5	-	(78)
14	Cy	24	tBu-allyl carbamate 5	10	LiCl 5	-	(> 95%)
15	Cy	24	1-octene 5	10	LiI 5	-	ND
16	Bu	24	1-octene 5	10	LiCl 5	-	42

[a] Percent conversion of the product determined by ^{31}P NMR analysis after work-up with aq. $Na_2S_2O_4$. NMR cannot be used to monitor the reaction due to the paramagnetic nature of manganese.

[b] Addition of phosphinate was completed slowly over the reaction time.

The removal of the sodium acetate as an additive increased the yield significantly to 72% isolated (entry 5), although trying to further lower the amount of 1-octene reduced the conversion to the product (entry 6). Under the same conditions as entry 6, the *H*-phosphinate was added slowly over the entire reaction period, but the amount of product isolated was low (entry 8). Ultimately, increasing the amount of $Mn(OAc)_2$ to 10 mol% and LiCl to 5 equivalents showed the most optimized conditions at 90% isolated yield (entry 11). Even styrene, which is non-reactive in the nickel-catalyzed hydrophosphinylation (see Chapter 3), reacted in moderate yield under conditions employing LiCl as an additive (entries 7 and 12). Using other lithium halide salts (LiBr, LiI) both resulted in lower yields (entries 13 and 15), which is consistent with the reactivities of halogen radicals (Cl > Br > I).

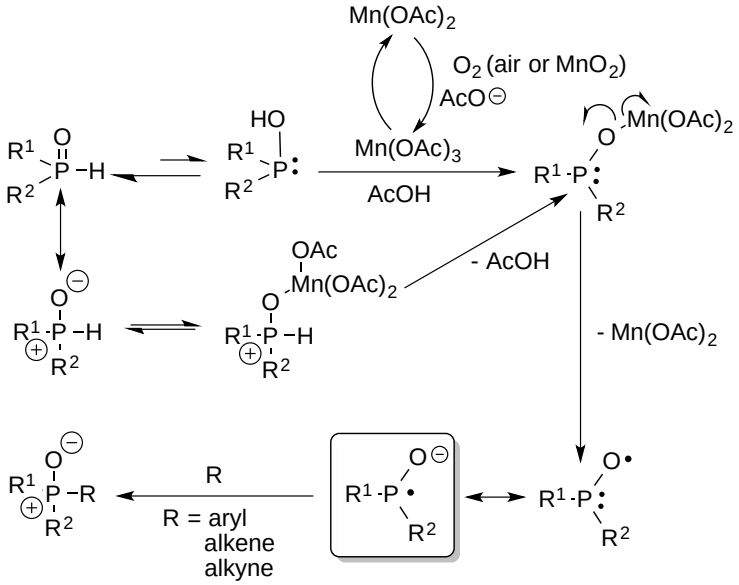
4.3 Mechanistic Considerations

A mechanism of manganese-catalyzed or promoted addition of alkenes, alkynes or aryl compounds can only be speculative at this time and is summarized in Scheme 4.4. Given the mechanisms postulated by Snider for β -keto esters,[175,177,178] it is plausible that the oxophilic manganese also promotes the formation of the phosphinylidene radical by the binding of Mn(III) to the oxygen.

P(V) to P(III) tautomerization could occur either prior or after the formation of the Mn-O bond, although as studied in Chapter 2 acetic acid acts as a catalyst for phosphinylidene tautomerization.

Formation of P-C bond with alkene, alkyne or an aryl compound should occur rapidly. The exact mechanism for the regeneration of manganese(III), the active catalyst, is also not completely understood, but MnO_2 is postulated to do that.

Scheme 4.4 Possible Mechanism for the Manganese-promoted P-C bond Formation.



4.4 Conclusion

In conclusion, the present methodology provides an inexpensive way to prepare disubstituted phosphinates in moderate to good yields. Furthermore, manganese-promoted reactions can also be used to achieve direct arylation, or heterocyclization. Since the manganese can be recycled through $KMnO_4$ oxidation as demonstrated in one example, the process should be practically useful. Perhaps more importantly, a new set of conditions employing $Mn(OAc)_2/MnO_2$ was established and ultimately used in an expanded study of manganese-promoted arylation.[180] To note, the $Mn(OAc)_2/MnO_2$ is much cheaper than the related silver(I)/$K_2S_2O_8$ system. This chapter also described the initial studies for manganese-promoted alkene addition/chlorination reactions. Further optimization reactions are currently being conducted to reduce the amount of alkene and LiCl used, and a reaction scope with a few applications will be the subject of a future publication.

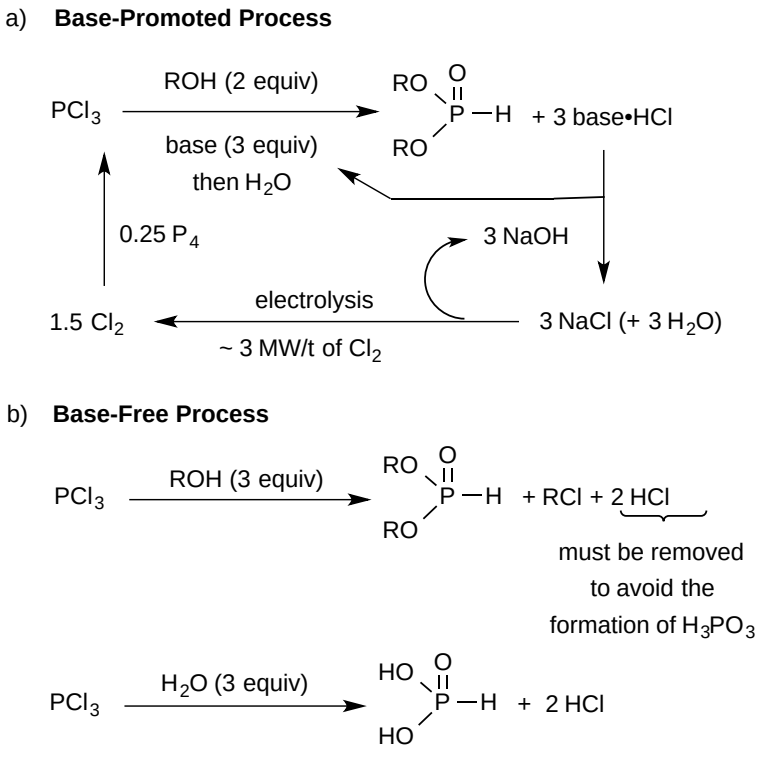
Chapter 5: Metal-catalyzed Oxidation of Alkyl Phosphinates to Form Phosphonates

5.1 Nickel-catalyzed Oxidation of Hypophosphite Esters to *H*-Phosphonates

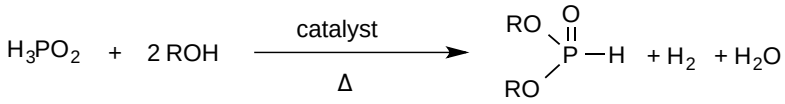
5.1.1 Introduction

H-Phosphonate diesters $(RO)_2P(O)H$ and phosphorous acid (R = H) constitute a major class of intermediates used in fine and industrial organophosphorus chemistry. They are currently prepared from the alcoholysis of PCl_3 (Scheme 5.1). Both the base (such as Et_3N) and chlorine can be recycled, but the process requires extensive manipulations and electric power.

Scheme 5.1 Preparation of *H*-Phosphonate Esters.

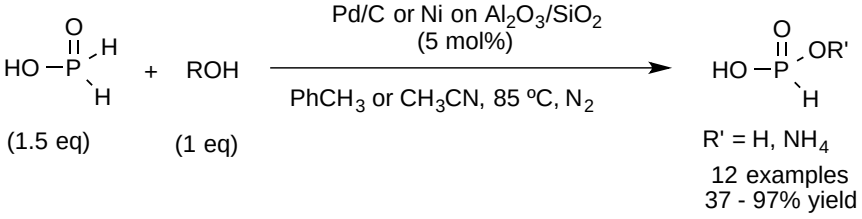


The exception is phenol, which does not require any base because PhCl cannot form. Herein, we describe the catalytic oxidative phosphorylation reaction of various alcohols with H_3PO_2 to form *H*-phosphonate diesters in a simple, yet chlorine-free and base-free process (Eq. 5.1). Also, this methodology formally constitutes a water splitting mechanism.



(Eq. 5.1)

Our laboratory previously reported two catalytic phosphorus-oxygen bond formations.[101,153] For example, with H_3PO_2 (1.5 equiv) and an alcohol (1 equiv) using either Pd/C or $Ni/Al_2O_3/SiO_2$ as catalysts, we were able to prepare *H*-phosphonate monoesters (Eq. 5.2).[153] These compounds are normally prepared from PCl_3 or a reagent derived from it.[181]



(Eq. 5.2)

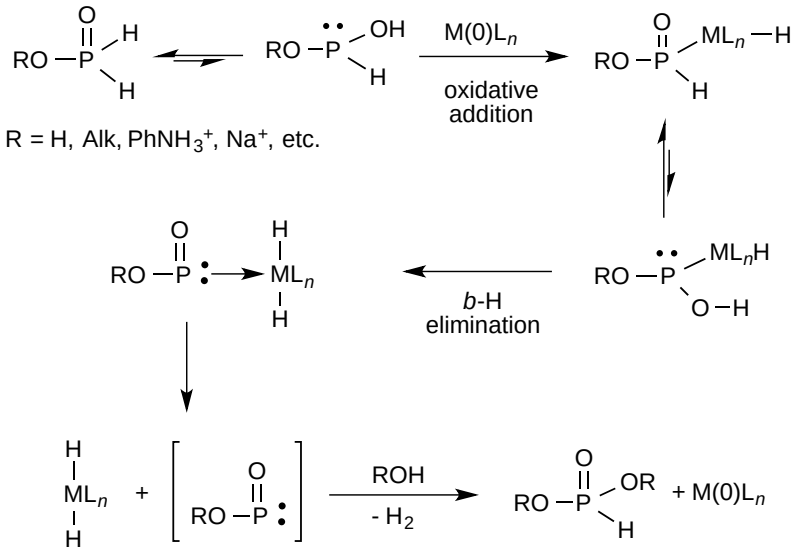
The work exploited the well known transfer hydrogenation pathway[140] to prepare organophosphorus compounds via catalytic P-O bond formation. Until this work, what happens to the hypophosphite in transfer hydrogenation was largely overlooked since the organic product was desired.[140] However, Dorfman and Aleshkova reported in 1998 a seminal study of the oxidation of sodium hypophosphite by alcohols using palladium or nickel catalysts, although no product was actually isolated.[182] The reaction produces ROP(O)(ONa)H and an equivalent amount of hydrogen.[182] The authors proposed a radical pathway, and a mechanism that involves the formation of the P(III) tautomer, (NaO)(OH)PH.

However, dialkyl *H*-phosphonates are much more important industrially than the monoesters because dialkyl phosphonates are ubiquitous. Perhaps the best illustration is for the synthesis of *N*-phosphonomethyl glycine, the active component of the herbicide glyphosate. Industrial preparations of glyphosate rely either on PCl_3 or its derivatives: phosphorous acid, or dialkyl *H*-phosphonates.[183,184]

5.2 Results and Discussion

Alkyl phosphinates $ROP(O)H_2$ can be prepared in several ways from HPA.[18,26,75] The most general and inexpensive methods use alkoxysilanes,[18,26] or the Dean-Stark method for higher boiling alcohols.[75] It occurred to us that alkyl phosphinates might be converted into symmetrical *H*-phosphonate diesters as long as excess alcohol ROH is available. Therefore, conditions that maximize transfer hydrogenation when both $ROP(O)H_2$ and excess ROH are combined could follow the mechanism shown in Scheme 5.2.

Scheme 5.2 Proposed mechanism for the metal-catalyzed formation of *H*-phosphonate diesters.



Ligandless metals are expected to catalyze the transfer hydrogenation process through facile β-hydrogen elimination. Also, because of their strong reducing properties, alkyl phosphinates are able to reduce metal salts easily.[139,185] Scheme 5.3 summarizes the conditions that were investigated.

Scheme 5.3 Reaction Conditions Employed for the Synthesis of *H*-Phosphonate Diesters.

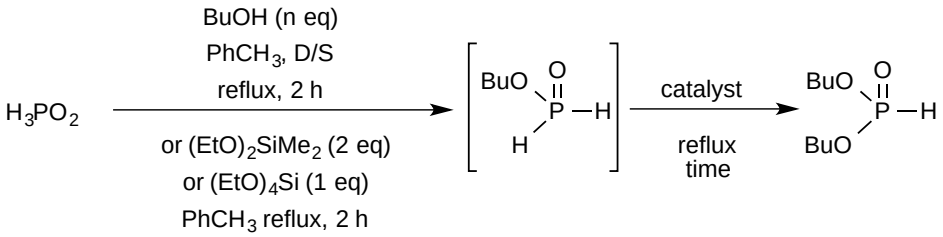


Table 5.1 shows the result of various experiments. First, a solution of $EtOP(O)H_2$ was treated with nickel chloride. Entries 1 and 2 show the influence of the amount of catalyst in the transformation. In order to avoid any additional silicate reagent, we next focused on $BuOP(O)H_2$ prepared by the Dean-Stark reaction,[18,185] since an excess alcohol could be used as the source of the second ester group. The decomposition of $ROP(O)H_2$ is well known[186] but entry 3 shows that this uncatalyzed process is inefficient as a synthetic procedure. Addition of $NiCl_2$ results in a clean reaction with near quantitative formation of $(BuO)_2P(O)H$ at 95% NMR yield. Entry 5 shows that the reaction is fast and that even inexpensive nickel chloride hexahydrate is an excellent catalyst.

Not surprisingly, other nickel(II) halides reacted satisfactorily (entries 6 and 7). On the other hand, nickel(II) acetate, acetylacetonate, and nickel powder gave poorer results. Because nickel on silica had given good results in the synthesis of *H*-phosphonate monoesters[153] it was investigated next. This catalyst was clearly less efficient than $NiCl_2$ (entries 4 and 5) but

increasing the reaction time gave clean reactions and high conversions (entry 15). It should be noted that adding the catalyst from the start of the reaction before esterification is unsatisfactory (entry 13). Using *n*-butanol as solvent instead of toluene also gave excellent results (entry 14 versus 15). This might be useful if BuOH is recycled in an industrial process. In spite of lower activity, one advantage of Ni/SiO_2 over $NiCl_2$ is that it can be recycled (entry 16). Finally, palladium (entries 17-19) and copper catalysts (20-22) were investigated but did not offer better results.

Table 5.1 Conditions Optimization.

Entry	R	ROH (equiv)	Catalyst	Catalyst (mol-%)	Time (h)	^{31}P-NMR yield % (isolated yield)[a]
1[b]	Et	0	$NiCl_2$	1.5	3	36
2[b]	Et	0	$NiCl_2$	3	3	95
3	Bu	2.5	none	0	18	17
4	Bu	3	$NiCl_2$	3	3	95
5	Bu	2.5	$NiCl_2•6H_2O$	3	3	95
6	Bu	2.5	$NiBr_2$	3	3	99
7	Bu	2.5	NiI_2	3	3	95
8	Bu	2.5	$Ni(OAc)_2$	3	3	51
9	Bu	2.5	$Ni(acac)_2$	3	3	67
10	Bu	2.5	Ni powder	3	3	27
11[b, c]	Et	0	Ni/SiO_2	3	16	53
12	Bu	2.5	Ni/SiO_2	3	3	55
13[d]	Bu	2.5	Ni/SiO_2	5	30	77
14	Bu	solvent	Ni/SiO_2	5	18	100 (84)
15	Bu	3	Ni/SiO_2	5	18	100 (90)
16[e]	Bu	3	Ni/SiO_2	5	18	100 (75)
17	Bu	2.5	Pd/C	2	3	65
18	Bu	3	Pd/C	5	16	72 (71)
19	Bu	2.5	$PdCl_2$	3	3	78
20	Bu	2.5	CuCl	3	3	16
21	Bu	2.5	$CuCl_2$	3	3	26
22	Bu	2.5	Cu powder	3	3	17

[a] NMR yields are determined by integration of all resonances in the ^{31}P-NMR spectra. For isolation, see experimental details. [b] Prepared by the alkoxysilane method. [c] An extra equivalent of $(EtO)_2SiMe_2$ was added in the second step. [d] Catalyst added at the start (before esterification). [e] The catalyst from entry 14 was recycled and used for this experiment on a 25 mmol scale.

After the above investigation, the conclusion was that $NiCl_2$ was a superior catalyst to convert $ROP(O)H_2$ into $(RO)_2P(O)H$, but because Ni/SiO_2 is solid that can be filtered off and recycled, it provides a greener process. Next we turned our attention to the scope of the reaction under conditions similar to those in Scheme 5.3. The results are shown in Table 5.2. For low boiling alcohols like ethanol, which cannot be conveniently used in azeotropic esterification, the alkoxysilane method was used. Diethyl *H*-phosphonate could be made in good yield (entry 1). For diisopropyl *H*-phosphonate, the intermediate phosphinate was prepared using a Soxhlet extractor with 3 Å MS to remove water, and substituting cyclohexane for toluene to give the product in excellent yield (entry 2).

Table 5.2 Scope of the Reaction.[a]

Entry	R	Catalyst	^{31}P-NMR yield % (isolated yield)[b]
1[c,d,e]	Et	Ni/SiO_2	92 (75)
2[f]	*i*Pr	Ni/SiO_2	100 (87)
3	*i*Bu	Ni/SiO_2	100 (84)
4[g]	*n*Pent	Ni/SiO_2	100 (55)
5	Cy	Ni/SiO_2	100 (75)
6	Bn	Ni/SiO_2	68 (64)
7	$PhCH_2CH_2$	Ni/SiO_2	100 (81)
8	(-)-Menthyl	Ni/SiO_2	100 (49)
9	Fenchyl	Ni/SiO_2	100 (82)
10	Cl_3CCH_2	Ni/SiO_2	81 (26)
11	1-Adamantyl	$NiCl_2$	68 (60)
12[n]	H	Ni/SiO_2	100 (84)
13[n]	Na	Ni/SiO_2	14[j]
14[n,ı]	Na	Ni/SiO_2	53[j]
15[κ]	3-butynyl	none	83 (51)
16[κ]	$ClCH_2CH_2$	none	100 (68)
17[κ]	Ph	none	74[ı] (63)

[a] Unless otherwise noted, the reactions were conducted with ROH (3 eq), 5 mol-% of catalyst, for 18 h. [b]NMR yields are determined by integration of all resonances in the ^{31}P-NMR spectra. For isolation, see experimental details. [c]Prepared by the alkoxysilane method. [d]40 h. [e]Anhydrous ethanol (3 eq) was added in the second step. [f]Cyclohexane was the solvent. [g]87 h. [h]Water is the

solvent. [i]The balance is NaH_2PO_4. [j]2 h. [k]The *H*-phosphonate diester was obtained in the absence of catalyst during the esterification step. [l] The remainder was PhOP(O)(OH)H.

Overall, a wide range of primary and secondary alcohols could be transformed into the corresponding *H*-phosphonate diester (entries 3-10), and chromatographic purification is completely avoided for the examples using alcohols with boiling points over 130 ºC. These alcohols can be removed under reduced pressure and slightly elevated temperatures using Kugelrohr distillation. In some cases isolation is difficult by distillation because the product forms an azeotrope with the alcohol.

One example is with the *H*-phosphonate prepared from (-)-menthol (entry 8). The product prepared from trichloroethanol is difficult to separate from the de-chlorinated products formed during the reaction because they have similar boiling points and polarities (entry 10). Adamantan-1-ol did react in moderate yield (entry 11) thus supporting the intermediacy of a highly reactive "phosphinidene oxide" (Scheme 5.2).[186] Other tertiary alcohols are problematic because of competing elimination in the esterification step. In the preparation of phosphorous acid (H_3PO_3), since H_3PO_2 is a 50 wt.-% solution in water, which is the desired nucleophile, heating the solution to reflux in the presence of catalyst gives an excellent yield of product. Oxidation of H_3PO_2 using Ni/Al_2O_3 provided slightly lower results with an isolated yield of 71 % (Table 5.2, entry 12 showed an 84% isolated yield). In a control experiment without any catalyst, the formation of H_3PO_3 was slow. The industrial potential of converting H_3PO_2 to H_3PO_3 yet been fully realized. The case of sodium hypophosphite is interesting because unlike with H_3PO_2, over-oxidation to sodium dihydrogen phosphate is the dominant pathway in our hands (entry 13). Shortening the reaction time improves the yield significantly (entry 14), but almost 50% of phosphate is still formed.

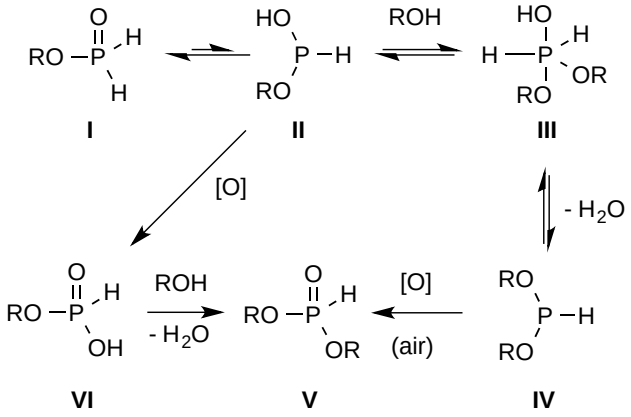
Surprisingly, 3-butyn-1-ol, 2-chloroethanol, and phenol (entries 15-17, respectively) were mostly or completely converted into the *H*-phosphonate diester during the Dean-Stark

esterification step without catalyst. Whereas a detailed explanation can only be speculative at this time, it must rely on a variation in the tautomeric equilibria of $ROP(O)H_2$ as a function of the R group, and the reactivity of the P(III) tautomer. Also, this result shows that oxygen may play a role.

Our laboratory is actively trying to understand these effects both experimentally and computationally, and the results of these initial studies were presented in Chapter 2.[136] A plausible mechanism for the uncatalyzed process is proposed in Scheme 5.4.

As before (Scheme 3.2) tautomerization of alkyl phosphinate **I** into P(III)-**II** occurs but now oxidative addition can take place with the alcohol to form pentacoordinate **III**. Intermediate **III** can isomerize via Berry pseudorotation to ultimately form dialkoxyphosphine **IV** which can be oxidized by air into the *H*-phosphonate diester **V**. There is significant support for this mechanism. Gallagher and Honegger have proposed a virtually identical one in the transesterification of alkylphosphinates.[187] Stec et al. have characterized by ^{1}H-NMR a species

Scheme 5.4 Plausible mechanism for the uncatalyzed formation of *H*-phosphonate diesters.



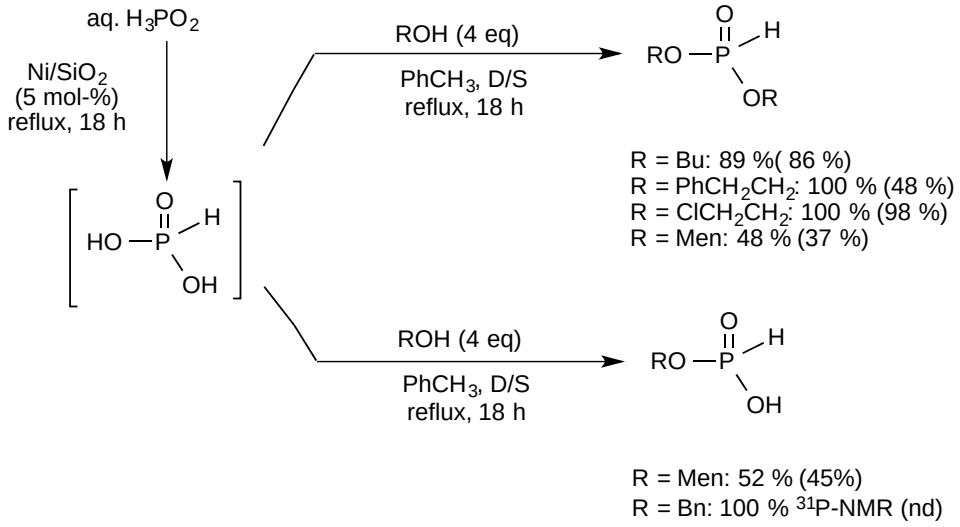
whose structure is related to **III**.[188] Several dialkoxyphosphines **IV** have been synthesized and some are so easily oxidized in the pure state that the reaction is pyrophoric.[189] Finally, in some

Dean-Stark esterifications, the presence of signals corresponding to small amounts of **IV** can sometimes be detected. However, an equally plausible alternative mechanism is the oxidation of **II** followed by esterification of the *H*-phosphonate monoester (vide infra).

Because H_3PO_2 can be oxidized easily into H_3PO_3 an alternative approach to bypass PCl_3 is to make it directly. As mentioned earlier, glyphosate, which uses about 50% of the PCl_3 supply annually, can be manufactured using H_3PO_3. In terms of *H*-phosphonate diesters, we briefly investigated the Dean-Stark esterification of H_3PO_3. This kind of reaction has been described previously.[190] In our process, the intermediate H_3PO_3 does not need to be isolated since it is formed in quantitative yield (see Table 5.2, entry 12).

Although the conversion of H_3PO_2 into H_3PO_3 is known,[191] our method is mild even if the subsequent conversion of H_3PO_3 into $(RO)_2P(O)H$ is limited, often only giving instead the monoester or a mixture of monoester and diester (Scheme 5.5).[190]

Scheme 5.5 One-pot conversion of H_3PO_2 into $(RO)_2P(O)H$ via H_3PO_3.



Isolated yields given in parentheses. ND = not determined.

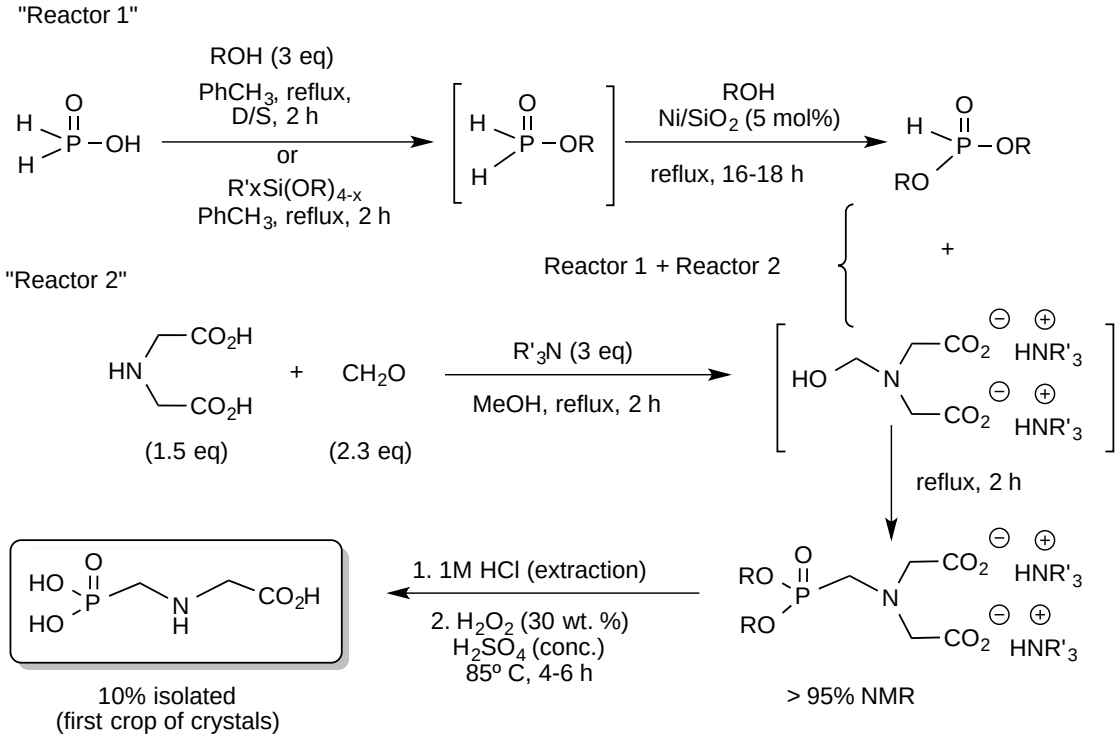
Nonetheless, 2-chloroethanol was an excellent substrate suggesting that the transformation **II** to **VI** in Scheme 5.4 might be an explanation for the uncatalyzed process observed in Table 5.2, entry 16.

The ease of oxidation of $ClCH_2CH_2OP(O)H_2$ would be due to a higher availability of its P(III) tautomer. The Dean-Stark esterification of H_3PO_3 with phenol is very slow (3 days) and gives a mixture like dialkyl *H*-phosphinate and the mono-ester PhOP(O)(OH)H. This suggests that ROP(O)(OH)H might be an intermediate.

5.3 Application to the Synthesis of Glyphosate

The development of a PCl_3-free synthesis of *H*-phosphonates using nickel catalysis was applied to the preparation of glyphosate (Scheme 5.6).[192] The overall reaction design takes industrial logistics into consideration, where both intermediates are reacted and left as crudes in

Scheme 5.6 Synthesis of Glyphosate using a PCl_3-free Method.



solution. After the condensation reaction between the *H*-phosphonate and N-hydroxylmethyldiacetate,[193] the crude mixture is filtered to remove the catalyst and then acidified using an aqueous HCl work-up.

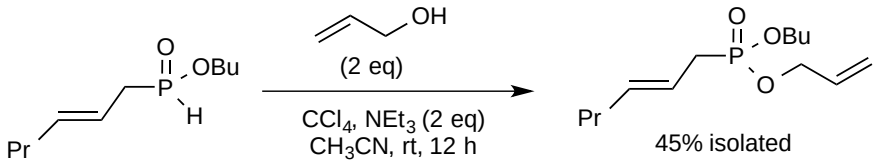
Oxidative cleavage of the imine occurs using hydrogen peroxide under acidic conditions as well as simultaneous hydrolysis of the phosphonate ester.[194] Glyphosate precipitates out of solution as a white powder upon cooling and a 10% isolated yield was obtained for the first crop of crystals. There were no attempts to obtain a second batch of crystals.

5.4 Copper-catalyzed Oxidation of Alkyl *H*-Phosphinates

5.4.1 Introduction

The metal-catalyzed oxidation of alkyl *H*-phosphinates, ROP(O)(R')H, with alcohols was also briefly explored. Currently, there are no methods to directly functionalize an alkyl phosphinate P-H bond with an alcohol to form a phosphonate diester.

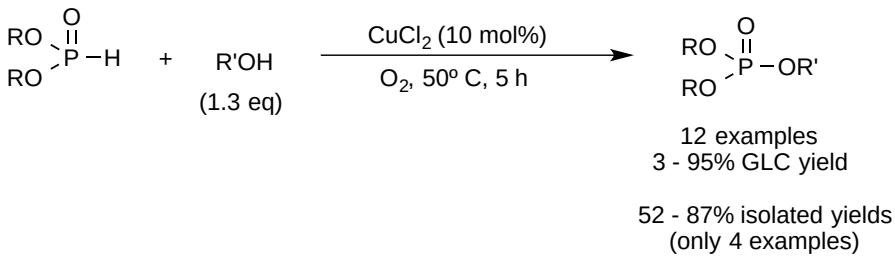
Because our laboratory has developed several methods to prepare *H*-phosphinates, this process would be competitive. Presently, the Atherton-Todd reaction[195] remains the most efficient way to prepare mixed alkyl phosphonate esters, but it is not very efficient with alcohols. Reactions with non-aromatic alcohols are typically less efficient than with amines (Alternatively, aryl-*H*-phosphinates also react more efficiently with all alcohols).[196] Eq. 5.3 depicts an olefin metathesis intermediate prepared via the Atherton-Todd reaction in moderate yield.[66]



(Eq. 5.3)

Alkyl phosphonates can also be prepared via palladium-catalyzed hydrophosphinylation of alkenes with alkyl-*H*-phosphonates.[79]

The work of Okamoto et al. describing the preparation of mixed trialkyl phosphates was used as a point of reference, where the phosphorylation of alcohols occurred neat under copper(II) chloride-catalyzed oxidative addition (Eq. 5.4).[197] Based on the results of this example, we considered the following in method optimization: a) preparation of mixed phosphonate esters in solution to set-up optimal conditions for cyclization in a later step; b) use air as the external oxidant instead of pure O_2; c) determine if the oxidation reaction occurs at lower catalyst loading.



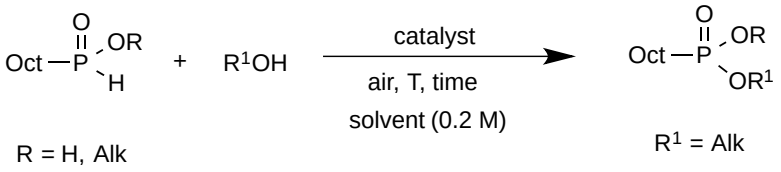
(Eq. 5.4)

5.5 Results and Discussion

The model substrates for the reaction optimization studies were either the ethyl- or butyl octyl-*H*-phosphinate most conveniently prepared from the octyl-*H*-phosphinic acid by either Dean-Stark or alkoxysilane esterification methods.[18,185] Table 5.3 summarizes the most significant results from the reaction condition studies. Earlier iterations of the reaction used ethanol as a reagent as well solvent. Right away, it was observed that slight heating was necessary (entry 1) and a larger amount of catalyst from 3 to 5 mol% was also needed (entries 2 and 3).

Decreasing at 81% isolated (entry 4). Entries 5-9 show that using lower equivalents of ethanol in solution with various solvents reduced the reaction efficiency significantly.

Table 5.3 Conditions Optimization for the copper-catalyzed oxidation of alkyl-*H*-phosphinates.



R = H, Alk

R^1 = Alk

entry	R	R^{1}OH (eq)	catalyst	amount (mol %)	solvent	T (° C)	time (h)	isolated yield % (% conversion)[a]
1	Et-	Et- (30)	CuCl	3	EtOH	25	18	- (49)
2	Et-	Et- (30)	CuCl	3	EtOH	50	18	- (22)
3	Et-	Et- (30)	CuCl	5	EtOH	50	18	81
4	Et-	Et- (86)	CuCl	5	EtOH	65	18	81
5	Et-	Et- (5)	CuCl	5	$PhCH_3$	70	18	NR
6	Et-	Et- (10)	CuCl	5	$PhCH_3$	65	18	43
7	Et-	Et- (10)	CuCl	5	DMF: $PhCH_3$ (1:1 v/v)	65	18	40
8	Et-	Et- (10)	CuCl	5	DMF	65	18	44
9	Et-	Et- (10)	CuCl	5	THF	65	18	< 10
10	Bu-	Bu- (55)	CuCl	5	BuOH	55 - 65	18	- (27)
11	Bu-	Et- (10)	CuCl	5	EtOH	55 - 65	18	67
12	Bu-	Bu- (10)	CuCl	5	DMF	65	18	50
13	Bu-	Bu- (5)	CuCl	5	THF	65	18	76
14	Bu-	Bu- (10)	CuCl	5	CH_3CN	65	18	- (15)
15	Et-	Et- (1.2)	$CuCl_2$	5	neat	65	16	NR
16	Et-	Et- (10)	$CuCl_2$	5	DMF	65	12	< 10
17	Et-	Et- (15)	$CuCl_2$	5	DMF	65	16	- (33)
18	Et-	Et- (86)	$CuCl_2$	5	EtOH	55	14	60
19	Et-	Et- (86)	Pd/C	2	EtOH	65	16	< 10
20	Et-	Et- (86)	Pd/C + $CuCl_2$	2 + 2	EtOH	65	16	- (100)
21	Et-	Et- (86)	CuBr	5	EtOH	65	16	- (12)
22	Et-	Et- (86)	CuI	5	EtOH	65	16	- (32)
23	Et-	Et- (86)	$CuAc_2$	5	EtOH	65	16	- (27)
24	Et-	Et- (86)	$CuSO_4 \bullet H_2O$	5	EtOH	65	16	- (49)
25	Et-	Et- (86)	$NiCl_2$	5	EtOH	65	16	NR

[a] Percent conversion of the product determined by ^{31}P NMR analysis and completed after extractive work-up due to the paramagnetic interference with copper.

A switch to the butyl ester was completed to reduce the dealkylating side reaction that can be observed using the *H*-phosphinate.

The preparation of the dibutyl phosphonate in neat butanol had low conversion due to the moisture in the solvent (entry 10).

Other than ethanol that is available anhydrous, the alcohols are not distilled prior to use.

The synthesis of the mixed Bu-, Et- ester in anhydrous ethanol was accomplished in moderate yield (entry 11).

Studies of solution conditions with various solvents showed that THF was a promising choice with 76% isolated yield of product and only 5 equivalents of butanol (entries 12-14).

However, this is not consistent with the result with using ethyl octyl-*H*-phosphinate perhaps due to the volatility of the ethanol (entry 9).

A reaction using $CuCl_2$ and conditions similar to Okamoto's failed (entry 15).[197] Overall, results using $CuCl_2$ were much poorer (entries 16-18) with the best comparable result at 60% isolated yield in ethanol as solvent (entry 18). A possible explanation for the lower yield of desired product is that copper(II) chloride is more reactive and can increase the rate of metal-catalyzed tautomerization to form more air-sensitive P(III) species.

Entries 19 to 25 summarize experiments completed using other metals and copper salts as catalysts, but the overall percent conversion to desired product was very low.

The only exception was entry 20 with a combination of Pd/C and $CuCl_2$ giving a clean conversion to product after extractive work-up. Not surprisingly, $NiCl_2$ does not work as a catalyst for oxidation with alcohols (entry 25).

This result is further supported by our studies with nickel-catalyzed hydrophosphinylation, where the formation of dialkyl esters are not observed even when using alkyl phosphinate solutions that contain an excess of alcohol.[185]

5.6 Conclusion

There are numerous literature methods to prepare *H*-phosphonate diesters, including transesterification.[198] However, the present methodology is the only one that does not rely on PCl_3 at any point and is atom economical by providing the valuable H_2 instead of HCl. The developed reaction is greener than the alternative because it only uses H_3PO_2, an alcohol, and nickel on silica gel as a catalyst, which be reused and no by-products are formed. Nickel chloride is a superior catalyst for this transformation, but it cannot be reused. The present reaction thus provides an important link between hypophosphorous chemistry, a phosphorus feedstock that is not fully exploited, and key intermediates that are normally prepared through PCl_3. Thus, it is another tool in the growing methodological toolbox for a phosphorus economy based on hypophosphites. Also the reaction via $ROP(O)H_2$ appears much more general than the direct esterification of phosphorous acid. Our process provides alternative access to an important class of industrial intermediates. The elucidation and prediction of subtle effects in phosphinylidene P(O)H chemistry are currently being investigated.

Initial studies were completed for the oxidative addition of alcohols to alkyl-*H*-phosphinates with promising results using 5 mol% copper(I) chloride, in ethanol as the solvent, and bubbling air into the reactor.

The results show that alkyl-*H*-phosphinates are less reactive than alkyl hyposphosphites or dialkyl phosphonates as substrates for catalytic addition of alcohol to form the diester phosphonate.

More optimization studies need to be completed to make the reaction more general by using near equal molar amounts of alcohol and preferably in a solvent system.

Experimental Section

Reagents and Solvents. All starting materials were purchased from commercial sources and used as received. The solvents were distilled under N_2 and dried according to standard procedures (Toluene and Acetonitrile from CaH_2; THF from Na/benzophenone ketyl; N, N-diisopropylethylamine was distilled from CaH_2 and stored over 4Å molecular sieves).

Purification. Flash chromatography experiments were carried out on Silica Gel premium Rf grade (40-75 μm). Ethyl acetate/hexane mixtures were used as the eluent for chromatographic purifications. TLC analyses were performed on sheets precoated with silica gel $60F_{254}$. Compound detection was achieved by exposure to UV light (254 nm), by immersion in iodine coated on silica gel or anisaldehyde stain (by volume: 93% ethanol, 3.5 % H_2SO_4, 1% AcOH and 2.5% anisaldehyde) followed by heating at 150°C.

NMR Data. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a 300 MHz or 400 MHz spectrometer.

Chemical shifts for ^{1}H NMR are given in ppm relative to internal tetramethylsilane (d = 0 ppm), using $CDCl_3$ as solvent. Chemical shifts for ^{13}C NMR are given in ppm relative to $CDCl_3$ (d = 77.0 ppm).

Chemical shifts for ^{31}P NMR spectra are given relative to external 85% phosphoric acid (d = 0 ppm).

Abbreviations used for signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet.

^{31}P NMR Yield Measurements. The NMR yields are determined by integration of all the resonances in the ^{31}P spectra, an approach which 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. Isolated yields are sometimes significantly lower in the case of H-phosphinate esters because these are polar compounds and hydrolytically labile. This does not reflect an inaccuracy in the NMR yield, but instead the fact that H-phosphinates can be difficult to purify. Validation of NMR yields was conducted in *J. Org. Chem*. **2005**, 70, 4064.

High resolution mass spectra (HRMS).

HRMS were obtained either by direct probe (EI/CI) and analyzed by magnetic sector, or by electrospray using a TOF analyzer.

Preparation of AlkOP(O)H_2 Stock Solution using Alkoxysilanes. The preparation of these compounds was conducted as described in the literature.[11a] In a typical procedure, a solution of the pre-concentrated hypophosphorous acid (125 mmol), alkoxysilane (125 mmol for $(RO)_4Si$, or 250 mmol for $(RO)_2SiMe_2$, in reagent grade toluene (to 0.5 M concentration) is refluxed for 2 h under N_2. After cooling to room temperature, the solution was bottled, sealed with a septum and the headspace was flushed with N_2. The solution was used for the subsequent hydrophosphinylation reactions directly without further purification.

Formation of AlkOP(O)H_2 with Alcohol using Azeotropic Removal of Water. Augmented procedure previously reported in the literature.[4a] A flask containing pre-concentrated H_3PO_2 (75 mmol) and alcohol (375 mmol) in reagent grade toluene (0.5 M) was equipped with a Dean-Stark

trap prefilled with toluene and fitted with a condenser. The solution was refluxed under N_2 for 3 h and then cooled to room temperature. The solution was bottled, sealed with a septum and the headspace was flushed with N_2. The solution was used for the subsequent hydrophosphinylation reactions directly without further purification.

Chapter Two-

Procedure for the Collection of Kinetic Data via ^{31}P NMR for Structure Influence Studies. Phosphosphinylidene compounds were diluted to 1 M using freshly distilled CH_3CN in a 4-dram glass vial (Note: Store solutions in the freezer when not in use). By 1 mL syringe, 0.5 mL of phosphinylidene solution (0.5 mmol) was added to a dry NMR tube and capped until needed. D_2O (99.99 atom %, no internal reference, 0.1 mL, 5.5 mmol, 11 equiv) was added by autopipette, recapped, and the tube was inverted one time to mix the solution. The time from the addition of D_2O to start of the data collection was noted. Data was collected at room temperature using four transients over regular time intervals as pre-determined by running a test sample, which was also used as a reference sample to lock, tune and shim the spectrometer before each run. The NMR kinetic experiments were completed in duplicate for each phosphinylidene sample.

Procedure for the Collection of Kinetic Data via ^{31}P NMR for Catalyst Studies. *Tert*-butyl octyl-*H*-phosphinate was diluted to 1.25 M using freshly distilled CH_3CN in a 4-dram glass vial (Note: Store solutions in the freezer when not in use). By 1 mL syringe, 0.4 mL of *H*-phosphinate solution (0.5 mmol) was added to a dry NMR tube and capped until needed. A 0.5 M stock solution of catalyst was prepared in a small glass vial using distilled CH_3CN, and 0.1 mL (0.05 mmol, 5 mol%) of this solution was added by syringe to the NMR tube. D_2O (99.99

atom %, no internal reference, 0.1 mL, 5.5 mmol, 11 equiv) was added by autopipette, recapped, and the tube was inverted one time to mix the solution. The time from the addition of D_2O to start of the data collection was noted. Data was collected at room temperature using four transients over regular time intervals as pre-determined by running a test sample, which was also used as a reference sample to lock, tune and shim the spectrometer before each run. The NMR kinetic experiments were completed in duplicate for each catalyst tested.

Preparation of Phosphinylidene Compounds for Structure Influence Kinetic Studies.

Diethyl phosphite, diphenyl phosphite, dibenzyl phosphite, phenylphosphinic acid, DOPO and sodium hypophosphite were all used as purchased without further purification. Hypophosphorous and phosphorous acids were acquired as 50 wt.-% solutions in water and pre-concentrated *in vacuo* at rt for 15 minutes before use. All other phosphinylidene compounds used for the kinetics studies were synthesized according to literature procedures.

Dibutyl phosphine oxide (Table 2, entry 2). Prepared from diethyl phosphite according to literature procedure.[199] Yield, 3.44 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 446 Hz, 1H), 1.81 (m, 4H), 1.63 (m, 4H), 0.968 (t, J = 7.4 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 34.9 (dm, J = 455 Hz).

5,5-Dimethyl-1,3,2-dioxaphosphinane-2-oxide (Table 2, entry 5).[200] After column chromatography on silica gel (80:20 Hexanes: EtOAc to 100% EtOAC), white solid, 3.53 g (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 676 Hz, 1H), 4.06 (m, 4H), 1.26 (s, 3H), 0.942 (s, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 3.02 (dm, J = 671 Hz).

Ethyl Octylphosphinate (Table 2, entry 6). Prepared from octylphosphinic acid according to literature procedure.[19] After column chromatography on silica gel (80:20 Hexanes: EtOAc to 100% EtOAC), clear oil, 2.76 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 526 Hz, 1H), 4.17 (m, 2H), 1.74 (m, 2H), 1.58 (m, 2H), 1.42-1.28 (m, 13H), 0.88 (t, J = 6.96 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 39.1 (dm, J = 526 Hz).

Dimethyl thiophosphonate (Table 2, entry 7). Prepared according to literature procedure.[201] Yield, 1.90 g (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36(d, J = 600 Hz), 3.86 (m, 6H, J = 15 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 75.2 (dm, J = 590 Hz).

Octylphosphinic acid (Table 2, entry 8). Prepared according to literature procedure,[185] Yield, 15.6 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.4 (br, 1H), 7.11 (d, J = 541 Hz), 1.77 (m, 2H), 1.61 (m, 2H), 1.41 (m, 2H), 1.29 (m, 8H), 0.92 (t, J = 7.09 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 34.8 (d, J = 536 Hz).

Ethyl phenylphosphinate (Table 2, entry 10). Prepared from phenylphosphinic acid according to literature procedure.[19] Yield, 2.72 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 563 Hz, 1H), 7.80 (m, 2H), 7.62 (m, 1H), 7.55 (m, 2H), 4.18 (m, 2H), 1.40 (t, J = 6.80 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.6 (d, J = 563 Hz).

4,4,5,5-Tetramethyl-1,3,2-dioxaphospholane-2-oxide (Table 2, entry). Prepared from diethyl phosphite according to literature procedure.[200] Yield, 2.93 g (17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 708 Hz, 1H), 1.48 (s, 6H), 1.38 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.7 (d, J = 708 Hz).

Octyl phenylphosphine oxide (Table 2, entry 12). Prepared according to literature procedure.[202] Yield, 1.43 g (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.54 (m, 3H), 7.50 (d, J = 463 Hz, 1H), 2.01 (m, 2H), 1.61 (m, 2H), 1.42 (m, 2H), 1.26 (t, J = 7.08 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4, 131.2 (d, J = 95.6 Hz), 129.9 (d, J_{PCC} = 11.1 Hz), 128.9 (d, J_{PCC} = 13.1 Hz), 31.7. 30.7, 30.6 (d, J = 20.1 Hz), 29.5 (d, J_{PC} = 99.6 Hz), 29.0, 22.6, 21.5 (d, J_{PCCC} = 4.02 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.4 (d, J = 481 Hz).

Diphenylphosphine oxide (Table 2, entry 14). Prepared from chlorodiphenylphosphine according to literature procedure.[203] Yield, 4.49 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 480 Hz, 1H), 7.73 (m, 4H), 7.58 (m, 2H), 7.51 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.4 (d, J = 481 Hz).

Preparation of Phosphinylidene Compounds and Organic Catalysts for Kinetic Studies.

***Tert*-butyl octylphosphinate.** The synthesis of tert-butyl hypophosphite solution is based on a procedure by Schwabacher et al.[22] Aqueous H_3PO_2 (50 wt.-%, 6.6 g, 50 mmol, 2 equiv) was weighed into a 250-mL round bottom flask, and concentrated *in vacuo* at rt for 15 min. Trimethyl orthoformate (16.4 mL, 150 mmol, 3 equiv) and *t*-BuOH (19.1 mL, 200 mmol, 4 equiv) was weighed into the flask, and stirred at rt under N_2 for 3 h. Triethylamine (3.2 mL) was added to stop the reaction with trimethyl orthoformate, and the solution was concentrated *in vacuo* for 10 minutes to remove the volatiles. Two cycles of *t*-BuOH addition (4 equiv), stirring for 2Hours, followed by concentration was completed. Distilled CH_3CN (100 mL) was added and the solution was filtered over filter paper. 1-Octene (25 mmol, 1 equiv) and AIBN (0.82 g, 5 mmol, 0.2 equiv) was added to the solution and refluxed under N_2 for 6Hours. After the intial reflux

period, another aliquot of AIBN was added and refluxed overnight. The crude solution was concentrated and column chromatography on silica gel (80:20 Hexanes: EtOAc to 100% EtOAC) was completed to produce 2.75 g (47%) of clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 520 Hz, 1H), 1.72 (m, 2H), 1.51 (m, 11H), 1.35 (m, 2H), 0.89 (t, J = 7.05 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 81.8 (d, J_{POC} = 9.1 Hz), 31.8, 30.4 (d, J_{POCC} = 16.1 Hz), 30.1 (d, J = 5.03 Hz), 29.5 (d, J_{PC} = 97.6 Hz), 29.0 (d, J = 8.04 Hz), 22.6, 21.0 (d, J = 3.02 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.3 (dm, J = 520 Hz).

Di-*tert*-butyl phosphite. Prepared from PCl_3, according to literature procedure.[204] Yield, 25.7 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 681 Hz, 1H), 1.51 (s, 18H); ^{31}P NMR (162 MHz, $CDCl_3$): δ -3.17 (d, J = 680 Hz).

Thiosaccharin. Prepared from saccharin according to literature procedure.[205] Yield, 7.93 g (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (br, 1H), 8.21 (d, J = 11.1 Hz, 1H), 7.81 (m, 3H).

Chapter Three-Section 3.2

General Procedure for the preparation of Alkyl *H*-phosphinates using $NiCl_2$/dppe (Tables 3.2, 3.3 and Scheme 3.3). In an oven-dried 25 ml round-bottomed flask, $NiCl_2$ (0.075 mmol, 3 mol %) was suspended in 10 ml of a $ROP(O)H_2$ solution in toluene (0.5 M, 5 mmol, 2 equiv). The mixture was stirred at rt for 2H and dppe (0.0825 mmol, 3.3 mol %) was added. After 30 min, the alkene (2.5 mmol, 1 equiv) was added and the mixture was stirred at rt for 24 h. The solution was then washed with water (10 ml x 2), sat. $NaHCO_3$ (10 ml) and brine (10 ml). Drying over $MgSO_4$ followed by rapid column chromatography on silica gel using ethyl acetate/hexanes

mixtures afforded the corresponding *H*-phosphinate. The *H*-phosphinate compounds should be stored in dichloromethane solution (at least 0.5 M) at 0 ºC until ready to use.

Ethyl octylphosphinate (Scheme 3.3, 4a).[76] Colorless oil, 20.6 g (79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 526 Hz, 1H), 4.15-3.95 (m, 2H), 1.69 (m, 2H), 1.64 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H), 1.19 (m, 10 H), 0.80 (t, J = 6.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$,) δ 40.1 (d, J_{PH} = 526 Hz).

Butyl octylphosphinate (Scheme 3.3, 4b).[79] Colorless oil, 0.369 g (63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 527 Hz, 1H), 4.17-3.93 (m, 2H), 1.82-1.27 (m, 18 H), 0.95 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$,) δ 40.8 (d, J_{PH} = 526 Hz).

Ethyl norbornylphosphinate (Scheme 3.3, 5a).[76] Colorless oil, 0.301 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 & 6.88 (d, 2*R* & 2*S* isomers, J = 521 Hz, 1H), 4.21-3.02 (m, 2H), 2.60 (dd, J = 36.6 Hz & J = 8.2 Hz, 1H); 2.38 (s, 1H), 1.92-1.22 (m, 9 H), 1.36 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$,) δ 44.2 & 42.4 (d, 2*R* & 2*S* isomers, J_{PH} = 521 Hz).

Butyl norbornylphosphinate (Scheme 3.3, 5b). Colorless oil, 0.470 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 & 6.87 (d, 2*R* & 2*S* isomers, J = 522 & 521 Hz, 1H), 4.16-3.92 (m, 2H), 2.60 (dd, J = 34.9 Hz & J = 8.9 Hz, 1H); 2.38 (s, 1H), 1.88-1.21 (m, 13H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.0 (d, CH_2, J_{POC} = 7.7 Hz), 40.4 (d, CH, J_{PC} = 95 Hz), 37.2 (CH_2), 37.1 (d, CH, J_{PCCC} = 10.1 Hz), 36.1 (d, CH, J_{PCC} = 9.2 Hz), 32.5 (d, CH_2, J_{POCC} = 5.8 Hz), 31.4 (d, CH_2, J_{PCC} = 17.4 Hz), 30.1 (d, CH_2, J_{PCCC} = 21.7 Hz), 28.6, 18.8 (CH_2), 13.6 (CH_3);

^{31}P NMR (121 MHz, $CDCl_3$) δ 44.7 & 43.0 (d, 2*R* & 2*S* isomers, J_{PH} = 520 & 521 Hz); HRMS (EI^+) m/z calcd. for $C_{11}H_{21}O_2P$ ($[M]^+$) 216.1279, found 216.1276.

Ethyl 4-(diethylmaleonate)propylphosphinate (Scheme 3.3, 6a). Colorless oil, 0.449 g (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 530 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 4H), 4.09 (m, 2H), 3.34 (t, *J* = 7.3 Hz, 1H), 1.99 (m, 2H), 1.81 (m, 2H), 1.65 (m, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$,) δ 168.9, 168.8 (C), 62.4, 61.3 (3 CH_2), 51.3 (CH), 29.2 (d, CH_2, J_{PCC} = 17.0 Hz), 28.5 (d, CH_2, J_{PC} = 96.2 Hz), 18.7 (CH_2), 16.2, 14.0, 13.9 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.3 (d, J_{PH} = 530 Hz); HRMS (methane chem ion) m/z calcd. for $C_{12}H_{24}O_6P$ ($[M + H]^+$) 295.1311, found 295.1308.

Butyl 4-(diethylmaleonate)propylphosphinate (Scheme 3.3, 6b). Colorless oil, 0.355 g (44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 530 Hz, 1H), 4.20 (q, *J* = 7.3 Hz, 4H), 4.15-3.96 (m, 2H), 3.34 (t, *J* = 7.3 Hz, 1H), 2.00 (m, 2H), 1.84-1.63 (m, 6H), 1.42 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1 (2 C), 66.4 (d, CH_2, J_{POC} = 6.9 Hz), 61.6 (2 CH_2), 51.5 (CH), 32.4 (d, CH_2, J_{POCC} = 6.0 Hz), 29.4 (d, CH_2, J_{PCC} = 17.0 Hz), 28.5 (d, CH_2, J_{PC} = 94.1 Hz), 18.9 (2 CH_2), 14.1, 13.6 (3 CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.8 (d, J_{PH} = 530 Hz); HRMS (ammonia chem ion) m/z calcd. for $C_{14}H_{28}O_6P$ ($[M + H]^+$) 323.1624, found 323.1620.

Ethyl hex-5-enyl-1-phosphinate (Scheme 3.3, 7a).[76] Colorless oil, 0.198 g (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 540 Hz, 1H), 5.40 (m, 2H), 5.05–4.95 (m, 1H), 4.26–4.03 (m, 2H), 2.07 (m, 2H), 1.81–1.51 (m, 6H), 1.456 (t, *J* = 6 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.8 (d, J_{PH} = 525 Hz).

Ethyl (5-oxohexyl)phosphinate (Scheme 3.3, 8a). Colorless oil, 0.293 g (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 529 Hz, 1H), 4.09 (m, 2H), 3.83 (m, 2H), 2.48 (t, J = 3 Hz, 2H), 2.15 (s, 3H), 1.83-1.59 (m, 4H), 1.36 (t, J = 7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.8 (C), 62.1 (d, CH_2, J_{POC} = 6.5 Hz), 42.5 (CH_2), 29.6 (CH_3), 28.1 (d, CH_2, J_{PC} = 93 Hz), 23.9 (d, CH_2, J_{PCC} = 16 Hz), 19.9 (d, CH_2, J_{PCCC} = 2.7 Hz), 15.9 (d, CH_3, J_{POCC} = 6.04 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.2 (d, J_{PH} = 528 Hz). HRMS (EI^+) m/z calcd. for $C_8H_{17}O_3P$ ($[M]^+$) 192.0915, found 192.0922.

Butyl (5-oxohexyl)phosphinate (Scheme 3.3, 8b). Yellow oil, 0.248 g (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 529 Hz, 1H), 4.07 (m, 2H), 2.48 (t, J = 3 Hz, 2H), 2.16 (s, 3H), 1.73 (m, 8 H), 1.43 (m, 2H), 0.95 (t, J = 7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.1 (C), 66.1 (d, CH_2, J_{POC} = 7.09 Hz), 42.7 (CH_2), 32.2 (d, CH_2, J_{POCC} = 6.1 Hz), 29.8 (CH_3), 28.3 (d, CH_2, J_{PC} = 95 Hz), 24.1 (d, CH_2, J_{PCC} = 16 Hz), 20.1 (d, CH_2, J_{PCCC} = 2.7 Hz), 18.6 (CH_2), 13.3 (CH_3) ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.6 (d, J_{PH} = 529 Hz). HRMS (EI^+) calcd. for $C_{10}H_{21}O_3P$ ($[M]^+$) 220.1228, found 220.1224.

Diethyl 3-(butoxy-H-phosphinoyl)propylphosphonate (Scheme 3.3, 9b). Yellow oil, 0.638 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 531 Hz, 1H), 4.15-4.09 (m, 6H), 1.92 (m, 6H), 1.70 (m, 2H), 1.46 (m, 2H), 1.33 (t, J = 7.5 Hz, 6H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.3 (d, CH_2, J_{POC} = 6.9 Hz), 61.7 (d, 2 CH_2, J_{POC} = 6.5 Hz), 32.3 (d, CH_2, J_{POCC} = 6.04 Hz), 29.2 (dd, CH_2, $J_{P(H)C}$ = 93 Hz & $J_{P(OEt)2CCC}$ = 14.7 Hz), 26.2 (dd, CH_2, $J_{P(OEt)2C}$ = 141 Hz & $J_{P(H)CCC}$ = 15.1 Hz), 18.8 (CH_2), 16.4 (d, 2 CH_3, J_{POCC} = 6.04 Hz), 14.6 (d, CH_2, J_{PCC} = 2.04 Hz), 13.6 (CH_3) ^{31}P NMR (121 MHz, $CDCl_3$) δ 37.3 (dd, J_{PH} = 532 Hz & $^{4}J_{P,P}$ = 4.0 Hz), 30.1

($^4J_{P,P}$ = 4.0 Hz). HRMS (methane chem ion) calcd. for $C_{11}H_{27}O_5P_2$ ($[M + H]^+$) 301.1334, found 301.1340.

Ethyl 3-(*N*-ethylcarbamoyl)propylphosphinate (Scheme 3.3, 10a). Colorless oil, 0.368 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 533 Hz, 1H), 4.99 (m, 1H), 4.26-4.01 (m, 4H), 3.28 (m, 2H), 1.83 (m, 4H), 1.37 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.9 (C), 62.6 (d, CH_2, J_{POC} = 6.8 Hz), 60.7 (CH_2), 40.9 (d, CH_2, J_{PCCC} = 16.9 Hz), 26.0 (d, CH_2, J_{PC} = 94.6 Hz) 21.5 (CH_2), 16.3 (d, CH_2, J_{POCC} = 6.3 Hz), 14.7 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.9 (d, J_{PH} = 534 Hz); HRMS (methane chem ion) calcd. for $C_8H_{19}NO_4P$ ($[M + H]^+$) 224.1017, found 224.1014.

Butyl 3-(*N*-ethylcarbamoyl)propylphosphinate (Scheme 3.3, 10b). Colorless oil, 0.270 g (43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 533 Hz, 1H), 5.60 (m, 1H), 4.10 (q, J = 6.2 Hz, 2H), 4.02 (m, 2H), 3.26 (m, 2H), 1.82 (m, 4H), 1.69 (m, 2H), 1.42 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) d 157.1 (C), 66.4 (d, CH_2, J_{POC} = 6.8 Hz), 60.8 (CH_2), 41.0 (d, CH_2, J_{PCCC} = 15.9 Hz), 32.5 (d, CH_2, J_{POCC} = 6.3 Hz), 26.1 (d, CH_2, J_{PC} = 94.6 Hz), 21.7, 18.9 (CH_2), 14.8, 13.7 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) d 39.7 (d, J_{PH} = 533 Hz); HRMS (methane chem ion) calcd. for $C_{10}H_{23}NO_4P$ ($[M + H]^+$) 252.1365 , found 252.1362.

Ethyl 3-(*N*-*tert*-butylcarbamoyl)propylphosphinate (Scheme 3.3, 11a).[76] Colorless oil, 0.210 g (33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 534 Hz, 1H), 4.78 (br, 1H), 4.26-4.01 (m, 2H), 3.23 (m, 2H), 1.83 (m, 4H), 1.42, (s, 9 H), 1.37 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.0 (d, J_{PH} = 532 Hz).

Butyl 3-(*N*-*tert*-butylcarbamoyl)propylphosphinate (Scheme 3.3, 11b).[76] Colorless oil, 0.335 g (43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 555 Hz, 1H), 4.18-3.95 (m, 2H), 3.21 (m, 2H), 1.85 (m, 4H), 1.70-1.59 (m, 8 H), 1.45, (s, 9 H), 0.95 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.4 (d, J_{PH} = 528 Hz).

Isobutyl 4-(butoxy-H-phosphinoyl)butanoate (Scheme 3.3, 12b). Colorless oil, 0.469 g (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 531 Hz, 1H), 4.12 (m, 2H), 3.87 (d, J = 6.90 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 1.92 (m, 4H), 1.69 (m, 2H), 1.41 (m, 2H), 0.93 (d, J = 6.7 Hz, 6H) ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.5 (C), 69.7 (CH_2), 65.3 (d, CH_2, J_{POC} = 7.2 Hz), 33.3 (d, CH_2, J_{PCCC} = 15.5 Hz), 31.4 (d, CH_2, J_{POCC} = 6.04 Hz), 26.9 (d, CH_2, J_{PC} = 93.9 Hz), 26.6 (CH), 18.0 (2 CH_3), 17.7 (CH_2), 15.4 (d, CH_2, J_{PCC} = 2.26 Hz), 12.6 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.0 (d, J_{PH} = 531 Hz) HRMS (ammonia chem ion) calcd. for $C_{12}H_{26}O_4P$ ($[M + H]^+$) 265.1569, found 265.1566.

Ethyl 4,4-diethoxybutylphosphinate (Scheme 3.3, 13a). Yellow oil, 0.167 g (28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 528 Hz, 1H), 4.48 (t, J = 4.7 Hz, 1H), , 4.20-4.09 (m, 2H), 3.64 (m, 2H), 3.49 (m, 2H), 1.71 (m, 6H), 1.37 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 102.5 (CH), 62.5 (d, CH_2, J_{POC} = 6.9 Hz), 61.1 (2 CH_2), 34.4 (d, CH_2, J_{PCCC} = 15.3 Hz), 28.7 (d, CH_2, J_{PC} = 93.6 Hz), 16.4 (d, CH_2, J_{PCC} = 2.9 Hz), 15.5 (3 CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.5 (d, J_{PH} = 528 Hz); HRMS (EI^+) calcd. for $C_{10}H_{23}O_4P$ ($[M - H]^+$) 237.1256, found 237.1257.

Butyl 4,4-diethoxybutylphosphinate (Scheme 3.3, 13b). Yellow oil, 0.240 g (36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 526 Hz, 1H), 4.47 (m, 1H), 4.05 (m, 2H), 3.65-3.39 (m, 4H), 1.83-

1.34 (m, 8 H), 1.20 (t, J = 7.0 Hz, 2H) 0.93 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 102.5 (CH), 66.3 (d, CH_2, J_{POC} = 5.13 Hz), 65.7 (CH_2), 34.0 (d, CH_2, J_{PCCC} = 11.4 Hz), 32.4 (d, CH_2, J_{POCC} = 4.60 Hz), 28.8 (d, CH_2, J_{PC} =93.9 Hz), 18.8 (CH_2), 16.3 (CH_2), 15.3(CH_3), 13.6 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.0 (d, J_{PH} = 525 Hz); HRMS (EI^+) calcd. for $C_{12}H_{27}O_4P$ ($[M - H]^+$) 265.1624, found 265.1621.

Ethyl 4-bromobutylphosphinate (Scheme 3.3, 14a).[158] Colorless oil, 0.303 g (53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 530 Hz, 1H), 4.24-4.04 (m, 2H), 3.43 (t, J = 6.5 Hz, 2H), 1.99 (m, 2H), 1.80 (m, 4H), 1.38 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.8 (d, J_{PH} = 532 Hz).

Butyl 4-bromobutylphosphinate (Scheme 3.3, 14b). Colorless oil, 0.270 g (42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 530 Hz, 1H), 4.19-3.95 (m, 2H), 3.42 (t, J = 6.5 Hz, 2H), 2.00-1.60 (m, 8 H), 1.41 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.4 (d, CH_2, J_{POC} = 6.8 Hz), 33.0 (d, CH_2, J_{PCCC} = 15.5 Hz), 32.8 (CH_2), 32.5 (d, CH_2, J_{POCC} = 5.8 Hz), 27.9 (d, CH_2, J_{PC} = 93.2 Hz), 19.6, 18.9 (CH_2), 13.7 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.1 (d, J_{PH} = 529 Hz); HRMS (methane chem ion) calcd. for $C_8H_{19}BrO_2P$ ($[M + H]^+$) 257.0306, found 257.0305.

Ethyl 5-bromopentylphosphinate (Scheme 3.3, 15a).[79] Colorless oil, 0.292 g (43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 528 Hz, 1H), 4.26-4.01 (m, 2H), 3.42 (t, J = 6.5 Hz, 2H), 1.93-1.75 (m, 4H), 1.72-1.53 (m, 4H), 1.37 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.9 (d, J_{PH} = 522 Hz).

Butyl 5-bromopentylphosphinate (Scheme 3.3, 15b).[79] Colorless oil, 0.386 g (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 525 Hz, 1H), 4.20-3.95 (m, 2H), 3.42 (t, J = 6.5 Hz, 2H), 1.93-1.53 (m, 12H), 1.37 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.9 (d, J_{PH} = 522 Hz).

Ethyl 2-(trimethylsilyl)ethylphosphinate (Scheme 3.3, 16a). Colorless oil, 0.383 g (79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 526 Hz, 1H), 4.23-4.04 (m, 2H), 1.68 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H), 0.71 (m, 2H), 0.00 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 64.4 (d, CH_2, J_{POC} = 6.9 Hz), 25.0 (d, CH_2, J_{PC} = 91.6 Hz), 18.5 (d, CH_3, J_{POCC} = 5.8 Hz), 8.3 (d, CH_2, J_{PCC} = 6.9 Hz), 0.00 (3 CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 43.5 (d, J_{PH} = 525 Hz); HRMS (ammonia chem ion) calcd. for $C_7H_{20}O_2PSi$ ($[M + H]^+$) 195.0970, found 195.0603.

Ethyl 4-phenylbutylphosphinate (Scheme 3.3, 17a).[19] Yellow oil, 0.283 g (50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5 H), 7.07 (d, J = 527 Hz, 1H), 4.20-3.98 (m, 2H), 2.63 (t, 2H, J = 7.3 Hz), 1.79-1.60 (m, 6H), 1.34 (t, J = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 39.6 (d, J_{PH} = 527 Hz).

Butyl 4-phenylbutylphosphinate (Scheme 3.3, 17b).[19] Yellow oil, 0.280 g (44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5 H), 7.14 (d, J = 527 Hz, 1H), 4.19-4.01 (m, 2H), 2.67 (t, J = 7.0 Hz, 2H), 1.89-1.65 (m, 8 H), 1.43 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.2 (d, J_{PH} = 530 Hz).

Ethyl 3-(2-hydroxyphenyl)propylphosphinate (Scheme 3.3, 18a). Light brown oil, 0.302 g (53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.12 (d, J = 535 Hz, 1H), 7.06 (m, 2H), 6.84 (m, 2H), 4.20-4.07 (m, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.05-1.74 (m, 4H), 1.36 (t, J = 7.0 Hz, 3H);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.3 (C), 130.4, 127.7 (CH), 127.1 (C), 119.8, 115.8 (CH), 63.0 (d, CH_2, J_{POC} = 6.9 Hz), 30.7 (d, CH_2, J_{PCC} = 15.3 Hz), 27.9 (d, CH_2, J_{PC} = 95.3 Hz), 21.3 (d, CH_2, J_{PCCC} = 2.3 Hz), 16.4 (d, CH_3, J_{POCC} = 6.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 41.5 (d, J_{PH} = 534 Hz); HRMS (EI^+) calcd. for $C_{11}H_{17}O_3P$ ($[M]^+$) 228.0915, found 228.0916.

Ethyl (*cis/trans*)-1-octenylphosphinate (Scheme 3.3, 23a).[139] Mixture of isomers, yellow oil, 0.485 g**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 549 Hz, 1H), 6.81-6.60 (m, 1H), 6.15-5.69 (m, 1H), 4.08-3.98 (m, 2H), 2.23-2.12 (m, 2H), 1.55-1.35 (m, 2H), 1.35-1.10 (m, 8 H), 0.80 (d, J = 7 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.5 (dm, J = 559 Hz); δ 24.7 (dm, J = 559 Hz).

Representative Procedure for the Hydophosphinylation of Alkenes followed by Hydrolysis (Table 4 and Equation 2). In an oven-dried 25-mL round-bottom flask, anhydrous $NiCl_2$ (0.075 mmol, 3 mol %) is suspended in 10 ml of a $BuOP(O)H_2$ solution in toluene (0.5 M, 5 mmol, 2 equiv). The mixture is heated for 10 min until the nickel starts to dissolve and the reaction mixture is cooled to room temperature (~15 minutes). Dppe (0.0825 mmol, 3.3 mol %) is added and after 30 min of stirring, the alkene (2.5 mmol, 1 equiv) is added and the mixture is stirred at room temperature for 24 h. Upon completion of the first reaction, aqueous sodium hydroxide solution (2 mL, 10 mmol, 4 equiv) is poured into the flask and refluxed for 12-14 h. The reaction mixture is first extracted with 10 mL of toluene, acidified with 10 mL of saturated $NaHSO_4$ solution (pH < 2), then extracted with 10 mL of ethyl acetate three times. The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation.

Octylphosphinic acid (Table 3.4, 28).[75] Yellow oil, 5.699 g (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.55 (br, 1H), 7.11 (d, J = 541 Hz, 1H), 1.78 (m, 2H), 1.61 (m, 2H), 1.29 (m, 10 H), 0.90 (t, J = 4.4 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 37.8 (d, J_{PH} = 540 Hz).

Decylphosphinic acid (Table 3.4, 29).[75] Yellow oil, 0.361 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (br, 1H), 7.05 (d, J = 537 Hz, 1H), 1.90-1.05 (m, 18 H), 0.88 (t, J = 6 Hz, 3H); ^{31}P NMR (121MHz, $CDCl_3$) δ 38.1 (d, J_{PH} = 540 Hz).

Norbornylphosphinic acid (Table 3.4, 30). Yellow oil, 0.348 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.59 (br s, 1H), 6.95 (d, J = 536 Hz, 1H), 2.63 (m, 1H), 2.40 (m, 1H), 1.83-1.23 (m, 9 H); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 40.4 (d, CH, J_{PC} = 97 Hz), 37.4 (CH_2), 37.2, 36.3 (CH), 31.6 (d, CH_2, J_{PCC} = 16 Hz), 30.2, 28.7 (CH_2); ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.8 (d, J_{PH} = 531 Hz). HRMS (EI^+) calcd. for $C_7H_{13}O_2P$ ($[M]^+$) 160.0653, found 160.0654.

Hex-5-enyl-1-phosphinic acid (Table 3.4, 31).[75] Yellow oil, 0.301 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (br, 1H), 7.12 (d, J = 530 Hz, 1H), 5.60-5.20 (m, 3H), 2.07 (m, 2H), 1.65 (m, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 41.3 (d, J_{PH} = 530 Hz).

(4-phenylbutyl)phosphinic acid (Equation 3.2, 32).[75] Yellow oil, 21.554 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (br, 1H), 7.08 (d, J = 540 Hz, 1H), 7.25 (m, 5 H), 2.64 (t, J = 7 Hz, 2H), 1.75 (m, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.0 (d, J_{PH} = 540 Hz).

Crystal Data and Data Collection Summary for Compound **32** (**Figure 3.1**).

Identification code	ys016	
Chemical formula	$C_{10}H_{15}O_2P$	
Formula weight	198.19	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.080 x 0.120 x 0.430 mm	
Crystal system	monoclinic	
Space group	C 1 c 1	
Unit cell dimensions	a = 5.5085(3) Å	α = 90°
	b = 26.3826(14) Å	β = 102.626(2)°
	c = 7.3148(4) Å	γ = 90°
Volume	1037.34(10) Å3	
Z	4	
Density (calculated)	1.269 g/cm3	
Absorption coefficient	0.231 mm-1	
F(000)	424	
Theta range for data collection	3.09 to 29.73°	
Index ranges	-7<=h<=7, -36<=k<=36, -10<=l<=10	
Reflections collected	21516	
Independent reflections	2936 [R(int) = 0.0211]	
Coverage of independent reflections	99.7%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2936 / 2 / 125	
Goodness-of-fit on F^2	1.091	
Final R indices	2894 data; I>2σ(I)	R1 = 0.0232, wR2 = 0.0601
all data	R1 = 0.0238, wR2 = 0.0606	
Largest diff. peak and hole	0.271 and -0.165 eÅ-3	
R.M.S. deviation from mean	0.043 eÅ-3	

Bond lengths (Å) for Compound **32.**

P1-O2	1.4909(12)	P1-O1	1.5497(13)
P1-C1	1.7805(16)	P1-H2	1.28(3)
O1-H1	0.86(3)	C1-C2	1.532(2)
C1-H1B	0.99	C1-H1A	0.99
C2-C3	1.528(2)	C2-H2A	0.99
C2-H2B	0.99	C3-C4	1.524(2)
C3-H3B	0.99	C3-H3A	0.99
C4-C5	1.511(2)	C4-H4A	0.99
C4-H4B	0.99	C5-C10	1.394(2)
C5-C6	1.399(2)	C6-C7	1.393(2)
C6-H6	0.95	C7-C8	1.389(2)
C7-H7	0.95	C8-C9	1.388(2)
C8-H8	0.95	C9-C10	1.390(2)
C9-H9	0.95	C10-H10	0.95

Bond angles (º) for Compound **32.**

O2-P1-O1	114.48(8)	O2-P1-C1	114.85(7)
O1-P1-C1	105.36(8)	O2-P1-H2	109.9(10)
O1-P1-H2	105.3(11)	C1-P1-H2	106.2(11)
P1-O1-H1	111.4(19)	C2-C1-P1	114.68(11)
C2-C1-H1B	108.6	P1-C1-H1B	108.6
C2-C1-H1A	108.6	P1-C1-H1A	108.6
H1B-C1-H1A	107.6	C3-C2-C1	111.24(12)
C3-C2-H2A	109.4	C1-C2-H2A	109.4
C3-C2-H2B	109.4	C1-C2-H2B	109.4
H2A-C2-H2B	108.0	C4-C3-C2	111.87(13)
C4-C3-H3B	109.2	C2-C3-H3B	109.2
C4-C3-H3A	109.2	C2-C3-H3A	109.2
H3B-C3-H3A	107.9	C5-C4-C3	115.71(13)
C5-C4-H4A	108.4	C3-C4-H4A	108.4
C5-C4-H4B	108.4	C3-C4-H4B	108.4
H4A-C4-H4B	107.4	C10-C5-C6	117.94(14)
C10-C5-C4	120.01(14)	C6-C5-C4	122.05(14)
C7-C6-C5	120.71(14)	C7-C6-H6	119.6
C5-C6-H6	119.6	C8-C7-C6	120.61(15)
C8-C7-H7	119.7	C6-C7-H7	119.7
C9-C8-C7	119.13(14)	C9-C8-H8	120.4
C7-C8-H8	120.4	C8-C9-C10	120.22(14)
C8-C9-H9	119.9	C10-C9-H9	119.9
C9-C10-C5	121.39(14)	C9-C10-H10	119.3
C5-C10-H10	119.3		

Representative Example of Hydrophosphinylation followed by Cross-Coupling (Equation 3.3). Nickel-catalyzed hydrophosphinylation was conducted as described in the procedure for Scheme 3 using 1-octene as the alkene (2.5 mmol, 1 equiv). The crude reaction mixture was washed once with deionized water and concentrated under vacuum at 50° C to remove the residual diethyl phosphite. To a solution of crude ethyl octylphosphinate (2.5 mmol, 1.0 equiv.) in freshly distilled acetonitrile (10 mL), was added an iodobenzene (2.5 mmol, 1.0 equiv.), N, N-diisopropylethylamine (5.2 mmol, 1.3 equiv.), $Pd(OAc)_2$ (0.025 mmol, 1 mol %) and dppf (0.028 mmol, 1.1 mol %) at room temperature. The solution was heated for 24 h at reflux in acetonitrile, under nitrogen. After cooling to room temperature, the crude mixture was concentrated in vacuo and the residue was partitioned between de-ionized water and ethyl acetate, followed by

extraction of the aqueous phase with EtOAc (3x). The organic fractions were combined and washed with brine (1x). Drying and concentration furnished the crude compound, which was purified by column chromatography using ethyl acetate/hexane mixtures to obtain 0.501 g (71%) of compound 24 as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.49 (m, 3H), 4.13-3.85 (dm, 2H), 1.84 (m, 2H), 1.70 -1.22 (m, 15 H), 0.85 (t, J = 6.1 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 44.9 (s).

Representative Procedure for the Hydrophosphinylation of Alkenes followed by formation of Phosphonothioic Acid O-Ethyl Ester (Scheme 3.4).[139] Nickel-catalyzed hydrophosphinylation of alkenes was conducted as described in the procedure for Scheme 3. The crude reaction mixture was washed once with deionized water and concentrated under vacuum at 50° C to remove the residual diethyl phosphite. The crude reaction mixture was dissolved in 10 mL of freshly distilled acetonitrile. To this solution was added sulfur (0.24 g, 7.5 mmol, 3 equiv) and triethylamine (0.762 g, 7.53 mmol, 3 equiv) at room temperature. The resulting mixture was stirred at room temperature overnight. The solution was extracted with hexane, and the acetonitrile layer was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes to hexanes/EtOAc, 90/10 v/v) produced the expected compounds as brown oils.

***O*-ethyl *O*-hydrogen octylphosphonothioate (Scheme 3.4, 33).** Brown oil, 0.309 g (52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 418 (m, 2H), 2.01 (m, 2H), 1.66 (m, 2H), 1.36-1.27 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 61.9 (CH_2), 34.6 (d, CH_2, J_{PC} = 109 Hz), 31.7, 30.4, 30.3, 30.1, 29.0, 22.6 (CH_2), 16.1 (d, CH_3, J_{POCC} = 7.3 Hz), 14.0 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 94.6 (s); HRMS (EI^+) calcd. for $C_{10}H_{23}O_2PS$ ($[M]^+$) 238.1156, found 238.1152.

***O*-ethyl *O*-hydrogen (4-phenylbutyl)phosphonothioate (Scheme 3.4, 34).** Brown oil, 0.381 g (59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5 H), 4.22-4.09 (m, 2H), 2.65 (m, 2H), 2.06 (m, 2H), 1.74 (m, 4H), 1.31 (t, J = 10 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.9 (C), 127.3, 124.8 (5 CH), 60.8, 34.3, 32.7, 31.1, 21.4 (CH_2), 15.1 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 94.3 (s); HRMS (EI^+) calcd. for $C_{12}H_{19}O_2PO_2S$ ($[M]^+$) 258.0843, found 258.0839.

Ethoxy(triisopropylsilyloxy)phenylbutylphosphine-borane (Scheme 3.4, 35).[53] Triisopropylchlorosilane (1.5 mL, 7 mmol, 1.4 equiv) was placed into a oven-dried round bottom flask and cooled to 0º C, under N_2. Et_3N (1 mL, 7.5 mmol, 1.5 equiv) was then added dropwise and the reaction mixture was stirred for approximately 10 min at 0 ºC. In a separate oven-dried round bottom flask, a solution of crude ethyl 4-phenylbutylphosphinate (5 mmol, 1 equiv) in freshly distilled CH_3CN (10 mL) was cooled to 0 ºC, under N_2. The mixture of TIPSCl/Et_3N was slowly added to the H-phosphinate solution via syringe and the reaction mixture maintained at 0º C for 10–15 min, at which time the reaction was allowed to warm up to room temperature and stirred for 14 h under nitrogen. The reaction mixture was treated with $BH_3{\cdot}Me_2S$ (2.0 M in THF, 5 mL, 10 mmol, 2 equiv) by dropwise addition at room temperature. After 5 h, the reaction mixture was concentrated under reduced pressure, and the residue partitioned between de-ionized H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers washed with brine (1x), dried over $MgSO_4$, and concentrated in vacuo to afford the crude compound. Purification by column chromatography over silica gel (hexanes–toluene, 100:0 to 90:10, v/v) afforded 0.476 g (48%) of the desired product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 529 Hz, 1H), 7.3-7.1 (m, 5 H), 4.25-3.95 (m, 2H), 2.63 (t, J = 7 Hz, 2H), 1.90-1.55 (m, 6H), 1.34 (t, J = 7 Hz, 3H), 1.06 (m, 21H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.9, 128.6, 126.1 (5 CH, 1 C), 62.5 (d, CH_2, J_{POC} = 7 Hz), 35.6 (CH_2), 32.4 (d, CH_2, J_{PCCC} = 15 Hz),

28.9 (d, CH_2, J_{PC} = 94 Hz), 20.6 (CH_2), 16.6 (6 CH_3), 16.5 (d, CH_3, J_{POCC} = 6 Hz), 11.6 (3 CH) ^{31}P NMR (121 MHz, $CDCl_3$) δ 134.7 (q, J_{PB} = 48 Hz); HRMS (EI^+) calcd. for $C_{21}H_{42}BO_2PSi$ ($[M]^+$) 396.2785, found 396.2788.

1-Ethoxy-phosphinane-1-oxide (Scheme 3.5, 36).[206] Compound **15a,** Ethyl 5-bromopentylphosphinate (5 mmol, 1 equiv), was prepared by the standard hydrodrophosphinylation procedure. The crude product was partioned between de-ionized water and ethyl acetate to remove the formed diethyl phosphite. The dried and concentrated product was diluted with anhydrous THF (25 mL) under nitrogen. The flask was placed at -78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 5 mL, 5 mmol, 1 equiv) was added at -78 °C. After 10 min, the temperature of the solution was slowly allowed to warm to rt. After 3 h at rt, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3x), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel using mixtures of EtOAc/hexanes to afford 0.603g (74%) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (m, 2H), 2.03-1.63 (m, 10 H), 1.37 (t, J =6.9 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 50.08 (s).

3-Hydroxy-2-phenyl-1,3-azaphosphorinane-3-oxide (Scheme 3.5, 37).[158] Compound **10a,** Ethyl 3-(*N*-ethylcarbamoyl)propylphosphinate (10 mmol), was prepared by the standard hydrophosphinylation procedure. Upon completion, the reaction mixture was concentrated in vacuo to remove the toluene, and hydrochloric acid (12 N, 50 mL) was added to the flask. After 16 h of reflux, the mixture was concentrated under high vacuum. The residue was diluted with water and washed with ethyl acetate (3 x 20 mL). Concentration of the aqueous layer afforded

1.830 g (82%) of 3-aminopropyl-*H*-phosphinic acid hydrochloride as a yellow oil. Immediately following, the H-phosphinic acid was diluted in n-butanol (0.2 M) and 1 equiv of the benzaldehyde was added. The mixture was refluxed for 16 h. After cooling, the precipitate was filtered and washed with n-butanol and then with diethyl ether and dried under high vacuum to obtain 0.970 g (56%) of the expected compound as a white solid. ^{1}H NMR (300 MHz, D_2O) δ 7.31 (m, 5 H), 4.21 (d, J = 6.6 Hz, 1H), 3.42 (d, J_{gem} = 13 Hz, 1H equatorial), 3.05 (m, 1H, axial), 2.20-2.06 (m, 2H), 1.74 (m, 2H); ^{31}P NMR (121 MHz, D_2O) δ 23.4 (m).

Ethyl 2-(1-ethoxy-2-methyl-1-oxidophosphinanyl)acetate (Scheme 3.5, 38). An ethyl *H*-phosphinate was prepared from ethyl 3-methylhepta-2,6-dienoate using the standard nickel hydrophoshinylation procedure. Ethyl 7-(ethoxy-*H*-phosphinoyl)-3-methyl-2-heptenoate was obtained as a yellow oil in 66% isolated yield. To a solution of *H*-phosphinate in THF (0.08 M, 0.76 mmol) at 0º C, was added potassium *tert*-butoxide (0.76 mmol, 1 equiv). The solution was stirred for 1 h at 0º C and rt for 16 h. The reaction mixture was neutralized with 1 N HCl and extracted with ethyl acetate (3x 10 mL). Initial analysis of the product showed significant cleavage of the ester group. The compound was diluted in dichloromethane and treated with ethanol (1.16 mmol, 1.5 equiv), EDC (1.16 mmol, 1.5 equiv) and DMAP (0.076 mmol, 10 mol%). After 2 h of stirring at rt, the solution was extracted with saturated $NaHSO_4$ (1x 10 mL), 1 N $NaHCO_3$ (1 x10 mL), and brine (1x 10 mL). After drying with $MgSO_4$ and concentrating in vacuo, 0.116 g (57%) of a brown oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19-4.08 (m, 4H); 2.65 (m, 2H); 2.05-1.43 (m, 8 H); 1.35-1.25 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1 (C), 60.6 (d, CH_2, J_{POC} = 8.68 Hz), 37.5 (C), 36.6 (d, CH_2, J_{PC} = 88 Hz), 35.3, 30.9 (CH_2), 24.1 (d, CH_2, J_{PCCC} = 3.40 Hz), 23.1, 21.2 (CH_2), 18.9 (CH_3), 16.9 (d, CH_3, J_{POCC} = 5.36 Hz), 14.1

(CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 53.3 (m); HRMS (EI^+) calcd. for $C_{12}H_{23}O_4P$ ($[M]^+$) 262.1334, found 262.1334.

Chapter 4-Section 4.2

General Procedure for Manganese-catalyzed Addition of Alkenes or Alkynes to *H*-phosphinates: To a selected *H*-phosphinate (1.2 mmol, 1.2 equiv) either neat or in DMSO (0.2 M, 5 mL) was added an alkene (1 mmol, 1 equiv) and $Mn(OAc)_2$ (9 mg, 0.05 mmol, 5 mol %). The reaction mixture was stirred for 20 h at 100 ^{0}C with the condenser open to the air. Ethyl acetate (~ 20 mL) and an aqueous solution of $Na_2S_2O_4$ at 0.5 M in brine (~40 mL) were added, partitioned and the two layers were separated. The organic layer was washed with saturated $NaHCO_3$/brine (~ 40 mL) and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product. Generally, the compound was ≥ 95% pure; however, column chromatography was used if further purification of the product was needed.

Ethyl dioctylphosphinate (Table 4.1, entry 1). Product was prepared using the representative procedure and ethyl octyl-*H*-phosphinate[185] to obtain a light brown oil (226 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 4.18-3.97 (m, 2H), 1.78-1.43 (m, 8 H), 1.42-1.19 (m, 23H), 0.89 (t, J = 6.6 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$,): δ 59.7 (d, J_{POC} = 6.6 Hz), 30.8 (d, J_{PCC} = 1.9 Hz, 2C), 30.7 (2 C), 29.0 (2 C), 28.9 (2 C), 27.9 (d, J_{PC} = 89.6 Hz, 2C), 22.5 (2 C), 21.8 (d, J_{PCCC} = 3.9 Hz, 2 C), 16.6 (d, J_{POCC} = 5.5 Hz), 13.9 (2 C); ^{31}P NMR (121 MHz, $CDCl_3$,): δ 57.8 (s); HRMS (EI+) m/z calcd for $C_{18}H_{39}O_2P$ ([M]+) 318.2688, found 318.2686.

Butyl dioctylphosphinate (Table 4.1, entry 13).[207] The product was prepared using the representative procedure with butyl octyl-*H*-phosphinate[185] to obtain a light brown oil (308 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (m, 2H), 1.78-1.47 (m, 10 H), 1.45-1.18 (m, 22H), 0.96-0.79 (t x 2, J = 7.2 Hz, 9 H); ^{31}P NMR (121 MHz, $CDCl_3$,): δ 57.6.

Cyclohexyl dioctylphosphinate (Table 1, entry 14). The product was prepared using representative procedure with cyclohexyl octyl-*H*-phosphinate.[110] After purification, the product was obtained as colorless oil (362 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 4.19-4.07 (m, 1H), 1.70-1.61 (2H), 1.54-1.19 (m, 12H), 1.18-0.97 (m, 24H), 0.64 (t, J = 6.7 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 72.8 (d, J_{POC} = 6.8 Hz), 34.0 (2 C), 31.6 (2 C), 30.6 (d, J_{PCC} = 15.0 Hz, 2C), 28.8 (2 C), 28.8 (2 C), 28.5 (d, J_{PC} = 90.0 Hz, 2 C), 25.0, 23.5 (2 C), 22.4 (2 C), 21.7 (d, J_{PCCC} = 3.8 Hz, 2 C), 13.8 (2 C); ^{31}P NMR (121 MHz, $CDCl_3$,): δ 56.4 (s); HRMS (EI+) m/z calcd for $C_{22}H_{45}O_2P$ ([M]+) 372.3157, found 372.3160.

Ethyl cyclooctyl(octyl)phosphinate (Table 4.2, entry 1a). The product was prepared using representative procedure with ethyl octyl-*H*-phosphinate[185] to obtain a light brown oil (206 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 4.18-3.95 (m, 2H), 2.09-1.42 (m, 18 H), 1.41-1.18 (m, 14H), 0.88 (t, J = 6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$,): δ 60.0 (d, J_{POC} = 6.6 Hz), 36.2 (d, J_{PC} = 87.6 Hz), 31.7, 31.0 (d, J_{PCC} = 14.3 Hz), 29.0 (d, J_{PCCC} = 2.2 Hz, 2 C), 26.7, 26.4 (d, J_{PCC} = 13.3 Hz), 26.0 (2 C), 25.9 (2 C), 25.6, 25.5 (d, J_{PC} = 90.0 Hz), 22.6, 21.7 (d, J_{PCCC} = 3.9 Hz), 16.7 (d, J_{POCC} = 5.0 Hz), 14.0; ^{31}P NMR (121 MHz, $CDCl_3$,): δ 61.7 (s); HRMS (EI+) m/z calcd for $C_{18}H_{37}O_2P$ ([M]+) 316.2531, found 316.2533.

Butyl cyclooctyl(octyl)phosphinate (Table 4.2, entry 1b). The product was prepared using the representative procedure with butyl octyl-*H*-phosphinate[185] to obtain a light brown oil (200 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01-3.96 (m, 2H), 1.99 (m, 2H), 1.83 (m, 2H), 1.72-1.45 (m, 15 H), 1.38 (m, 4H), 1.29 (m, 10 H), 0.97-0.90 (t x 2, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 63.8 (d, J_{POC} = 7.0 Hz), 36.2 (d, J_{PC} = 87.5 Hz), 32.9 (d, J_{PCCC} = 6.0 Hz), 31.7, 31.0 (d, J_{PCC} = 15.1 Hz), 29.0 (d, J_{PCCC} = 3.0 Hz), 26.7, 26.5 (d, J_{PCC} = 13.1 Hz), 26.0 (2 C), 25.9 (2 C), 25.7, 25.5 (d, J_{PC} = 87.5 Hz), 22.6, 21.7 (d, J_{PCCC} = 4.0 Hz), 18.8, 14.0, 13.6; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 61.4 (s); HRMS (EI+) m/z calcd for $C_{20}H_{41}O_2P$ ([M]+) 344.2844, found 344.2848.

Cyclohexyl cyclooctyl(octyl)phosphinate (Table 4.2, entry 1c). The product was prepared using the representative procedure with cyclohexyl octyl-*H*-phosphinate.[110] After purification, the product was obtained as light brown oil (196 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (m, 1H), 2.15-1.85 (m, 5 H), 1.80-1.41 (m, 18 H), 1.39-1.21 (m, 16H), 0.9 (t, J = 6.80 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.8 (d, J_{POC} = 7.0 Hz), 36.7 (d, J_{PC} = 88.5 Hz), 34.2 (d, J_{POCC} = 3.0 Hz), 34.1 (d, J_{POCC} = 4.0 Hz), 31.7, 31.0 (d, J_{PCC} = 14.1 Hz), 29.0 (d, J_{PCCC} = 3.0 Hz), 26.8, 26.5 (d, J_{PCC} = 14.1 Hz), 26.2 (d, J_{PCCCC} = 1.0 Hz), 26.2 (d, J_{PC} = 86.5 Hz), 26.1 (2 C), 25.9 (2 C), 25.6 (d, J_{PCCCC} = 1.0 Hz), 25.2, 23.6, 22.6 (2 C), 21.8 (d, J_{PCCC} = 5.0 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 60.6 (s); HRMS (EI+) m/z calcd for $C_{22}H_{43}O_2P$ ([M]+) 370.3001, found 370.3003.

Ethyl (3-(ethoxy(octyl)phosphoryl)propyl)carbamate (Table 4.2, entry 2). The product was prepared using the representative procedure with ethyl octyl-*H*-phosphinate[185] to obtain a brown oil (184 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 5.30 (m, 1H), 4.03 (m, 4H), 4.23 (m, 2H), 1.89-1.58 (m, 6H), 1.55 (m, 2H), 1.45-1.19 (m, 16H), 0.86 (t, J = 7.0 Hz); ^{13}C NMR (101 MHz,

$CDCl_3$,): δ 156.8, 60.7, 60.1 (d, J_{POC} = 7.0 Hz), 41.3 (d, J_{CN} = 15.1 Hz), 31.8 (2 C), 30.9 (d, J_{PCC} = 15.1 Hz), 29.0 (2 C), 28.2 (d, J_{PC} = 89.6 Hz), 25.3 (d, J_{PC} = 90.6 Hz), 22.5 (2 C), 21.6 (d, J_{PCCC} = 5.0 Hz), 16.7 (d, J_{POCC} = 5.0 Hz), 14.6, 14.1; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 57.3 (s); HRMS (EI+) m/z calcd for $C_{16}H_{34}NO_4P$ ([M]+) 335.2225, found 335.2222.

Diethyl 2-(3-(butoxy(octyl)phosphoryl)propyl)malonate (Table 4.2, entry 3). The product was prepared using the representative procedure with butyl octyl-*H*-phosphinate[185] to obtain a light brown oil (313 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 4.18 (q, J = 6.8 Hz, 4H), 3.95 (q, J = 6.8 Hz, 2H), 3.33 (t, J = 7.6 Hz, 1H), 1.97 (q, J = 7.6 Hz, 2H), 1.78-1.50 (m, 9 H), 1.46-1.21 (m, 19 H), 0.96-0.82 (t x 2, J = 7.6 Hz, 6H) ; ^{13}C NMR (101 MHz, $CDCl_3$,): δ 169.1 (2 C), 63.8 (d, J_{POC} = 7.0 Hz), 61.4 (2 C), 51.6, 32.8 (d, J_{PCCC} = 5.0 Hz), 31.8, 30.9 (d, J_{PCC} = 15.1 Hz), 29.8 (d, J_{PCC} = 16.1 Hz), 29.0 (2 C), 28.0 (d, J_{PC} = 90.6 Hz), 27.9 (d, J_{PC} = 89.6 Hz), 22.6, 21.9 (d, J_{PCCC} = 5.0 Hz), 20.0 (d, J_{POCC} = 4.0 Hz), 18.8, 14.1 (3 C), 13.7; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 56.4 (s); HRMS (EI+) m/z calcd for $C_{22}H_{43}O_6P$ ([M]+) 434.2797, found 434.2795.

Cyclohexyl cyclohexyl(octyl)phosphinate (Table 4.2, entry 4). The product was prepared using the representative procedure with cyclohexyl octyl-*H*-phosphinate.[110] After purification, the product was obtained as light brown oil (250 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 4.39 (m, 1H), 1.92 (m, 4H), 1.84 (m, 2H), 1.74 (m, 3H), 1.72-1.45 (m, 8 H), 1.42-1.20 (m, 18 H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$,): δ 72.9 (d, J_{POC} = 6.0 Hz), 37.9 (d, J_{PC} = 91.6 Hz), 34.2 (d, J_{POCC} = 9.1 Hz, 2 C), 31.8 (2 C), 31.1 (d, J = 14.1 Hz), 29.0 (2 C), 26.4 (d, J_{PC} = 90.0 Hz), 26.3 (d, J_{PCC} = 14.1 Hz), 25.9, 25.3 (d, J_{PCC} = 14.1 Hz), 25.2, 23.7 (2 C), 22.6 (2 C), 21.7, 14.0; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 57.5 (s); HRMS (EI+) m/z calcd for $C_{20}H_{39}O_2P$ ([M]+) 342.2688, found 342.2687.

Cyclohexyl (5-bromopentyl)(octyl)phosphinate (Table 4.2, entry 5). The product was prepared using the representative procedure with cyclohexyl octyl-*H*-phosphinate.[110] After purification, the product was obtained as light brown oil (220 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 4.37 (m, 1H), 3.43 (t, J = 6.4 Hz, 2H), 1.90 (m, 4H), 1.81-1.45 (m, 16H), 1.43-1.20 (m 17 H), 0.89 (t, J = 5.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$,): δ 73.3 (d, J_{POC} = 6.0 Hz), 34.3 (d, J_{POCC} = 4.0 Hz), 34.2 (d, J_{POCC} = 4.0 Hz), 33.4, 32.3, 31.7, 30.9 (d, J_{PCC} = 15.1 Hz), 29.3 (d, J_{PCC} = 10.0 Hz), 29.0 (2 C), 28.9 (d, J_{PC} = 89.6 Hz), 25.2, 23.8 (2 C), 28.6 (d, J_{PC} = 95.6 Hz), 22.6, 21.7 (d, J_{PCCC} = 4.0 Hz), 21.6 (d, J_{PCCC} = 4.0 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 56.0 (s); HRMS (EI+) m/z calcd for $C_{19}H_{38}BrO_2P$ ([M]+) 408.1793, found 408.1790.

Cyclohexyl (4-phenylbutyl)octylphosphinate (Table 4.2, entries 6 and 7). In a flask equipped with a Dean-Stark trap was introduced 4-phenylbutylphosphinic acid (0.99 g, 5 mmol, 1 equiv), cyclohexanol (1.06 ml, 10 mmol, 2 equiv) and toluene (10 ml). After 16 h at reflux under N_2, the reaction was cooled down to rt and the solvent was evaporated under vacuum. The residue obtained was solubilized in DMSO (25 mL). 1-octene (0.78 mL, 5 mmol, 1 equiv) and $Mn(OAc)_2$ (43 mg, 0.25 mmol, 5 mol %) were added and the reaction mixture was stirred for 24H at 100 ºC under air. Ethyl acetate and an aqueous solution of $Na_2S_2O_4$ at 0.5 M were added and the two layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 8:2 to 6:4) to afford the product as colorless oil (1.05 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.22-7.29 (m, 2H), 7.13-7.19 (m, 3H), 4.28-4.41 (m, 1H), 2.63 (t, J = 7.3 Hz, 2H), 1.80-1.93 (m, 2H), 1.40-1.76 (m, 15 H), 1.18-1.39 (m, 13H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$,): δ 141.9, 128.4 (2 C), 128.3 (2 C), 125.8, 73.3 (d, J_{POC} = 6.9 Hz), 35.4, 34.2 (d, J_{POCC} = 3.1 Hz), 34.2 (d, J_{POCC} = 3.0 Hz), 32.6 (d, J_{PCC} = 15.1 Hz),

31.8, 30.9 (d, J_{PCC} = 15.0 Hz), 29.0 (2 C), 28.8 (d, J_{PC} = 90.1 Hz), 28.6 (d, J_{PC} = 93.6 Hz), 25.2, 23.7 (2 C), 22.6, 22.0 (d, J_{PCCC} = 4.1 Hz), 21.6 (d, J_{PCCC} = 4.0 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 56.5 (s); HRMS (EI+) m/z calcd for $C_{24}H_{41}O_2P$ ([M]+) 392.2844, found 392.2838.

Cyclohexyl (3-ethylcarbamate)octylphosphinate (Table 4.2, entry 8). To a solution of cyclohexyl (3-ethylcarbamate)-*H*-phosphinate (400 mg, 1.52 mmol, 1 equiv) in DMSO (5mL) was added 1-octene (0.24 mL, 1.52 mmol, 1 equiv) and $Mn(OAc)_2$ (13 mg, 0.076 mmol, 5 mol %). The reaction mixture was stirred for 24 h at 100 ºC under air. Ethyl acetate and an aqueous solution of $Na_2S_2O_4$ at 0.5 M were added and the two layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 2:8 to 0:10 + 10% of acetone) to afford the product as colorless oil (282 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 5.88-6.00 (m, 1H), 4.30-4.45 (m, 1H), 4.09 (q, J = 6.9 Hz, 2H), 3.15-3.32 (m, 2H), 1.63-1.95 (m, 9 H), 1.43-1.61 (m, 5 H), 1.18-1.42 (m, 12H), 1.23 (t, J = 6.7 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$,): δ = 156.8, 73.3 (d, J_{POC} = 6.8 Hz), 60.4, 41.2 (d, J_{PCCC} = 14.9 Hz), 34.0 (d, J_{POCC} = 2.9 Hz), 34.0 (d, J_{POCC} = 2.8 Hz), 31.6, 30.7 (d, J_{PCC} = 15.3 Hz), 28.9, 28.9, 28.7 (d, J_{PC} = 90.5 Hz), 25.8 (d, J_{PC} = 90.9 Hz), 25.0, 23.6 (2 C), 22.5 (2 C), 21.9 (d, J_{PCCC} = 3.8 Hz), 14.5, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 56.4 (s); HRMS (EI+) m/z calcd for $C_{20}H_{40}NO_4P$ ([M]+) 389.2695, found 389.2702.

(R_p)-Menthyl octylphenylphosphinate (Table 4.2, entry 9).[168] In a round bottom flask was introduced (R_p)-menthyl phenyl-*H*-phosphinate (280 mg, 1 mmol, 1 equiv) 1-octene (0.39 mL, 2.5 mmol, 2.5 equiv) and $Mn(OAc)_2$ (9 mg, 0.05 mmol, 5 mol%). The reaction mixture was stirred for 16 h at 100 ºC under air. Ethyl acetate and an aqueous solution of $Na_2S_2O_4$ at 0.5 M

were added and the two layers were separated. The organic layer was washed with brine, dried over MgSO4, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 8:2) to afford the product as yellow oil (309 mg, 79%, de = 95%). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 7.73-7.84 (m, 2H), 7.41-7.56 (m, 3H), 4.22-4.35 (m, 1H), 2.25 (dquin, J = 2.4 and 7.0 Hz, 1H), 1.48-1.98 (m, 5 H), 1.13-1.48 (m, 14H), 0.70-1.10 (m, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.74 (d, J =6.5 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$,): δ 42.4 (s); $[\alpha]_D^{22}$ = -27.40 (c 1.00, $CHCl_3$).

(R_p)-Menthyl (acetylmethyl)-*H*-phosphinate (Table 4.2, entry 10). To a solution of (R_p)-menthyl hydroxymethyl-*H*-phosphinate (703 mg, 3 mmol, 1 equiv) in dichloromethane (15 mL) at 0 °C under N_2 was added pyridine (0.30 mL, 3.75 mmol, 1.25 equiv) and acetic anhydride (0.34 mL, 3.6 mmol, 1.2 equiv). The ice-bath was removed and the reaction mixture was stirred for 16 h at rt. The solvent was removed under vacuum and the residue obtained was solubilized in ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product as a white solid (829 mg, 100%, 95% de). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dt, J = 1.8 and 567 Hz, 1H), 4.09-4.21 (m, 2H), 3.94-4.05 (m, 1H), 2.01-2.08 (m, 1H), 1.95 (s, 3H), 1.83-1.92 (m, 1H), 1.47-1.55 (m, 2H), 1.20-1.36 (m, 2H), 1.10 (q, J = 11.1 Hz, 1H), 0.79-0.92 (m, 1H), 0.60-0.79 (m, 1H), 0.76 (d, J = 7.1 Hz, 3H), 0.75 (d, J = 6.4 Hz, 3H), 0.63 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$,): δ 170.0 (d, J_{PCOC} = 6.5 Hz), 79.6 (d, J_{POC} = 7.8 Hz), 60.0 (d, J_{PC} = 113 Hz), 48.4 (d, J_{POCC} = 6.1 Hz), 43.2, 33.6, 31.4, 25.5, 22.8, 21.7, 20.7, 20.1, 15.6; ^{31}P NMR (162 MHz, $CDCl_3$,): δ 26.8 (dm, J = 567 Hz); HRMS (CI+, methane) m/z calcd for $C_{13}H_{25}O_4P$ ([M+H]+) 277.1569, found 277.1566; $[\alpha]_D^{20}$ = -34.90 (c 1.04, $CHCl_3$).

Octyl phenylphosphinic acid (Table 4.2, entry 11).[110,114] To a solution of phenylphosphinic acid (142 mg, 1 mmol, 1 equiv) in DMSO (5mL) was added 1-octene (0.16 mL, 1 mmol, 1 equiv) and $Mn(OAc)_2$ (9 mg, 0.05 mmol, 5 mol%). The reaction mixture was stirred for 24 h at 100 ºC under air. Ethyl acetate and an aqueous solution of $Na_2S_2O_4$ at 0.5 M were added and the two layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product as colorless oil (221 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.53 (s, 1H), 7.62-7.88 (m, 2H), 7.31-7.50 (m, 3H), 1.70-1.93 (2H), 1.37-1.55 (m, 2H), 1.10-1.32 (m, 10H), 0.85 (t, J = 6.7 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 44.1 (s).

Dioctylphosphinic acid (Table 4.2, entry 12).[110,185] To a solution of octylphosphinic acid (214 mg, 1.2 mmol, 1.2 equiv) in DMSO (5mL) was added 1-octene (0.16 mL, 1 mmol, 1 equiv) and $Mn(OAc)_2$ (9 mg, 0.05 mmol, 5 mol%). The reaction mixture was stirred for 24 h at 100 ºC under air. Ethyl acetate and an aqueous solution of $Na_2S_2O_4$ at 0.5 M were added and the two layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product as colorless oil (261 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (bs, 1H), 1.81-1.60 (m, 7 H), 1.19-1.54 (m, 12H), 1.50-1.21 (m, 21H), 0.88 (t, J = 7.2 Hz, 6H). ^{31}P NMR (162 MHz, $CDCl_3$): δ 59.5 (s).

Hexane-1, 1-diylbis(octylphosphinic acid) (Table 4.2, entry 13). The reaction was completed using diisopropyl hexyl-1,1-bis-*H*-phosphinate prepared according to the literature.[5] The subsequent reaction was completed as described in the representative procedure followed by hydrolysis using concentration HCl at reflux for 18 h. After the standard work-up as described, the product was obtained as a clear oil (300 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20-1.45

(m, 11H), 1.43-1.19 (m, 23H), 0.9 (t, J = 7.0 Hz, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 40.2 (t, J_{PCP} = 72.4 Hz), 31.9 (3 C), 31.4 (d, J_{PC} = 88.5 Hz, 2 C), 31.0 (2 C), 29.7, 29.4 (4 C), 24.2, 22.7 (2 C), 22.4, 21.4 (2 C) 14.1 (2 C), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 53.4 (s); HRMS (ESI+) m/z calcd for $C_{22}H_{48}O_4P_2$ ([M+H]+) 439.3106, found 439.3097.

Dicyclohexyl octane-1,2-diylbis(octylphosphinate) (Table 4.2, entry 14). The product was prepared via the representative procedure using two equivalents of cyclohexyl octyl-*H*-phosphinate[3] to 1-octyne. After purification, the product was obtained as light brown oil (322 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (m, 2H), 2.20-2.05 (m, 2H), 1.93 (m, 4H), 1,84-1.65 (m, 10 H), 1.63-1.45 (m, 12H), 1.42-1.19 (m, 33H), 0.92 (t, J = 7.0 Hz, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 73.6 (m, 2 C), 34.2 (4 C), 34.1, 32.5 (ddd, J_{PC}, P_{CC} = 41.0, 16.5, 4.0 Hz), 31.8 (2 C), 31.6, 31.0 (d, J_{PCC} = 15 Hz, 2 C), 29.6, 29.0 (5 C), 27.4 (d, J_{PC} = 85.6 Hz), 27.2 (d, J_{PC} = 86.3 Hz, 2 C), 25.2 (2 C), 23.7 (3 C), 22.6 (4 C), 21.8 (d, J_{PCCC} = 4.0 Hz, 2 C), 14.1 (3 C); ^{31}P NMR (162 MHz, $CDCl_3$): δ 58.4 (dd, J = 45.4 Hz, 4.9Hz), 58.0 (dd, J = 48.6 Hz, 14.6 Hz), 55.0 (J = 47.0 Hz, 17.8 Hz), 54.5 (dd, J = 48.6, Hz 13.0 Hz); HRMS (EI+) m/z calcd for $C_{36}H_{72}O_4P_2$ ([M]+) 630.4906, found 630.4912.

4-butyl-1, 3-diisopropoxy-2-pentyl-1,3-diphospholane 1,3-dioxide (Table 4.2, entry 15). The reaction was completed using diisopropyl hexyl-1,1-bis-*H*-phosphinate prepared according to the literature.[5] The subsequent reaction was completed as described in the representative procedure to obtain the product as clear oil (152 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85-4.61 (m, 2H), 2.36-2.15 (m, 1H), 2.14-1.97 (m, 1H), 1.96 (m, 2H), 1.73-1.47 (m, 3H), 1.45-1.19 (m, 24H), 0.89 (t, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.3-70.0 (d, J_{POC} = 7.0 Hz, 2 C), 38.2 (d, J_{PC} = 90.2 Hz), 37.3 (d, J_{PC} = 91.7 Hz), 33.8, 32.0-31.5 (d, J_{PCC} = 17.7 Hz), 30.1-38.9 (d,

J_{PCCC} = 4.0 Hz), 27.0 (ddd, $J_{PC,\ PCC}$ = 57.0, 18.0, 6.0 Hz), 24.7-23.6 (m, 4 C), 23.1-22.3 (m, 4 C), 14.1, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 64.9 (d, J = 79.0 Hz), 63.6 (d, J = 72.0 Hz), 58.9 (d, J = 91.0 Hz), 58.3 (d, J = 76.0 Hz), 58.0 (d, J = 90.0 Hz), 57.2 (d, J = 92.0 Hz), 54.7 (d, J = 74.0 Hz), 53.6 (d, J = 92.0 Hz), 52.7 (d, J = 93.0 Hz), 52.4 (d, J =74.0 Hz), 52.2 (d, J = 69.0 Hz), 50.0 (d, J = 75.0 Hz), 48.7 (d, J = 58.0 Hz), 46.6 (d, J = 63.0 Hz), 46.1 (d, J =87.0 Hz), 45.7 (d, J =83.0 Hz); HRMS (ESI+) m/z calcd for $C_{18}H_{38}O_4P_2$ ([M+H]+) 381.2323, found 381.2292.

General Procedure for $Mn(OAc)_3$-promoted Arylation of *H*-phosphinates: To a solution of cyclohexyl octyl-*H*-phosphinate (260 mg, 1 mmol, 1 equiv) in a mixture of acetic acid and benzene (2.5 mL: 2.5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The suspension was stirred for 24 h at 100^{o}C under N_2. 100 mL of ethyl acetate was added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 6:4).

Cyclohexyl (phenyl)octylphosphinate (Equation 4.2).[110] After using the general procedure for the $Mn(OAc)_3$-promoted arylation of *H*-phosphinates, the product was obtained as yellow oil (124 mg, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73-7.84 (m, 2H), 7.40-7.58 (m, 3H), 4.18-4.32 (m, 1H), 1.12-2.08 (m, 24H), 0.86 (t, J = 6.7 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 43.1 (s).

1-ethyloxy-1,2,3,4-tetrahydro-1-phosphinoline-1-oxide (Scheme 4.1, 41a).[208] To a solution of ethyl-3-phenylpropyl-*H*-phosphinate (212 mg, 1 mmol, 1 equiv) in acetic acid (5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The

suspension was stirred for 24 h at 100 ºC under N_2. 100 mL of ethyl acetate was added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (ethyl acetate/acetone 100:0 to 95:5) to afford the product as colorless oil (102 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.91 (m, 1H), 7.39-7.46 (m, 1H), 7.30-7.38 (m, 1H), 7.16-7.25 (m, 1H), 3.95-4.25 (m, 2H), 2.85-2.93 (m, 2H), 2.00-2.29 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 37.1 (s).

Cyclohexyl-3-phenylpropyl-*H*-phosphinate (starting material Scheme 4.1 and Equation 4.3). A flask containing H_3PO_2 (50% aqueous, 1.32 g, 20 mmol, 2 equiv) and cyclohexanol (4 g, 40 mmol, 4 equiv) in toluene (40 mL) was equipped with a Dean-Stark trap pre-filled with toluene and fitted with a condenser. The solution was refluxed under N_2 for 4 h. After cooling to room temperature, $NiCl_2$ (39 mg, 0.3 mmol, 3 mol %) was added and the mixture was stirred overnight and dppe (120 mg, 0.3 mmol, 3 mol %) was added. After 30 min, allylbenzene (1.18 g, 10 mmol, 1 equiv) was added and the reaction mixture was stirred 48 h. The solution was washed with saturated $NaHCO_3$ and brine. Drying over $MgSO_4$ followed by column chromatography (hexane/ethyl acetate 9:1 to 5:5) afford the desired product as a colorless oil (1.03 g, 39%). The *H*-phosphinate should be stored in CH_2Cl_2 solution at 0 ºC until ready to use. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.29 (m, 2H), 7.26-7.22 (m, 1H), 7.22-7.17 (m, 2H), 7.15 (d, J = 526 Hz, 1H), 4.42-4.31 (m, 1H), 2.75 (t, J = 7.5 Hz, 2H), 2.03-1.88 (m, 4H), 1.83-1.72 (m, 4H), 1.62-1.46 (m, 3H), 1.42-1.21 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.6, 128.3 (2 C), 128.3 (2 C), 126.0, 75.5 (d, J_{POC} = 6.8 Hz), 36.1 (d, J_{PCC} = 15.7 Hz), 33.8 (d, J_{POCC} = 3.7 Hz), 32.9 (d, J_{POCC} = 3.7 Hz), 28.2 (d, J_{PC} = 94.3 Hz), 25.0, 23.4 (d, J_{POCCC} = 3.5 Hz, 2 C), 22.4 (d,

J_{PCCC} = 2.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 35.3 (d, J = 526 Hz); HRMS (EI+) m/z calcd for $C_{15}H_{23}O_2P$ ([M]+) 266.1436, found 266.1440.

1-cyclohexyloxy-1,2,3,4-tetrahydro-1-phosphinoline-1-oxide (Scheme 4.1, 41b). To a solution of Cyclohexyl-3-phenylpropyl-*H*-phosphinate (266 mg, 1 mmol, 1 equiv) in acetic acid (5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The suspension was stirred for 24 h at 100 ºC under N_2. 100 mL of ethyl acetate was added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (ethyl acetate/acetone 100:0 to 95:5) to afford the product as colorless oil (177 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.89 (m, 1H), 7.36-7.42 (m, 1H), 7.27-7.34 (m, 1H), 7.13-7.19 (m, 1H), 4.40-4.52 (m, 1H), 2.78-2.93 (m, 2H), 2.01-2.25 (m, 4H), 1.91-2.00 (m, 1H), 1.62-1.79 (m, 3H), 1.14-1.61 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.8 (d, J_{PCC} = 9.6 Hz), 131.7 (d, J_{PCCCC} = 2.2 Hz), 129.8 (d, J_{PCCC} = 5.2 Hz), 129.2 (d, J_{PC} = 121 Hz), 129.0 (d, J_{PCC} = 11.3 Hz), 126.4 (d, J_{PCCC} = 11.2 Hz), 74.1 (d, J_{POC} = 6.7 Hz), 34.3 (d, J_{POCC} = 3.0 Hz), 33.8 (d, J_{POCC} = 3.6 Hz), 31.2 (d, J_{PCC} = 8.8 Hz), 26.6 (d, J_{PC} = 93.1 Hz), 25.1, 23.7, 23.6, 21.3 (d, J_{PCCC} = 5.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 36.1 (s); HRMS (EI+) m/z calcd for $C_{15}H_{21}O_2P$ ([M]+) 264.1279, found 264.1281.

1-phenyl-2,3,4-trihydrophosphinoline-1-oxide (Scheme 4.1, 42).[208] To a solution of (3-phenylpropyl)phenyl-*H*-phosphine oxide (244.3 mg, 1 mmol, 1 equiv) in acetic acid (5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The suspension was stirred for 24 h at 100 ºC under N_2. 100 mL of ethyl acetate was

added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 5:5 to 0:10 + 20% acetone) to afford the product as colorless oil (142 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.66 (m, 3H), 7.38-7.52 (m, 4H), 7.22-7.31 (m, 2H), 2.89-3.11 (m, 2H), 2.00-2.44 (m, 4H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.6 (s).

1-(2-phenylethyl)-3,4-tetrahydro-1-phosphonoline-1-oxide (Scheme 4.1, 43). To a solution of di(2-phenylpropyl)phosphite[8] (290.3 mg, 1 mmol, 1 equiv) in acetic acid (5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The suspension was stirred for 24 h at 100 ºC under N_2. 100 mL of ethyl acetate was added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 5:5 to 0:10 + 20% acetone) to afford the product as colorless oil (184 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.69 (m, 1H), 7.37-7.45 (m, 1H), 7.12-7.32 (m, 7 H), 4.22-4.41 (m, 4H), 2.80-3.07 (m, 2H), 2.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 141.7 (d, J_{PCC} = 7.4 Hz), 137.3, 132.4 (d, J_{PCCCC} = 2.4 Hz), 130.7 (d, J_{PCCC} = 8.3 Hz), 129.0 (2 C), 128.5 (2 C), 128.4 (d, J_{PCCC} = 13.0 Hz), 127.2 (d, J_{PCC} = 14.7 Hz), 126.6, 124.9 (d, J_{PC} = 175 Hz), 131.4 (d, J_{PCCC} = 10.7 Hz, 2 C), 66.9 (d, J_{POC} = 6.0 Hz), 66.3 (d, J_{POC} = 6.5 Hz), 36.9 (d, J_{POCC} = 6.4 Hz), 31.0 (d, J_{POCC} = 7.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 13.7 (s); HRMS (EI+) m/z calcd for $C_{16}H_{17}O_3P$ ([M]+) 288.0915, found 288.0914.

2-phenylethyl phenyl-*H*-phosphinate (Scheme 4.1). In a flask equipped with a Dean-Stark trap was introduced phenylphosphinic acid (3.55 g, 25 mmol, 1 equiv), cyclohexanol (6.11 ml, 50 mmol, 2 equiv) and toluene (50 ml). After 16 h at reflux under N_2, the reaction was cooled down to rt and the solvent was concentrated under vacuum. The residue obtained was dissolved in EtOAc and washed with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 5:5) to afford the product as a colorless oil (5.25 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.73 (m, 3H), 7.51 (d, J = 566 Hz, 1H), 7.44-7.53 (m, 2H), 7.18-7.36 (m, 5 H), 4.19-4.39 (m, 2H), 3.04 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 137.0, 133.0 (d, J_{PCCCC} = 2.8 Hz), 130.8 (d, J_{PCCC} = 12.2 Hz, 2 C), 129.6 (d, J_{PC} = 131 Hz), 129.0 (2 C), 128.7 (d, J_{PCC} = 13.8 Hz, 2 C), 128.5 (2 C), 126.7, 66.1 (d, J_{POC} = 6.6 Hz), 36.9 (d, J_{POCC} = 6.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.2 (d, J = 566 Hz); HRMS (CI+, methane) m/z calcd for $C_{14}H_{15}O_2P$ ([M+H]+) 247.0888, found 247.0895.

1-phenyl-2-oxy-3, 4-dihydro-1-phosphinoline-1-oxide (Scheme 4.1, 44b).[209] To a solution of 2-phenylethyl phenyl-*H*-phosphinate (246 mg, 1 mmol, 1 equiv) in acetic acid (5 mL) was added $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmol, 2 equiv) and sodium acetate (164 mg, 2 mmol, 2 equiv). The suspension was stirred for 24 h at 100 ºC under N_2. 100 mL of ethyl acetate was added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 8:2 to 5:5) to afford the product as colorless oil (204 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.72 (m, 2H), 7.48-7.57 (m, 1H), 7.35-7.41 (m, 1H), 7.26-7.34 (m, 3H), 7.11-

7.21 (m, 2H), 4.51-4.62 (m, 1H), 4.31-4.43 (m, 1H), 3.14-3.27 (m, 1H), 2.81-2.91 (m, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.3 (s).

General Procedure for $Mn(OAc)_2/MnO_2$-promoted Intramolecular Arylation of *H*-phosphinates: To a solution of cyclohexyl-3-phenylpropyl-*H*-phosphinate (133 mg, 0.5 mmol, 1 equiv) in acetic acid (2.5 mL) was added $Mn(OAc)_2$ (4.3 mg, 0.025 mmol, 5 mol %), MnO_2 (85% activated, 102 mg, 1 mmol, 2 equiv) and sodium acetate (82 mg, 1 mmol, 2 equiv). The suspension was stirred for 12 h at 70 ^oC under N_2. Ethyl acetate (40 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ saturated with NaCl (20 mL) was added. The mixture was stirred for 5 min and the suspension was filtered over Celite®. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.1M saturated with NaCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 6:4) to afford the product as colorless oil (86 mg, 65%).

1-cyclohexyloxy-1,2,3,4-tetrahydro-1-phosphinoline-1-oxide (Equation 4.6). After using the general procedure for the $Mn(OAc)_2/MnO_2$-promoted arylation of *H*-phosphinates, the product was obtained as colorless oil (86 mg, 65%). This compound was fully characterized previously.

2-butoxy-1,2-dihydro-3,4-dipropyl-2-isophosphinoline-2-oxide (Equation 4.7, 45): To a solution of benzyl-*H*-phosphinic acid butyl ester[67] (212 mg, 1 mmol, 2 equiv) and 4-octyne (55 mg, 0.5 mmol, 1 equiv) in acetic acid (2.5 mL) was added $Mn(OAc)_2$ (4.3 mg, 0.025 mmol, 5 mol %), MnO_2 (85% activated, 154 mg, 1.5 mmol, 3 equiv). The suspension was stirred for 6 h at 70 ^oC under N_2. Ethyl acetate (40 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ (saturated with

NaCl, 20 mL) was added. The mixture was stirred for 5 min and the suspension was filtered over Celite®. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.1 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 7:3 to 3:7) to afford the product as colorless oil (80 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.9 Hz, 1H), 7.31-7.25 (m, 1H), 7.22-7.13 (m, 2H), 3.89 (q, J = 7.3 Hz, 2H), 3.27-3.04 (m, 2H), 2.75-2.54 (m, 3H), 2.53-2.39 (m, 1H), 1.65-1.43 (m, 6H), 1.20 (sext, J = 7.5 Hz, 2H), 1.03 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.6 (d, J_{PCCC} = 7.7 Hz), 133.9 (d, J_{PCC} = 17.3 Hz), 131.1 (d, J_{PCCC} = 8.0 Hz), 130.7 (d, J_{PCC} = 11.1 Hz), 129.2 (d, J_{PC} = 120 Hz), 127.9, 127.4 (d, J_{PCCCC} = 1.7 Hz), 126.4 (d, J_{PCCCC} = 2.4 Hz), 74.1 (d, J_{POC} = 6.7 Hz), 34.3 (d, J_{POCC} = 3.0 Hz), 33.8 (d, J_{POCC} = 3.6 Hz), 31.2 (d, J_{PCC} = 8.8 Hz), 26.6 (d, J_{PC} = 93.1 Hz), 25.1, 23.7, 23.6, 21.3 (d, J_{PCCC} = 5.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 33.9 (s); HRMS (EI+) m/z calcd for $C_{15}H_{21}O_2P$ ($[M]^+$) 264.1279, found 264.1281.

Chapter 4- Section 4.2.4

Representative Example for the Manganese-promoted Chlorination Reaction (Table 4.3, entry 11): Cyclohexyl octyl-*H*-phosphinate (260 mg, 1 mmol, 1 equiv) was weighed into a 25-mL round bottom flask along with $Mn(OAc)_2$ (17.3 mg, 10 mol%), MnO_2 (85% activated, 261 mg, 3 mmol, 3 equiv), LiCl (212 mg, 5 mmol, 5 equiv), and 1-octene (561 mg, 5 mmol, 5 equiv). Glacial acetic acid (5 mL, 0.2 M) was added and the reaction was stirred for 24 h under N_2 at 70 ºC. The reaction mixture was cooled and the acetic acid was removed by rotary evaporator under high vacuum. Ethyl acetate (30 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ (saturated with NaCl, 20 mL) was added. The mixture was stirred for 5 min and the suspension was filtered over

Celite®. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.1 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum resulting in 366 mg (90%) of yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 (m, 1H), 3.68-3.52 (m, 1H), 2.43-2.14 (m, 2H), 2.00-1.85 (m, 6H), 1.84-1.67 (m, 8 H); 1.47-1.10 (m, 20 H), 1.03-0.81 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 74.0 (d, J_{POC} = 20.5 Hz), 61.2, 56.8 (d, J_{PCC} = 9.6 Hz), 48.3, 39.8, 34.6 (d, J_{PC} = 88.5 Hz), 31.7 (d, J_{POCC} = 12.1 Hz), 29.1, 28.6, 26.2 (d, J_{PCC} = 12.1 Hz), 25.8, 25.2, 23.1 (d, J_{PC} = 105.7 Hz), 22.5, 14.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 52.7 (s), 51.8 (s); HRMS (methane chem ion) m/z calcd for $C_{22}H_{44}ClO_4P$ ($[M-H]^+$) 405.2689, found 405.2680.

Chapter 5-Section 5.2

General Procedure for the Nickel-Catalyzed Transformation of HPA into $(RO)_2P(O)H$: (Table 5.1, entry 14). Aqueous H_3PO_2 (50 wt.-%, 25 mmol) was concentrated *in vacuo* for 15 min at r.t. [Note: this step can be omitted as long as the esterification time is monitored]. Butanol (3 equiv, 75 mmol) followed by toluene (reagent grade, 50 mL) was added to the flask, and a Dean-Stark trap filled with excess toluene was fitted on the flask. The reaction was heated to reflux for 2 h under nitrogen atmosphere. The solution was cooled and the yield of $BuOP(O)H_2$ was quantitative as determined by ^{31}P-NMR. The Dean-Stark trap was removed, and Ni/SiO_2 (64 wt.-%, 5 mol-%) was added to the $BuOP(O)H_2$ solution. The solution was refluxed under nitrogen for 18 h. After cooling down, the reaction was filtered through Celite® and rinsed with ethyl acetate (20 mL). The organic layer was washed with brine (50 mL), and the aqueous layer was further extracted with ethyl acetate (3 x 15 mL). The combined organic layers was dried over $MgSO_4$ and concentrated *in vacuo* to afford dibutyl *H*-phosphonate as a light yellow liquid in 4.37 g (90 % isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, $^1J_{HP}$ = 691.9 Hz, 1H, H-P); 4.09 (q, ^{3}J = 7.46 Hz, 4H, CH_2); 1.70 (p, ^{3}J= 6.68 Hz, 2H, CH_2); 1.43 (p, ^{3}J = 7.25 Hz,

2H, CH_2); 0.96 (t, ^3J = 5.33 Hz, 6H, CH_3) ^{31}P NMR (121 MHz, $CDCl_3$) δ 7.82 (dp, $^1J_{PH}$ = 693.23 Hz; $^3J_{POC}$ = 9.72 Hz).[210,211]

Purification of *H*-Phosphonate Diesters in Table 5.2, entry 5-11, 17. Dialkyl Phosphites prepared from alcohols with boiling points > 140º C were purified to remove excess starting material using a Kugelrohr distillation apparatus under high vacuum with heating. Depending on the alcohol, distillation times varied from 3 to 6 hours with the progress of the purification monitored by ^1H NMR.

Diethyl Phosphite (Table 5.2, entry 1).[210] Aqueous H_3PO_2 (50 wt.-%, 25 mmol) was concentrated *in vacuo* for 30 min at r.t. Octyltriethoxysilane (1 equiv, 25 mmol) and toluene (reagent grade, 50 mL) were added, and the reaction was heated to reflux for 3 h. After completion, the solution was cooled to r.t. and Ni/SiO_2 (64 wt.-%, 5 mol-%) and anhydrous ethanol (3 equiv, 75 mmol) were added. The reaction was heated to reflux and allowed to react under nitrogen for 40 h. After cooling down, the reaction was filtered through Celite® and was rinsed with ethyl acetate (20 mL). The organic layer was concentrated and subsequently dissolved in CH_3CN (HPLC grade, 50 mL). The CH_3CN layer was partitioned with hexanes (4 x 15 mL), and concentrated *in vacuo* to obtain a discolored liquid in 2.59 g (75 % isolated yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, $^1J_{HP}$ = 692.8 Hz, 1H); 4.16 (p, ^3J = 7.20 Hz, 4H); 1.37 (t, 6.80 Hz, 6H) ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.77 (dm, $^1J_{PH}$ = 692 Hz).

Di-isopropyl Phosphite (Table 5.2, entry 2).[210–212] Aqueous H_3PO_2 (50 wt.-%, 62.5 mmol) was concentrated *in vacuo* for 30 min at r.t. Isopropanol (7 equiv, 438 mmol) and cyclohexane (92 mL) were added and a soxhlet extractor was placed on the reaction flask with 3Å molecular

sieves placed inside the extraction thimble. The solution was refluxed for a total of 18 h with the molecular sieves replaced after 4 and 8 hours. Ni/SiO_2 (64 wt.-%, 5 mol%) was added to the $iPrOP(O)H_2$ solution (25 mmol, 50 mL) and heated to reflux for 18 h under nitrogen. The cooled solution was filtered through Celite® and concentrated *in vacuo* to obtain a clear liquid in 4.15 g (87 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, $^1J_{HP}$ = 687.60 Hz, 1H); 4.74 (m, 2H); 1.36 (d, ^{3}J = 8.40 Hz, 12H) ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.45 (dt, $^1J_{PH}$ = 686.75 Hz; $^3J_{POC}$ = 8.10 Hz).

Di-isobutyl Phosphite (Table 5.2, entry 3).[211,212] Light yellow liquid, 4.08 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, $^1J_{HP}$ = 692.7 Hz, 1H), 3.88-3.82 (m, 4H), 1.97 (m, 1H), 0.97 (d, 6H, ^3J = 6.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 7.99 (d, $^1J_{PH}$ = 693 Hz, $^3J_{POC}$ = 7.76 Hz).

Dineopentyl Phosphite (Table 5.2, entry 4).[212] Light yellow liquid, 3.06 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, $^1J_{HP}$ = 693.6 Hz, 1H); 3.77-3.73 (p, ^{3}J = 6.8 Hz, 4H), 0.98 (s, 18 H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.38 (d, $^1J_{PH}$ = 695 Hz, $^3J_{POC}$ = 8.10 Hz).

Dicyclohexyl Phosphite (Table 5.2, entry 5).[212] Clear liquid, 6.16 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, $^1J_{HP}$ = 688.4 Hz, 1H), 4.46-4.44 (m, 2H), 1.96-1.93 (m, 4H), 1.78-1.74 (m, 4H), 1.58-1.53 (m, 6H), 1.37-1.1.30 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.46 (d, $^1J_{PH}$ = 688 Hz).

Dibenzyl Phosphite (Table 5.2, entry 6).[213] Light yellow liquid, 4.20 g (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 10 H, ArCH), 6.97 (d, $^1J_{HP}$ = 706.8 Hz, 1H, H-P), 5.08 (m, 4H, CH_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.74 (dp, $^1J_{PH}$ = 706 Hz, $^3J_{POC}$ = 9.3 Hz).

Bis(2-phenethyl) Phosphite (Table 5.2, entry 7).[214] Light yellow liquid, 7.26 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 10 H), 6.66 (d, $^{1}J_{HP}$ = 700.8 Hz, 1H), 4.24-4.20 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.65 (dp, $^{1}J_{PH}$ = 700 Hz, $^{3}J_{POC}$ = 8.10 Hz).

Dimenthyl Phosphite (Table 5.2, entry 8).[215] Clear liquid, 4.39 g (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, $^{1}J_{HP}$ = 686.8 Hz, 1H), 4.28–4.18 (m, 2H), 2.20–2.16 (m, 2H), 2.15–2.04 (2 x m, 2H), 1.69, 1.65 (2 x s-br), 1.47-1.44 (m, 2H), 1.26-1.16 (m, 2H), 1.07–0.96 (m, 4H), 0.92 (2 x d, ^{3}J = 1.32 Hz, ^{3}J = 1.68 Hz, 12H), 0.89–0.84 (m, 2H), 0.82 (d, ^{3}J = 1.68 Hz, 3H), 0.79 (d, 3H, ^{3}J = 1.68 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.45 (dt, $^{1}J_{PH}$ = 686.8 Hz, $^{3}J_{POC}$ = 8.73 Hz).

Difenchyl Phosphite (Table 5.2, entry 9). Light brown liquid, 7.27 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, $^{1}J_{HP}$ = 686.4 Hz, 1H), 4.06-3.98 (m, 2H), 1.74-1.70 (m, 6H), 1.56-1.53 (m, 2H), 1.49-1.44 (m, 2H), 1.23-1.20 (m, 2H), 1.14 (d, ^{3}J = 8.6 Hz, 6H), 1.09 (m, 8 H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.3 (d, $^{2}J_{COP}$ = 7.3 Hz), 49.1, 40.9, 39.5, 29.8, 25.8, 21.4, 19.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.12 (dt, $^{1}J_{PH}$ = 688.4 Hz, $^{3}J_{POC}$ = 10.6 Hz); HRMS (ESI) calcd. for $C_{20}H_{35}O_3P$ ($[M + H]^+$) 355.2402, found 355.2489.

Bis(2,2,2-trichloroethyl) Phosphite (Table 5.2, entry 10).[216] Light yellow liquid, 2.24 g (25%). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.22 (d, $^{1}J_{HP}$ = 746 Hz, 1H), 4.75-4.66 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.23 (dp, $^{1}J_{PH}$ = 753 Hz, $^{3}J_{POC}$ = 8.75 Hz).

Diadamantyl Phosphite (Table 5.2, entry 11). White solid, 5.61 g (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, $^{1}J_{HP}$ = 680 Hz, 1H), 2.18 (m, 6H), 2.10 (m, 12H), 1.63 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.3 (d, $^{2}J_{COP}$ = 7.62 Hz), 44.0 (d, $^{3}J_{CCOP}$ = 4.51 Hz), 35.7, 31.0; ^{31}P NMR

(162 MHz, $CDCl_3$) δ -4.06 (d, $^1J_{PH}$ = 680 Hz); HRMS (ESI) calcd. for $C_{20}H_{31}O_3P$ ($[M + H]^+$) 351.2089, found 351.2104.

Phosphorous acid (Table 5.2, entry 12).[217,218] Clear liquid, 1.72 g (84%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, $^1J_{HP}$ = 663.2 Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.37 (d, J_{PH} = 664 Hz).

Dibutynyl Phosphite (Table 5.2, entry 15). Clear liquid, 2.37 g (51%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, $^1J_{HP}$ = 711 Hz, 1H), 4.28-4.17 (m, 4H), 2.65-2.61 (td, ^3J = 6.68 Hz, ^4J = 2.64 Hz), 2.07 (t, ^4J = 2.64 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.3, 70.7, 63.5 (d, $^2J_{COP}$ = 6.01 Hz), 20.9 (d, $^3J_{CCOP}$ = 6.26 Hz) ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.74 (dp, $^1J_{PH}$ = 712 Hz, $^3J_{POC}$ = 9.72 Hz); HRMS (ESI) calcd. for $C_8H_{11}O_3P$ ($[M + H]^+$), 187.0524, found 187.0570.

Bis(2-chloroethyl) Phosphite (Table 5.2, entry 16).[212] Clear liquid, 5.17 g (68%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, $^1J_{HP}$ = 720.8 Hz, 1H), 4.40-4.33 (m, 4H), 3.76-3.71 (t, ^3J = 8.4 Hz, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.18 (dp, $^1J_{PH}$ = 720 Hz, $^3J_{POC}$ = 8.9 Hz).

Diphenyl Phosphite (Table 5.2, entry 17).[219,220] Light yellow liquid, 3.69 g (63%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.22 (m, 10H), 7.34 (d, $^1J_{HP}$ = 728.4 Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.34 (d, $^1J_{PH}$ = 733 Hz).

Preparation of dibutyl *H*-phosphonate from phosphorous acid (Scheme 5.5). Ni/SiO_2 (64 wt.-%, 5 mol-%) was added to a round-bottom flask containing aqueous H_3PO_2 (50 wt.-%, 25 mmol), and the mixture was heated to reflux for 18 h under nitrogen. [Note: if the reaction is conducted open to air, the reaction time is lowered to 6H.] Once cooled, ^{31}P- NMR analysis

showed that the formation of phosphorous acid was complete. The solution was filtered through Celite® and rinsed with several aliquots of deionized water (~ 20 mL total). The acid was concentrated, and butanol (4 equiv, 100 mmol) and toluene (reagent grade, 50 mL) were added. A Dean-Stark trap pre-filled with toluene was place on the reaction vessel and the solution was heated to reflux for 18 h under nitrogen. After cooling, the solution was extracted with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a light yellow liquid in 4.18 g (86 %) isolated yield.

Chapter 5- Section 5.6

Representative Example for Copper -catalyzed Oxidation of Alkyl *H*-Phosphinates (Table 5.3, entry 4). Ethyl octyl-*H*-phosphinate (413 mg, 2 mmol, 1 equiv) was weighed into a 25-mL round bottom flask and 10 mL of anhydrous ethanol (86 equiv) was added. Next, copper(I) chloride (9.9 mg, 0.1 mmol, 5 mol-%) was added to the solution. After the flask was fitted with a condenser, the reaction was stirred for 16 h at 65 ºC with dry air bubbling (using a long needle going down the condenser) into the solution. After cooling, the solution was concentrated to remove the ethanol. The crude product was dissolved in ethyl acetate (15 mL) and the organic layer was washed with aqueous $NaHCO_3$ (15 mL), followed by brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford 406 mg (81%) of clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (m, 4H), 1.80-1.58 (m, 4H), 1.45-1.19 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.8 (s).

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VITA

Henry Craig Fisher, JR was born on February 7, 1980 in Shreveport, Louisiana, USA. He is the son of Henry Craig Fisher, SR and Yi Hae Suk. He was raised in Dickinson, Texas, a small suburb outside of Houston, Texas. He received his Bachelors of Arts degree in Chemistry from Baylor University in May 2003, and received his Master of Science degree in Chemistry in December 2005 from the same university.

In March 2006, he started a 3.5 year stint as a research chemist at Champion Technologies, an oilfield service company, in Houston, Texas working in new product Research and Development. In 2009, he contributed to the filing of one patent on a new product he helped develop and gave an international talk on his work at the International Oilfield Chemistry Symposium in Geilo, Norway.

In January 2010, he joined the chemistry Ph.D. program at Texas Christian University in Fort Worth, Texas. While working on his doctorate, he worked as a Graduate Teaching Assistant for four semesters. He won 1st place for the best graduate research poster in chemistry at the Michael and Sally McCracken Annual Student Research Symposium in 2013. He currently has a total of four peer-reviewed publications, two conference proceedings and two patent applications.

ABSTRACT

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

by Henry C. Fisher, Ph.D., 2014
Department of Chemistry
Texas Christian University

Dissertation Advisor: Jean-Luc Montchamp, Professor

The work in this dissertation deals with the continued development of new methodologies for P-C and P-O bond formation using alternative methods that avoid the use of PCl_3. A review of the relevant literature that proceeds this work is presented in Chapter 1.

Chapter 2 describes the study of the P(III) to P(V) tautomerization of phosphinylidene compounds and the structural influences that effect the thermodynamic and kinetic properties to favor the more reactive P(III) species. A collaboration using both computational and experimental methods, show that electron withdrawing groups such as phenyl stabilize the tautomerization of phosphinylidene compounds. The second part of this work highlights the influence of various catalysts on P(III) to P(V) tautomerization. Using computational chemistry as a screening tool, a variety of organic acids and bases were tested. The calculations and experimental results are in good agreement.

Chapter 3 describes the work to develop the nickel-catalzyed hydrophosphinylation of unactivated alkenes, an extension of the work started with the nickel-catalyzed hydrophosphophosphinylation of alkynes. The results show that nickel chloride is pre-activated to an active Ni(0) species and can be stabilized by the inexpensive bisphosphine ligand,

ethylbis(diphenylphosphine), dppe. The reaction occurs at room temperature and works on a variety of different alkene substrates. Other manipulations used in tandem with the initial nickel hydrophosphinylation are highlighted, and show the reaction to be a versatile tool for making alkyl-*H*-phosphinate derivatives as precursors for further use.

Chapter 4 details the development of manganese-promoted intermolecular and intramolecular additions of alkenes, alkynes and aryl compounds with *H*-phosphinates is described. The system utilizing catalytic $Mn(OAc)_2$ either neat or in DMSO, is successful for a variety of different alkenes and two alkyne substrates. A more efficient and cost-effective system was recently developed for *H*-phosphinate arylations using catalytic $Mn(OAc)_2$ and MnO_2 as an oxidant, and further applied to alkene phosphonochlorination with LiCl.

In Chapter 5, nickel-catalyzed oxidation of alkyl hypophosphites is utilized to prepare ubiquitous alkyl-*H*-phosphonates starting from hypophosphorous acid and avoiding the use of PCl_3. The reaction can be considered a form of water splitting. The studies show that after the intitial esterification step, $NiCl_2$ or Ni/SiO_2 is enough to oxidize the first P-H bond to form the desired phosphonate. The reaction has been applied to the synthesis of the global herbicide glyphosate.