METHODOLOGY AND SYNTHESIS USING HYPOPHOSPHOROUS DERIVATIVES: PHOSPHORUS-CARBON BOND FORMATION AND GABA ANALOGUES

by

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ABSTRACT

LIST OF ABBREVIATIONS

AHP	Anilinium hypophosphite
AIBN	Azobisisobutyronitrile
BOC	*tert*-Butyl carbamate
BSA	N,O-Bis(trimethylsilyl)acetamide
N-BuIm	N-Butylimidazole
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEA	N,N-Diethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazane
NMP	N-Methylpyrrolidinone
PCC	Pyridinium chlorochromate
PEG	Poly(ethyleneglycol)
Pht	Phthalimide
Pyr	Pyridine
r.t.	Room temperature
TBAF	Tetrabutylammoniumfluoride

Xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene
Z (CBZ)	Benzyl carbamate

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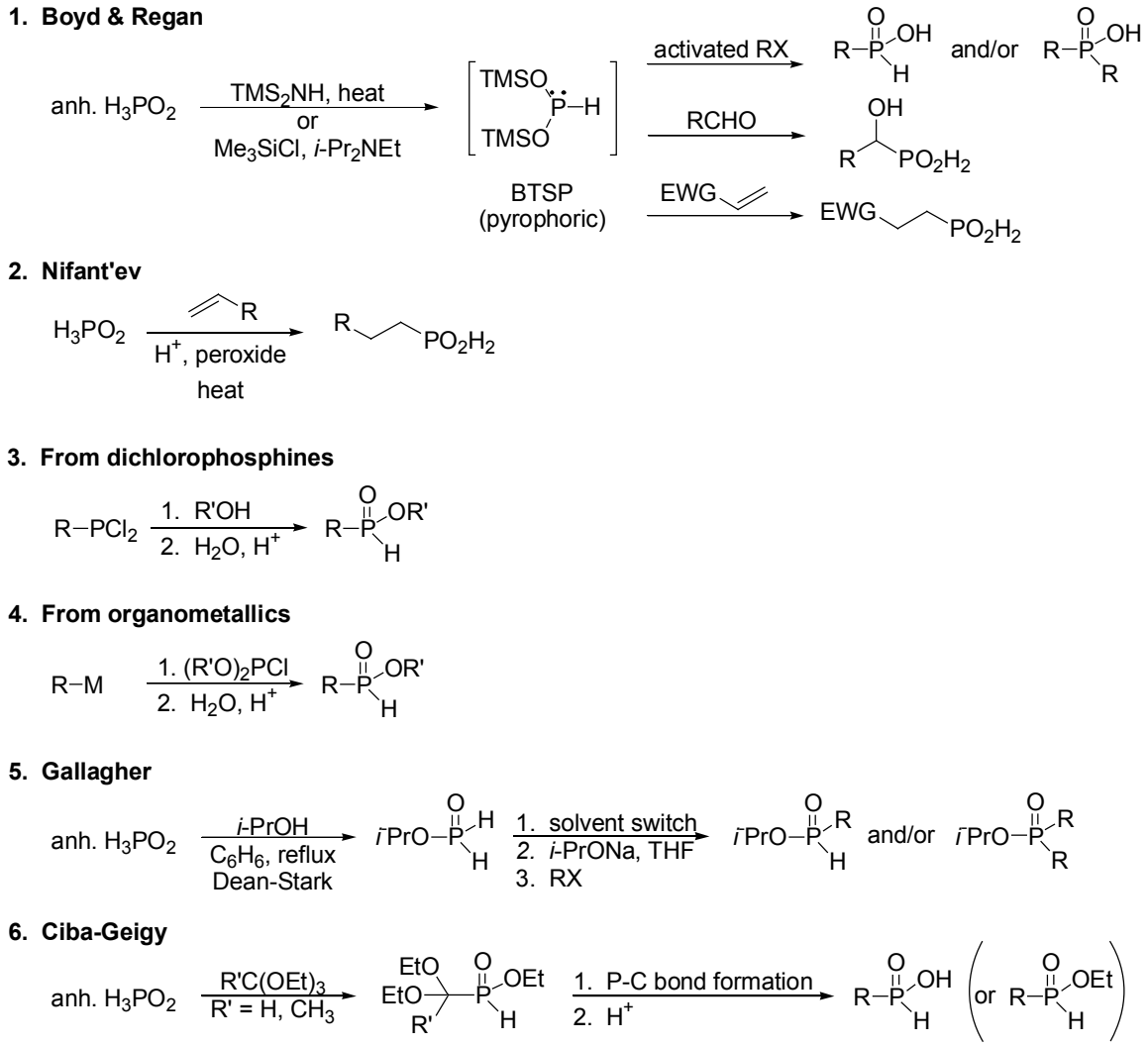
<u>Chapter One:</u> Phosphorus-carbon bond forming methodology developed in the Montchamp group

The literature offers various methods for the formation of the phosphorus-carbon bond. Depending on the type of organophosphorus compound desired, many published methods have limitations due to safety or scope, which reduce their practicality (Scheme 1.1).[1] For instance, the Boyd and Regan method of phosphinate synthesis produces $(TMSO)_2PH$, or bis(trimethylsiloxy)phosphine (BTSP) as a pyrophoric intermediate, which is then involved in an Arbuzov-like reaction.[2] Large excess is required to avoid formation of the disubstitued phosphinate, and foul-smelling byproducts are unavoidable. It also requires the use of hazardous anhydrous hypophosphorous acid. Furthermore, this method cannot be used with many alkyl halides. Gallagher reported the only examples of alkylation with alkyl halides using *i*-PrOP(O)H_2/*i*-PrONa.[3,4] The instability of the anion is well known[5-7], and the success of his alkylation relies on the use of the bulky isopropyl phosphinate. Ciba-Geigy (currently Novartis) created a reagent that has been widely used in the synthesis of γ-amino butyric acid (GABA) analogues (H-phosphinic acids or H-phosphinates).[8-15] However, their method requires separate protection and deprotection steps. Deprotection requires the use of strong acid, which conflicts with the presence of acid-sensitive functionalities.

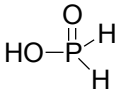
Scheme 1.1 Methods for preparation of H-phosphinates



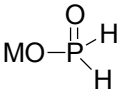
Over the past several years, the Montchamp group has developed new methodologies for the formation of P-C bonds with a focus on the reactions of hypophosphorous derivatives. Chart 1.1 shows some organophosphorus nomenclature. Some of the chemistry developed includes palladium-catalyzed cross-coupling, room temperature and thermal radical addition, palladium and nickel catalyzed hydrophosphinylation and alkylation.

Chart 1.1 Hypophosphorous acid and its derivatives

Hypophosphorous acid

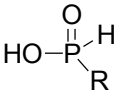


Hypophosphites

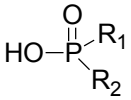


M = cation of base

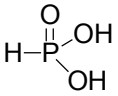
H-phosphinic acids



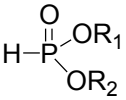
Phosphinic acids



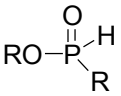
Phosphonic acid



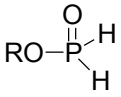
H-phosphonates



H-phosphinates



Alkyl/aryl phosphinates
Alkyl/aryl hypophosphites



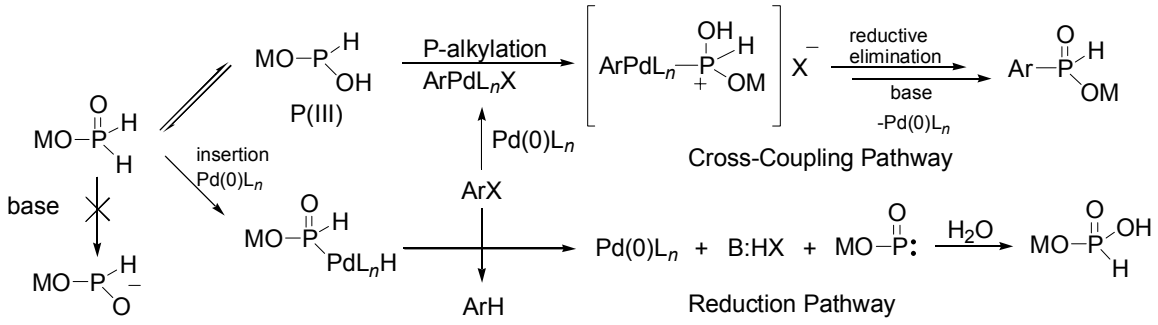
1.1 Palladium-catalyzed cross-coupling with hypophosphorous derivatives

Cross-coupling methodology in the context of P-C bond formation has in the past been limited. Schwabacher and co-workers were the first to report the palladium-catalyzed cross-coupling of alkyl phosphinates with aryl iodides.[16-19] Holt and Erb reported one example of cross-coupling between triethylammonium hypophosphite and a steroid-derived dienyl triflate, but the generality of the reaction was not established.[20]

The cross-coupling of a variety of electrophiles with hypophosphorous acid derivatives has been developed.

Transfer hydrogenation has long been known to occur between hypophosphorous acid or its sodium and amine salts and alkenes, alkynes, aldehydes, ketones and aryl halides under the influence of virtually all transition metals.[21-29] This can be useful for preparative purposes, but it is the major competing pathway with cross-coupling. The proposed mechanism involves the insertion of the metal into the P-H bond and subsequent formation of a metal hydride, which is a catalytically active reducing agent, thereby oxidizing the hypophosphorous acid derivative. To avoid transfer hydrogenation, the metal must insert into the C-X bond instead of the P-H bond (Scheme 1.2).

Scheme 1.2 Proposed mechanism of cross-coupling and the competing transfer hydrogenation pathway[30]



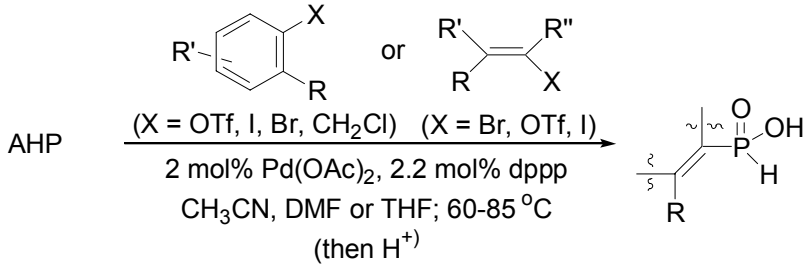
The phosphorus in the P(III) form would act as a nucleophile, displacing the halide to form the phosphonium intermediate, which would then undergo reductive elimination to form the final cross-coupled product (Scheme 1.2). Cross-coupling was accomplished with both anilinium hypophosphite[30,31] and alkyl hypophosphites[32,33].

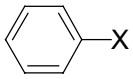
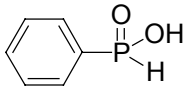
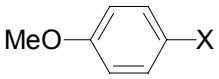
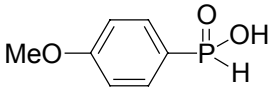
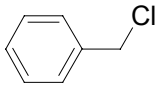
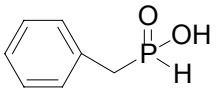
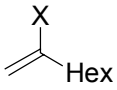
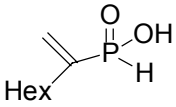
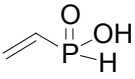
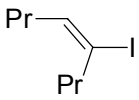
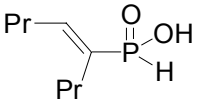
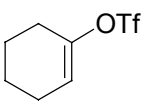
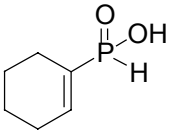
1.1.1 Cross-coupling with anilinium hypophosphite

The approach of this research was to modify the ligands surrounding palladium in order to control the relative rates of these two competing reactions. Anilinium hypophosphite (AHP), which is a stable, non-hygroscopic salt introduced by the Montchamp group and now commercially available through Aldrich (#654116), readily coupled with aryl, heteroaryl, alkenyl, benzylic and allylic halides and triflates (Table 1.1).

Conditions varied slightly depending on the ease with which the metal inserts into the C-X bond (oxidative addition). For iodides, which undergo C-X insertion more readily than bromides and chlorides, CH_3CN was the ideal solvent. Bromides reacted better in DMF, whereas unactivated chlorides were unsuccessful substrates. Palladium (II) acetate ($Pd(OAc)_2$) with dppp, with a loading of (2 mol % Pd/2.2 mol % ligand) was the most generally effective system. Even bromoanisole, which is deactivated toward oxidative addition, reacted well with this combination (Table 1.1, entry 2). In the case of Z-substituted alkenyl halides, dppf proved to be a better ligand. As little as 0.02 mol % $Pd(PPh_3)_4$ provided quantitative yield in the cross-coupling of iodobenzene in CH_3CN.

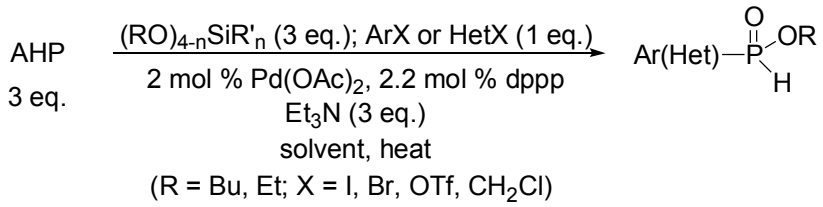
Table 1.1 Palladium-catalyzed cross-coupling reactions of anilinium hypophosphite[30,31]



Entry	Alkene	Product	X	NMR Yield (Isolated) %
1			I Br OTf	97 (87) 81 (-) 81 (-)
2			I Br	91 (85) 85 (-)
3			-	81 (66)
4			Br OTf	85 (75) 69 (-)
5			-	64 (-)
6			-	17 (-)
7			-	96 (74)

1.1.2 Cross-coupling with alkyl phosphinates

The goal of this project was to expand and generalize the work of Schwabacher, whose scope was limited due to the rapid thermal decomposition of methyl hypophosphite ($MeOP(O)H_2$).[14] With a new method to prepare thermally stable alkyl phosphinates developed, this goal seemed attainable.[34] Direct esterification of alkyl phosphinates with various aryl- and heteroaryl iodides, bromides, triflates, benzylic chlorides and alkenyl halides was developed to proceed in a one-pot, one-step process (Equation 1.1).[32,33]



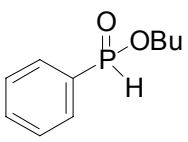
(Equation 1.1)

The one-step process has advantages over the two-step cross-coupling that forms first the salt and then the H-phosphinic ester. No acidic work-up is necessary before esterification: Alkoxysilane esterification of pure H-phosphinate salts is very inefficient. In addition, this is important for highly water-soluble H-phosphinic acids that are difficult to extract and for substrates whose acidification is problematic, for example nitrogen heterocycles. The separate esterification step requires a long reaction time, 12-24 hours. Manipulations and reaction times are minimized in this direct esterification to the H-phosphinate esters, which can be purified by standard chromatography. While DABCO initially was used as the base, Et_3N gave similar results and was used thereafter.

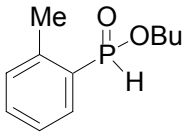
$Pd(OAc)_2$ (2 mol %)/dppp (2.2 mol %) is the best catalyst system. Chart 1.2 summarizes some of the products.

Chart 1.2 H-phosphinate esters synthesized via palladium-catalyzed cross-coupling[32,33]

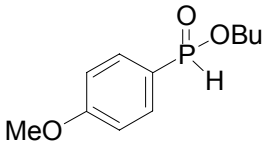
From iodides



80%



83%



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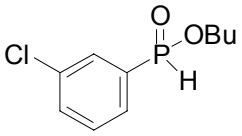

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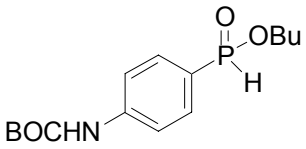

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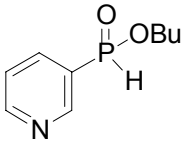

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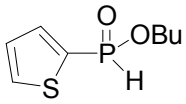
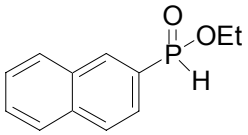


36%

From bromides



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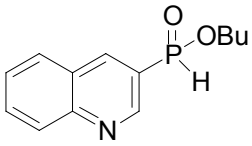

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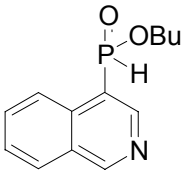

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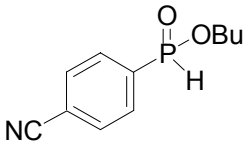
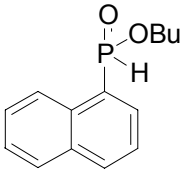


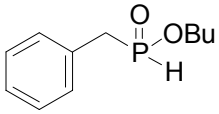
51%

From a triflate



80%

From benzylic chlorides



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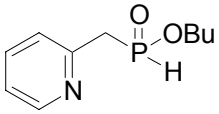
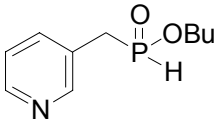


24%

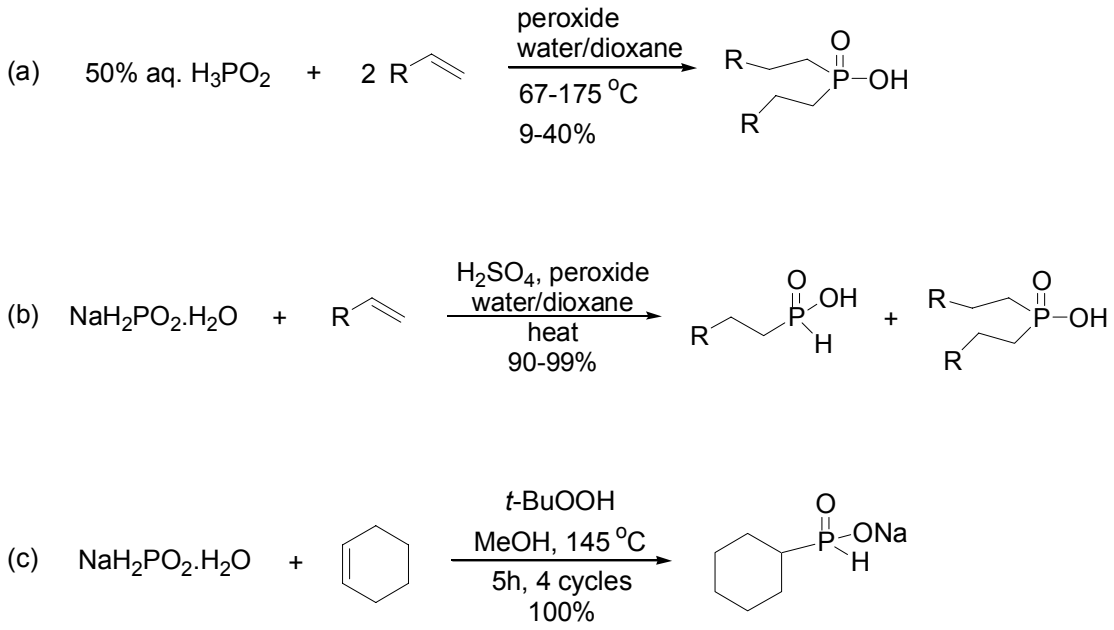


46%

1.2 Room temperature and thermal radical addition

Radical additions of phosphorus-centered radicals as P-C bond-forming reactions have been known for several decades. While Williams and Hamilton[35] (Scheme 1.3a) studied the reaction of aqueous hypophosphorous acid as early as 1955, Nifant'ev and coworkers[36,37] were chiefly responsible for this methodological contribution, and theirs had become one of the most convenient methods for the synthesis of phosphinic acids. Nifant'ev investigated the use of sodium hypophosphite as a suitable reagent (Scheme 1.3c).[36] However, conditions are impractical and affect acid-sensitive functionalities. Due to the limited solubility of sodium hypophosphite, high temperatures and pressure were required, in addition to multiple portions of a peroxide initiator. The yields were excellent, but the conditions were simply not practical. Nifant'ev determined that it would be beneficial to form hypophosphorous acid in situ through the addition of sulfuric acid (Scheme 1.3b).[37] A peroxide initiator was still required, and the sulfuric acid allowed the reduction of pressure and temperature while still providing near quantitative yields (90-99%). These conditions are not compatible with acid-sensitivefunctionalities.

Scheme 1.3 Radical reactions between hypophosphite derivatives and alkenes

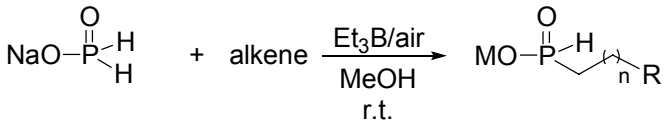


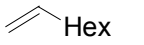
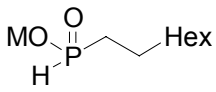
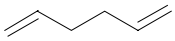
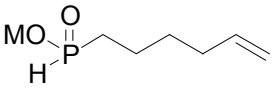
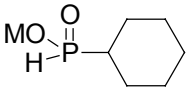
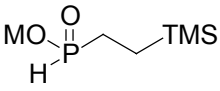
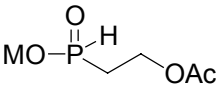
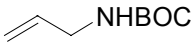
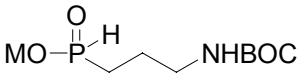
1.2.1 Triethylborane-initiated room temperature addition

As the Montchamp group was searching for a method of preparing non-hydrolyzable building blocks of DNA analogues, acidic conditions precluded using Nifant'ev's methods and forced them to develop their own.

Previously reported conditions for the radical addition of sodium hypophosphite or hypophosphorous acid include the use of harsh conditions. The Montchamp group studied alternative conditions and determined that triethylborane and oxygen formed an excellent initiator pair and allowed the reaction to proceed efficiently at ambient temperature, under neutral conditions, and provided the desired monosubstituted phosphinic acid by straightforward workup (Table 1.2).[38] The neutral, mild conditions of the Et_3B/air initiated radical reaction are in complete contrast to previous literature conditions.

Table 1.2 Radical reaction of sodium hypophosphite with alkenes[a,38]



Entry	Alkene	Product	NMR Yield[b] %	Isolated Yield[c] %
1			90	80
2			70	40
3			98	86
4			85	50
5			69	--
6			100	51

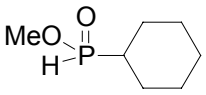
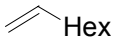
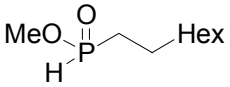
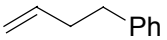
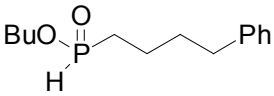
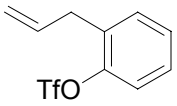
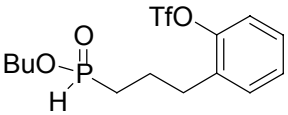
[a]All reactions were conducted in reagent grade MeOH (0.2 M in alkene) for 1.5-2h at room temperature in an open flask. NaH_2PO_2/Et_3B/alkene = 2.5:1:1. [b]Yield of phosphinate salt (M = Na), as determined by integration of all ^{31}P NMR signals. [c]Isolated by extraction with aqueous $KHSO_4$/EtOAc. Monosubstituted phosphinic acid products (M = H) were > 90% pure.

Derivatives of hypophosphite salts add to olefins via a phosphorus-centered radical (Table 1.2). Because P-centered radicals are electrophilic, electron-rich olefins

are necessary. As mentioned above, this reaction is conveniently conducted at room temperature in an open flask, thereby making it applicable to a wide-range of functionalities (Table 1.2). Excellent selectivity is observed for monoaddition, and symmetrical dialkyl phosphinates do not form in significant amounts, even when excess alkene is used. The best conditions were determined to be (2.5:1:1) NaH_2PO_2:Et_3B:alkene. Typically, the salt (5 mmol) and the olefin (2 mmol) were solubilized in methanol (10 mL). The borane (2 mmol) was added at room temperature to the open flask, and the reaction was allowed to proceed for 2 hours.

Alkyl hypophosphites were investigated, as well (Table 1.3). Ideal reaction conditions were different from those for the sodium hypophosphite: 3 equivalents of methyl- or butyl hypophosphite were required, and as little as 0.1 to 0.2 equivalents of Et_3B proved successful. Alkyl hypophosphites appear to be much more prone to H-abstraction and therefore have a more efficient chain reaction than the salts. Isolated yields were lower with the alkyl hypophosphites than with the salts. This is due to the polarity and subsequent increase in hydrolysis during work-up or column chromatography.

Table 1.3 Radical reactions of alkyl hypophosphites with alkenes[a,38]

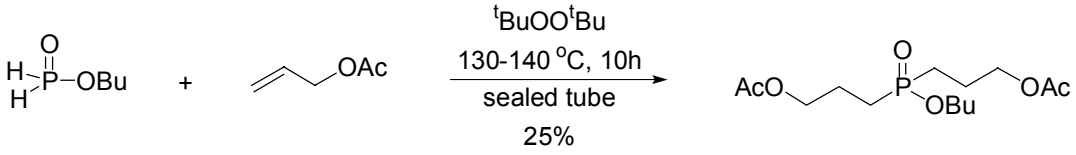
Entry	Alkene	Product	NMR Yield[b] %	Isolated Yield[c] %
1			97	60
2			-	96[d]
3			76	65
4			62	59

[a]All reactions were conducted in reagent grade MeOH (0.2 M in alkene) for 1.5-2h at room temperature in an open flask. [b]Yield of phosphinate ester, as determined by integration of all ^{31}P NMR signals. [c]Isolated by extraction with aqueous $KHSO_4$/EtOAc followed by chromatography. [d]Obtained in ca. 90% purity after extraction.

The alkene substrate determines the choice of alkyl hypophosphite or hypophosphite salt. If the olefin is highly sensitive, one may use the alkyl phosphinate, which, although the isolated yield may be lower, allows for the formation of the ester directly, thereby bypassing the acidification and esterification steps. In addition, a catalytic amount of the organoborane may be used in the case of alkyl phosphinates, whereas 0.5 to 1.0 equivalent of the borane is required for the hypophosphite salts.

1.2.2 AIBN-initiated addition

The radical P-C bond formation work of Nifant'ev is described above. Another contributor to the radical hydrophosphinylation reaction is Karanewsky, who used AIBN in the radical addition of H_3PO_2 to alkenes and alkynes.[39] Karanewsky used refluxing solvent, usually ethanol. Before the 2006 publication of Antczak and Montchamp's paper[40], only one report of the use of an alkyl phosphinate in a thermally-initiated radical reaction was known[41], i.e. the reaction of butyl phosphinate with allyl acetate in the presence of di-*tert*-butyl peroxide (130-140 ºC, 10h, sealed tube) to obtain bis(3-acetoxypropyl)-phosphinate in 25% yield (Equation 1.2). The symmetrically disubstituted phosphinate was obtained, probably due to the forcing conditions.



(Equation 1.2)

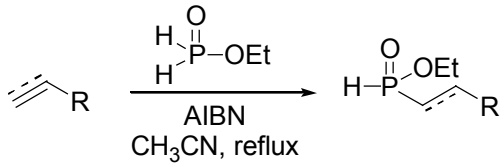
Alkyl phosphinates prepared via alkoxysilane esterification of hypophosphorous acid or anilinium hypophosphite ($Me_2Si(OEt)_2$ with H_3PO_2 or AHP) have proven to be unusually thermally resistant.[34] Reaction by-products include the dialkyl phosphite, which is known to add to a double bond. The addition does not occur under these conditions.

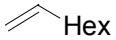
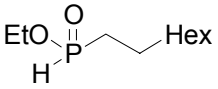
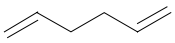
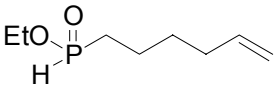
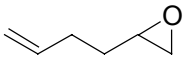
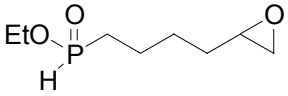
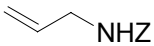
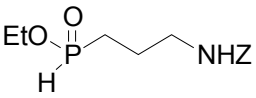
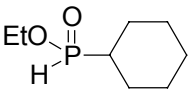
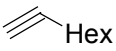
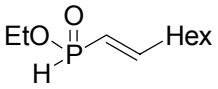
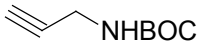
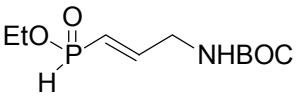
The use of AIBN in a thermal radical addition involving these alkyl phosphinates was investigated. Ideal conditions were determined to be 2.5 equivalents of the alkyl phosphinate in acetonitrile (0.5 M), 1.0 equivalent of the alkene or alkyne, and two

portions of 0.10 equivalent of recrystallized AIBN. The reaction mixture was heated to reflux for 3-6 hours before the addition of the second portion of AIBN, after which the mixture was allowed to reflux overnight. A variety of substrates was successfully employed, and isolated yields generally range from 60-80% (Table 1.4). Terminal alkynes, acid and base-sensitive CBZ and BOC-protected amines, epoxides, cycloalkenes and dienes all fared well under the neutral conditions. It should be noted that terminal alkynes, whose reactions predominantly yield the *trans* product, fail to react in the Et_3B/air initiated radical reaction. The corresponding product may be obtained via cross-coupling of alkenyl halides or palladium- or nickel-catalyzed hydrophosphinylation of terminal alkynes. However, in the case of cross-coupling, the required alkenyl halides or triflates are sometimes inaccessible, whereas the latter reaction yields mixtures of linear and branched isomers that are not readily separated.

Hence, the AIBN-initiated method fills a significant methodological void. In addition, the dialkyl phosphite, the esterification by-product, does not add to the olefin under the reaction conditions, and disubstitution from over-reaction of the H-phosphinate product is not observed.

Table 1.4 AIBN-initiated radical addition to alkenes and alkynes[40]



Entry	Alkene/Alkyne	Product	Isolated Yield %	Trans/Cis[a]
1			72	-
2			76	-
3			61	-
4			75	-
5			40	-
6			68 (1/0)	3.5/1
7			63	1/0

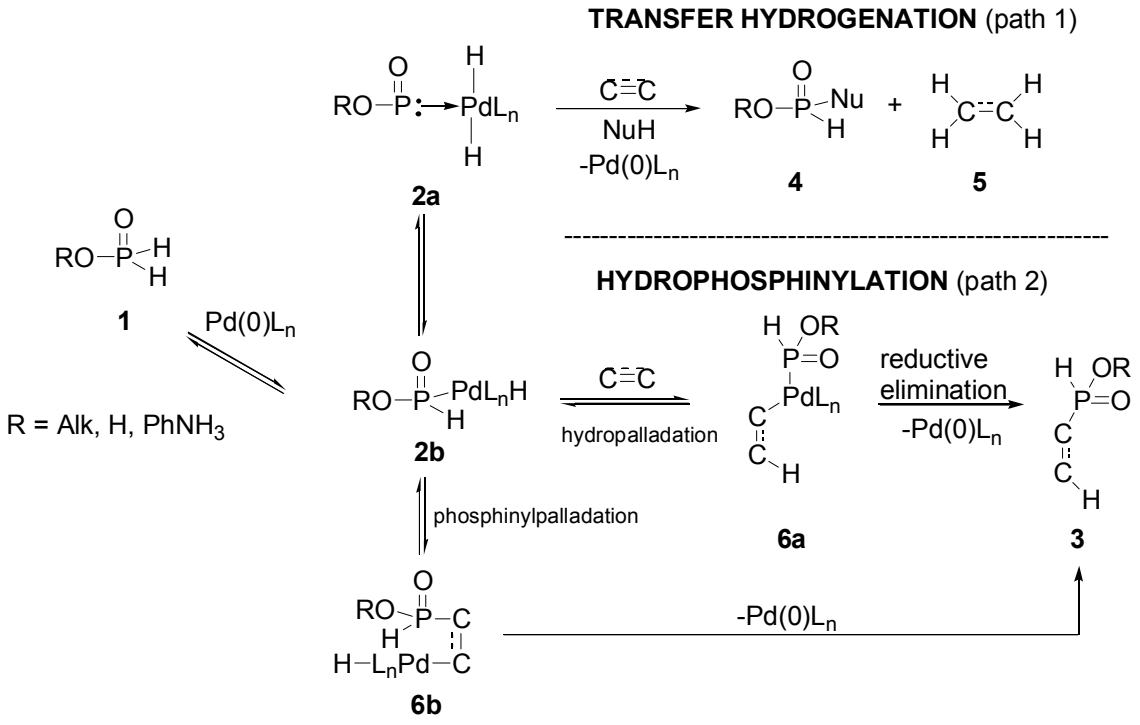
[a]Ratios were determined by ^{31}P NMR.

1.3 Hydrophosphinylation of alkenes and alkynes

1.3.1 Palladium-catalyzed hydrophosphinylation

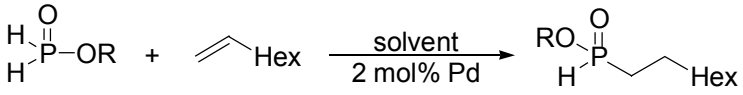
During the cross-coupling work, it was noted that the competing transfer hydrogenation could be minimized, depending on the choice of ligand. Of those investigated, the best ligand for this cause is dppp. Catalytic transfer hydrogenation of various compounds using hypophosphorous acids or its salts as hydrogen donors has been known for years.[21-29] The proposed mechanism involves oxidative addition of Pd(0) into the P-H bond to form **2b** and then the reactive species palladium hydride **2a** (Scheme 1.4), which can lead to undesired **4** or **5** via transfer hydrogenation. It was proposed to trap species **2b** through hydropalladation to form **6a** or through phosphinylpalladation to form **6b**, which would then undergo reductive elimination to form the desired H-phosphinate product. This would require a ligand that slows down β-hydrogen eliminationfrom **2b** to **2a**.

Scheme 1.4 Postulated mechanistic pathways in the palladium-catalyzed reaction of hypophosphorous derivatives[42]



A remarkably general and rugged method was developed for the hydrophosphinylation of alkenes and alkynes with hypophosphorous derivatives **1**.[42] In a typical procedure, a solution of hypophosphite **1** (5 mmol) in solvent (10 mL) was heated with 1-octene (2.5 mmol) in the presence of a catalyst (2-3 mol%). Four main catalyst/ligand systems provided the best results: $Cl_2Pd(PPh_3)_2$/MeLi in toluene, THF, or acetonitrile; Pd_2dba_3/xantphos (or DPEphos, or dppf) in acetonitrile (Table 1.5, entries 1-3, 4-6).

Table 1.5 Hydrophosphinylation of 1-octene[42]



Entry	R	Solvent[a]	Catalyst[b]	Yield[c] %
1	Bu	CH_3CN	$Cl_2Pd(PPh_3)_2$/MeLi	65
2	Bu	THF	$Cl_2Pd(PPh_3)_2$/MeLi	100
3	Bu	Toluene	$Cl_2Pd(PPh_3)_2$/MeLi	78
4	Bu	CH_3CN	Pd_2dba_3/dppf	86
5	Bu	CH_3CN	Pd_2dba_3/xantphos	100
6	Bu	CH_3CN	Pd_2dba_3/DPEphos	100
7	Bu	CH_3CN (r.t.)	Pd_2dba_3/xantphos	90
8	H	CH_3CN (r.t.)	Pd_2dba_3/xantphos	100
9	H	H_2O, CH_3CN (r.t.)	Pd_2dba_3/xantphos	79

[a]Unless otherwise noted, reactions were conducted at the reflux temperature. Reaction times (unoptimized): 12-16h. For R = Bu, Et, reagent grade solvents were used. 1-Octene concentration was 0.2 M. [b]Catalysts: 2 eq. MeLi were used per Pd. 1 mol % Pd_2dba_3 + 2.2 mol % bisphosphine ligand. [c]Yields were determined by ^{31}P NMR analysis of the crude reaction mixtures and integration of all the resonances.

While the reaction works well and was usually conducted in the refluxing solvent, the addition of aqueous hypophosphorous acid and butyl hypophosphite also occurs at room temperature in some cases (Table 1.5, entries 7, 8). Butyl hypophosphite in acetonitrile adds to 1-octene in the presence of Pd_2dba_3/xantphos at room temperature to give a crude yield of 90%. Under the same conditions, aqueous hypophosphorous acid adds quantitatively. Furthermore, hydrophosphinylation remained the major pathway,

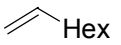
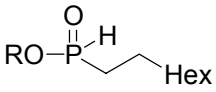
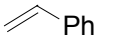
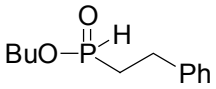
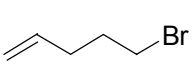
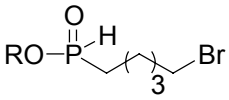
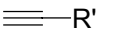
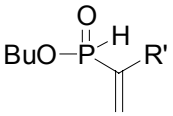
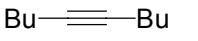
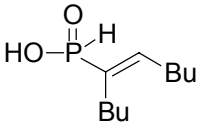
even with the addition of excess alcohol or water, which would be expected to favor formation of **2a** via driving the equilibrium through trapping of (RO)P(O). At room temperature, hypophosphorous acid added in 79% crude yield to 1-octene in acetonitrile in the presence of additional water (Table 1.5, entry 9). This points to the marked preference of the system toward hydrophosphinylation over transfer hydrogenation, or reduction.

A difference in regioselectivity is observed depending on the palladium catalyst chosen. Terminal alkynes give the branched vinylphosphinate exclusively with catalytic $Cl_2Pd(PPh_3)_2$/2MeLi, whereas the linear product is the major component with catalytic Pd_2dba_3/xantphos (Table 1.5, entries 6, 7, 8). This was recently improved.[43]

Because the H-phosphinic esters **3** (Scheme 1.4) are unreactive under the reaction conditions, there is no observed formation of the symmetrically disubstituted phosphinates.

The palladium-catalyzed hydrophosphinylation is a nice complement to the borane-initiated radical addition in that styrene (Table 1.6, entry 3) and 5-bromo-1-pentene (Table 1.6, entries 4-5) work well under the hydrophosphinylation conditions, whereas they are poor substrates in the borane work. Conversely, cyclohexene works well in the radical reaction but does not in the hydrophosphinylation (Table 1.2, entry 3) and (Table 1.3, entry 1).

Table 1.6 Hydrophosphinylation of various alkenes and alkynes[a,42]

Entry	Substrate	Product	Catalyst[b]		Yield[c] (Isolated) %
1 2			Pd_2dba_3/ xantphos	R = Bu R = H	89 (76) 100 (67)
3			Pd_2dba_3/ xantphos		100 (69)[d]
4 5			Pd_2dba_3/ xantphos	R = Et R = H	100 (61) 100 (83)
6 7			$Cl_2Pd(PPh_3)_2$/ 2MeLi	R' = Oct R' = H	70[e] 85 (50)[e]
8			Pd_2dba_3/ xantphos		100 (88)

[a]Reactions were conducted in refluxing CH_3CN, except for entries 2 and 5, which were conducted at room temperature. 1.5 eq. $ROP(O)H_2$ was employed. Alkene/alkyne concentration was 0.3 M. [b]Catalyst: 0.05-1.0 mol % Pd. [c]Yields of H-phosphinic acid derivative determined by ^{31}P NMR analysis. Isolated yields are unoptimized. [d]Linear/branched: 4.4:1. [e]Branched only. This reaction was run with 3 mol % catalyst in refluxing toluene.

1.3.2 Nickel-catalyzed hydrophosphinylation

The use of a nickel catalyst in the addition of hypophosphorous acid derivatives to alkenes and alkynes was investigated in attempt to find a cheaper and perhaps more reactive catalyst than the previously reported palladium[44]. Initial investigation gave fair results (Table 1.7, entries 1 and 2), up to 70% NMR yield for the reaction of 1-octene, ethyl hypophosphite, $Cl_2Ni(dppp)$ in toluene at room temperature. Still, this was not an improvement over what had been reported using palladium[42].

Table 1.7 Comparison of Pd versus Ni as catalyst in hydrophosphinylation with $ROP(O)H_2$[44]

Entry	Substrate	R	Solvent	Catalyst[a]	NMR Yield[b] %
1	1-octene	Bu	CH_3CN, reflux	$Cl_2Ni(dppf)$	14
2	1-octene	Et	Toluene, r.t.	$Cl_2Ni(dppp)$	69
3	1-octene	Et	Toluene, r.t.	$Cl_2Ni(PPh_3)_2$	65
4	1-octene	Bu	CH_3CN, reflux	Pd_2dba_3/xantphos	100
5	4-octyne	Et	CH_3CN, reflux	Pd_2dba_3/xantphos	40
6	4-octyne	Et	CH_3CN, reflux	$NiCl_2$	100

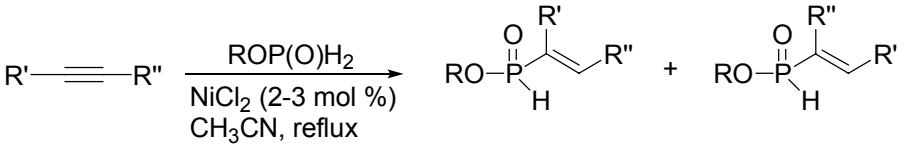
[a]Catalyst loadings vary from 1 to 4 mol %. [b]NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

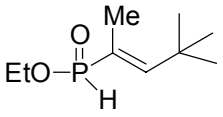
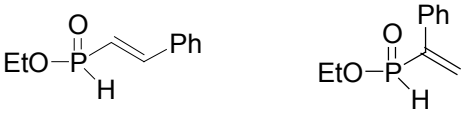
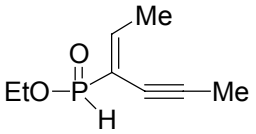
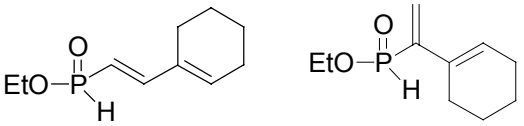
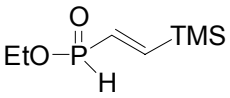
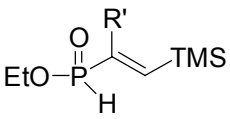
The case of alkynes gave a very different result than that with alkenes (Table 1.7, entry 6 versus 1). With palladium, internal alkynes are poor substrates with alkyl phosphinates (Table 1.7, entry 5), whereas with nickel both terminal and internal alkynes are excellent substrates. However, lower regioselectivity is observed with nickel versus palladium and terminal alkynes. With terminal alkynes, the regioselectivity ranges from 1:1 to 3:1 (linear:branched), and the low isolated yields reflect the difficulty in separating the isomers (Table 1.8). The previously reported palladium work is more selective toward linear products with Pd_2dba_3/xantphos and highly selective for the branched isomer with $Cl_2Pd(PPh_3)_2$/MeLi (Table 1.6). However, some substrates still display useful regioselectivities with the nickel catalysts when significant steric or electronic biases are present. Alkynes with a terminal *tert*-butyl or trimethylsilyl group react regioselectively to afford the β-substituted H-phosphinate (Table 1.8, entries 1, 7-9).

Other alkynes with a phenyl, alkene or ethoxy group tend to give the “branched“ product, with addition taking place at the substituted carbon. Terminal alkynes give the linear product as the major isomer (Table 1.8, entry 6), but inductively electron-withdrawing substituents increase the formation of the branched isomer (Table 1.8, entries 2,4,5). In all cases, excellent stereospecificity was observed for syn addition and formation of the E-isomer.

Various nickel catalysts were tried, but inexpensive $NiCl_2$ (2-4 mol %) proved to be the best choice. Notice from the above equation in Table 1.8 that no additional ligand is needed for the reaction to proceed successfully. It is proposed that the alkyl phosphinate, $ROP(O)H_2$, reduces Ni(II) to the catalytically active Ni(0), which then complexes with excess phosphinate in the reaction mixture.

Table 1.8 $NiCl_2$-Catalyzed hydrophosphinylation of alkynes[44]

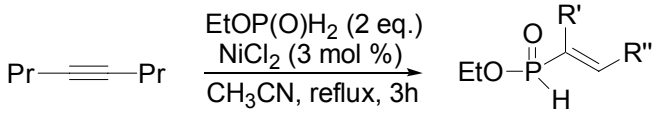


Entry	R′	R″	R	Product(s)	Isolated Yield[a] %
1	*t*-Bu	Me	Et		77
2	Ph	H	Et		100 (1:1)
3	MeC≡C	Me	Et		57
4	1-cyclo-hexenyl	H	Et		63 (1.5:1)
5	EtO	H	Et		42/0 (3:1)
6	Hex	H	Et		100 (3:1)
7	TMS	H	Et		75
8	Bu	TMS	Et		64
9	Pr	TMS	Et		46

[a]All yields are isolated. Ratios in parentheses indicate regioselection, determined on the crude reaction mixture. All reactions were conducted in refluxing reagent grade CH_3CN.

The reaction is quite rugged, as well; quantitative crude yields were obtained even in the presence of 1 eq. of water, 3 eq. of ethanol or dry air (Table 1.9, entries 2, 3, 4). $NiCl_2 \cdot 6H_2O$ also yields excellent results (Table 1.9, entry 5). The choice of solvent is not as flexible with nickel than as with palladium: acetonitrile is the ideal solvent, while toluene works well in some cases; and tetrahydrofuran gave only low yields. Various alkyl phosphinates ($ROP(O)H_2$, R = Me, Et, Bu, *i*-Pr) react in high yield. Stoichiometry for the reaction is the alkyl hyposphosphite in solution (0.5 M) (2 eq.), alkyne (1 eq.) and 2-4 mol % of the catalyst, relative to the alkyne. The reaction mixture was brought to reflux until completion of the reaction, which was generally 3 hours. This reaction also works well under microwave conditions.

Table 1.9 Influence of additives on $NiCl_2$-catalyzed hydrophosphinylation[44]



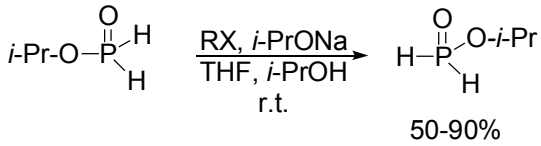
Entry	Catalyst	Additive	NMR Yield[a] (Isolated Yield) %
1	$NiCl_2$	none	100 (75)
2	$NiCl_2$	H_2O (1 eq.)	100 (80)
3	$NiCl_2$	EtOH (3 eq.)	100 (81)
4	$NiCl_2$	air[b]	100 (86)
5	$NiCl_2 \cdot 6H_2O$	none	99 (84)

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

Nickel-catalyzed hydrophosphinylation is yet another building block in the complementary P-C bond formation methodologies that have been developed in the Montchamp group over the past few years. Where one method fails, another is eventuallysuccessful.

1.4 Base-promoted phosphorus-carbon bond formation of alkyl and H-phosphinates

Direct alkylation of alkyl phosphinates ($ROP(O)H_2$) under basic conditions had only been successful in the hands of Gallagher, whose scope was extremely limited and worked only with isopropyl phosphinate in the presence of sodium isopropoxide (Equation 1.3).[3] Alkylation had failed because of decomposition of the anion formed from the deprotonation of unhindered esters (R = Me, Et) of hypophosphorous acid.[45,46] Gallagher's bulky isopropyl group slowed down anion decomposition. Alkyl phosphinate equivalents [$(EtO)_2CHP(O)(OEt)H$, and $(EtO)_2CMeP(O)(OEt)H$, "Ciba-Geigy reagents"] have been employed to bypass decomposition, even though the reaction requires a protection-deprotection sequence.[8]

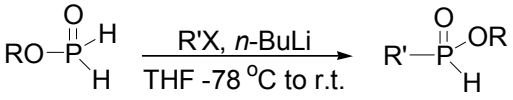


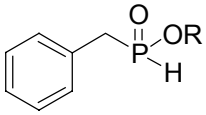
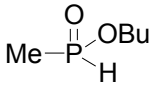
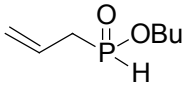
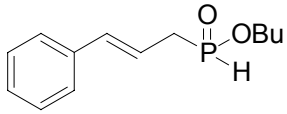
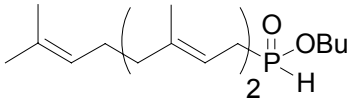
RX = CH_3I, CH_2=$CHCH_2Br$, BnBr, n-$C_5H_{11}I$, $Br(CH_2)_4Br$

(Equation 1.3)

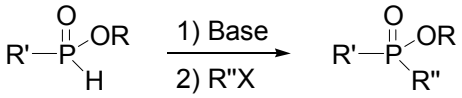
Primary alkyl phosphinates, prepared from the alkoxysilane method, were alkylated with reactive electrophiles (alkyl iodides, allylic and benzylic bromides) in the presence of butyl lithium. Less reactive halides, such as octyl bromide, did not react successfully. Barbier-like conditions were employed. That is, the base is added to a mixture of the electrophile and nucleophile in nearly stoichiometric ratios. Table 1.10 lists some of the fifteen successful reactions with various alkyl phosphinates and electrophiles.

Table 1.10 Butyl lithium-promoted alkylation of alkyl phosphinates under Barbier-like conditions

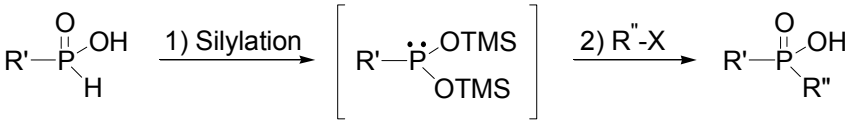


Entry	R	Electrophile	Product	Isolated Yield %
1	Et Bn	Benzylbromide		71 45
2	Bu	Methyliodide		82
4	Bu	Allylbromide		71
5	Bu	Cinnamylbromide		60
6	Bu	Farnesylbromide		80

Many examples of base-promoted H-phosphinate alkylation have been published over the years (Equation 1.4), but there had been no standard reaction conditions. Several bases have been employed (RONa, NaH, BuLi, LDA, KHMDS), and a somewhat more general approach consisting of silylation of the alkyl H-phosphinic acid followed by an Arbuzov-like reaction has been published (Equation 1.5), as well.[47] However, further manipulations of this acidic product would likely require subsequent esterification; thus, a direct, standard route to the alkylated H-phosphinate esters was desired. The Montchamp group has produced standard, efficient conditions for the second P-C bond formation via alkylation of H-phosphinate esters.[48]



(Equation 1.4)

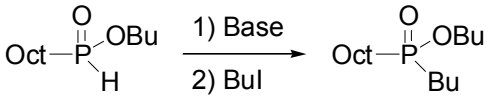


(Equation 1.5)

To determine the optimum base, butyl octyl-H-phosphinate was selected as the model phosphorus compound, along with *n*-butyl iodide as the electrophile. Sodium, *i*-PrMgCl, MeLi, BuLi, LDA and LiHMDS were tested (Table 1.11). Alkylation occurred in all instances, but the use of nucleophilic bases such as MeLi and BuLi lowered the yield (entries 3, 4), due to competing direct substitution of the butyl ester to form the

secondary phosphine oxide. Strong, non-nucleophilic bases such as LDA and LiHMDS fared better (entries 5, 6).

Table 1.11 Role of base in alkylation of butyl octyl-H-phosphinate with butyl iodide[49]



Entry	Conditions	Base	NMR Yield %[b]
1	0 ºC to r.t.	Na	16
2	-78 ºC to r.t.	*i*-PrMgCl	64
3	-78 ºC to r.t.	MeLi	56
4	-78 ºC to r.t.	BuLi	60
5	-78 ºC to r.t.	LDA	89
6	-78 ºC to r.t.	LiHMDS	100

[a]All reactions were conducted in freshly distilled anhydrous THF, under N_2. [b]NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

As LiHMDS gave quantitative NMR yield, this was chosen to investigate various electrophiles. Primary alkyl iodides, bromides, chlorides, tosylates and a secondary iodide were tested (Table 1.12). As the reactivity of the electrophile decreased, i.e. use of octyl chloride versus octyl iodide, an increase of oxidation byproducts was noticed if the reaction required heating. To avoid this, a modified deoxygenation technique was implemented: Vacuum was pulled on the reactants at –78 ºC for several minutes before

the flask was filled with nitrogen. The deoxygenation enabled the alkylation with octyl chloride to take place in moderate yield (51% isolated) (entry 6), thereby becoming the first known successful alkylation with an alkyl chloride. The secondary isopropyl iodide required deoxygenation but alkylated in moderate (64% isolated) yield (entry 8). This is the first known reaction of this type with a secondary alkyl iodide. Stoichiometry for this reaction is equimolar.

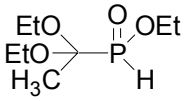
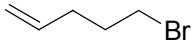
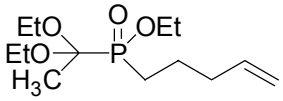
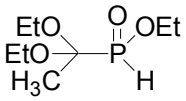
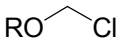
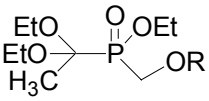
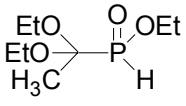
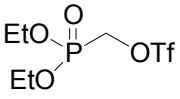
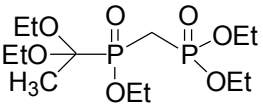
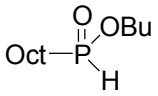
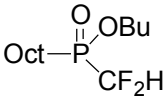
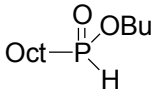
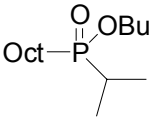
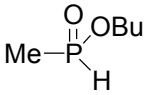
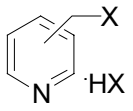
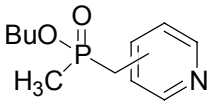
Table 1.12 Role of the electrophile in the alkylation of butyl phenyl-H-phosphinate with LiHMDS[48]

Entry	RX	Deoxygenation[a]	Temperature	NMR Yield[b] (Isolated) %
1	CH_3I	No	-78 ºC to r.t.	100 (98)
2	OctI	No	-78 ºC to r.t.	100 (80)
3	OctBr	No	-78 ºC to r.t.	80 (57)
4	OctBr	Yes	-78 ºC to r.t.	92 (71)
5	OctCl	No	-78 ºC to reflux	1 (-)
6	OctCl	Yes	-78 ºC to reflux	77 (51)
7	OctOTs	Yes	-78 ºC to reflux	88 (62)
8	*i*-PrI	Yes	-78 ºC to reflux	97 (64)

[a]Deoxygenation was conducted by placing a THF solution of the H-phosphinate under vacuum at –78 ºC for 5 min, then adding N_2. [b]NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

A large variety of H-phosphinate esters was alkylated in moderate to good (40% to 95%) isolated yields with a broad range of electrophiles (Table 1.13).

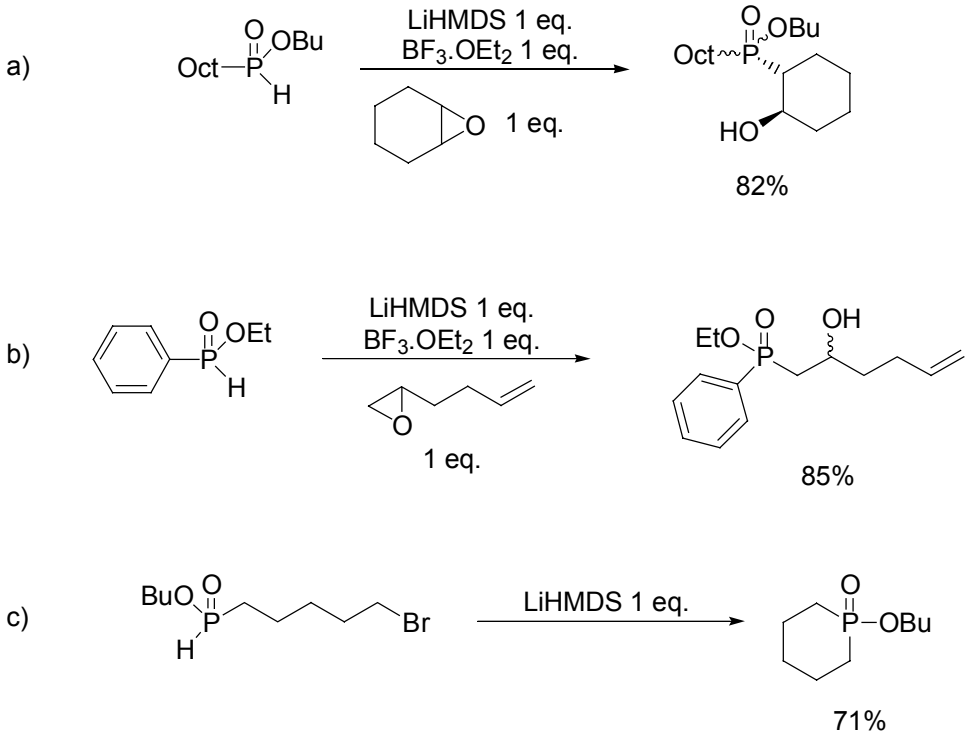
Table 1.13 Alkylation of H-phosphinate esters with various electrophiles[a,48]

Entry	H-Phosphinate Ester	Electrophile	Product	Isolated Yield %
1				66
2		 R = Piv		50
3		R = Bn		70
4				81
5		F_2CHCl		78
6		*i*-PrI		73
7		 X = Cl, p		50
8		X = Br, m		62
9		X = Br, o		68

[a]Deoxygenation was conducted by placing a THF solution of the H-phosphinate under vacuum at −78 ºC for 5 min, then adding N_2.

Epoxide ring openings (Scheme 1.5a,b) as well as intramolecular ring closings (Scheme 1.5c) were successful, as well.

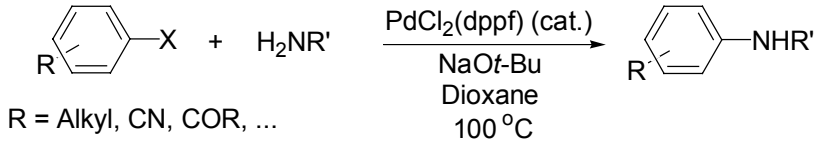
Scheme 1.5 Epoxide ring opening and intramolecular cyclization under alkylation conditions[48]



Chapter Two: Transition-metal catalyzed cross-coupling of alkyl halides and hypophosphorous salts

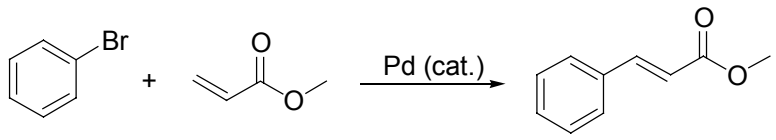
Cross-coupling is a commonly used catalytic method to construct a bond between C_{sp}^3 and C_{sp}^2 or C_{sp} centers. There are many well-known reactions (Scheme 2.1).[49,50] Less common is the coupling of two C_{sp}^3 centers, although some examples exist.[51-59] Recent reviews of the subject have been published.[60-62] Scheme 2.2 shows the general catalytic cycle between an organohalide and an organometallic nucleophile. The process involves oxidative addition, transmetallation and reductive elimination. Oxidative addition into the R-X bond occurs more efficiently into an activated, electron-deficient bond. Furthermore, insertion of the electron-rich metal occurs more readily on iodides than bromides and chlorides. In the presence of β-hydrogens, elimination occurs during the slow transmetallation step and is a source of major byproduct formation. Transfer hydrogenation, or reduction, of the β-hydrogen-containing compound is the other source of byproduct formation. The product forms via reductive elimination of the ML_n complex.

Scheme 2.1 Common cross-coupling reactions

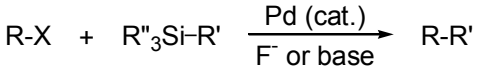


R = Alkyl, CN, COR, ...

Buchwald-Hartwig

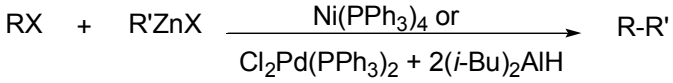


Heck



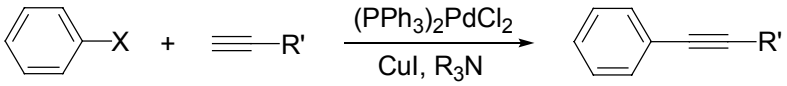
R" = $(RO)_3Si$, $Me_{(3-n)}F_nSi$

Hiyama

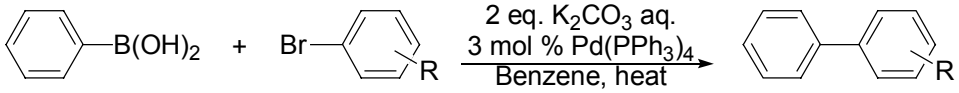


R = alkenyl, aryl, allyl, benzyl, propargyl
R' = alkenyl, aryl, alkynyl, alkyl, benzyl, allyl

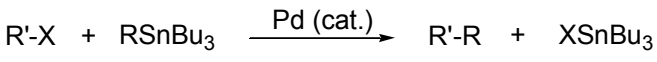
Negishi



Sonogashira

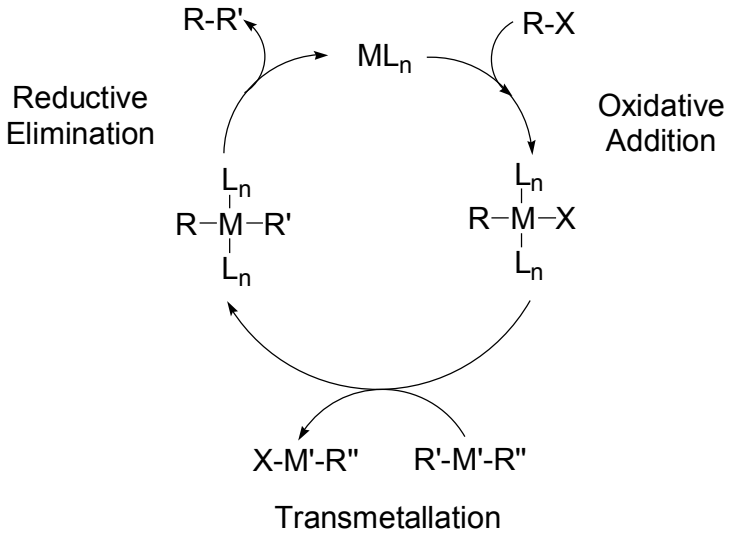


Suzuki



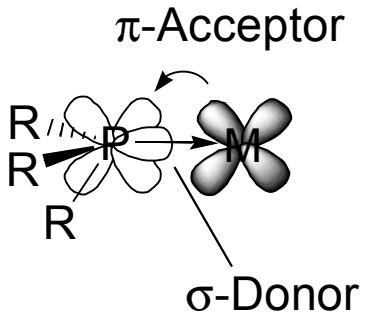
Stille

Scheme 2.2 General cross-coupling catalytic cycle



Metal and ligand choice plays an important role. Low-valent nickel and palladium complexes are most often used, and ligand structure varies widely. Phosphines are often chosen as ligands and are generally good σ-donors and weak π-acceptors (Figure 2.1). Bulkier, electron-donating ligands (good σ-donors) dissociate more easily than smaller ligands, which have higher π-acceptor ability and dissociate later in the reaction.[63] Choice of ligand therefore allows tuning of the metal-ligand complex and greater reaction control.

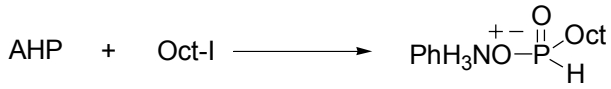
Figure 2.1 Orbital depiction of σ-donor and π-acceptor properties of phosphine ligands



Existing examples of alkyl-alkyl cross-coupling involve organometallic nucleophiles i.e. Negishi, Grignard or Suzuki reagents, and therefore do not apply to P-C bond formation. Hence, this research addressed the cross-coupling of primary alkyl halides with hypophosphite salts as the nucleophile.

2.1 Cross-coupling of iodooctane and anilinium hypophosphite

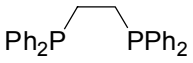
Research initially focused on the cross-coupling of iodooctane and AHP (Equation 2.1).



(Equation 2.1)

The approach to this project was combinatorial-like: Palladium, platinum and nickel complexes served as catalysts, while a wide range of ligands was screened (Chart 2.1).

Chart 2.1 Ligands screened for cross-coupling with AHP



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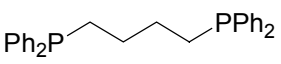

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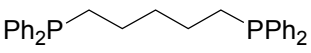

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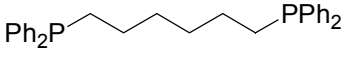

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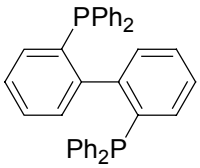
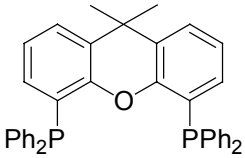
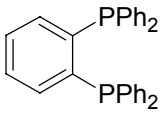
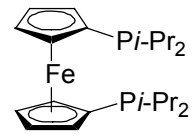
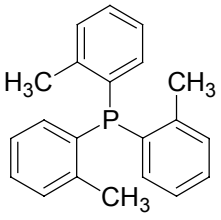
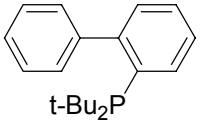


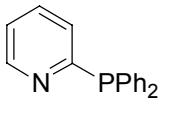


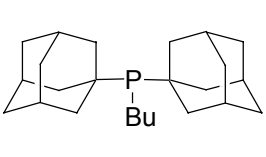


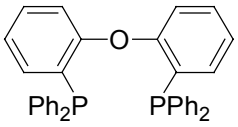


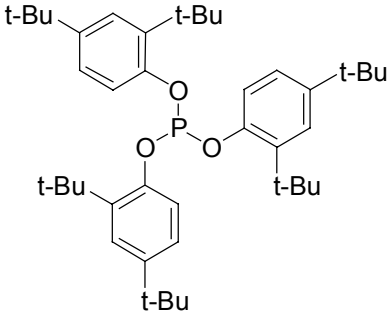


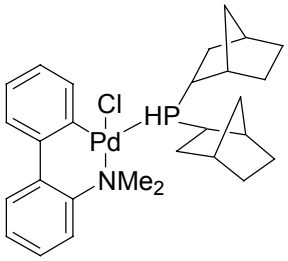




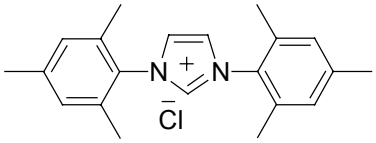








12



Ph_3As

$Bu_3P\text{-}HBF_4$

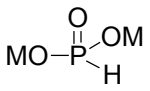
$Cy_3P\text{-}HBF_4$

$t\text{-}Bu_2MeP\text{-}HBF_4$

$t\text{-}Bu_3P\text{-}HBF_4$

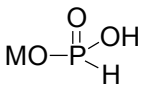
$Cy_2PhP\text{-}HBF_4$

While the byproduct and starting material distribution varied among conditions, no product formed (Table 2.1). Columns labeled **13, 14** and **16** are yields of byproducts, formed through oxidation **(13, 14)** or reduction **(16)** of the phosphorus starting material. Column **15** indicates the percentage of starting material remaining in the crude reaction mixture. Oxygen's counterion in **13-16** is the protonated base, indicated by M.



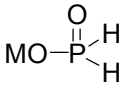
13

δ (ppm) = -1.5(dt)



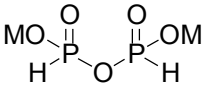
14

δ (ppm) = -3.6(d)



15

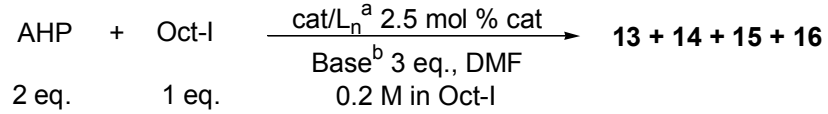
δ (ppm) = -5.6(t)



16

δ (ppm) = -12.4(dt)

Table 2.1 Cross-coupling of iodooctane with anilinium hypophosphite



Entry	Catalyst	Ligand	13[c] (%)	14[c] (%)	15[c] (%)	16[c] (%)
1	Pd_2dba_3	tBu_3P-HBF_4	31	55	97	11
2	$Cl_2Pd(PPh_3)_2$	Cy_2PhP	28	40	119	0
3	$Pd(PPh_3)_4$	-	39	53	97	0
4	Dichloro(1,10-phenanthroline) Pd (II)	tBu_3P-HBF_4	40	62	82	11
5	$PdCl_2$	Cy_3P-HBF_4	29	62	83	9
6	Palladacycle **(12)**	-	42	54	103	0
7	$Cl_2Pt(PPh_3)_2$	tBu_3P-HBF_4	29	59	92	17
8	Pd_2dba_3	dppp	37	57	98	6
9	Pd_2dba_3	dppb	41	54	77	21
10	Pd_2dba_3	dpppen	43	58	62	26
11	Pd_2dba_3	dpphex	44	49	92	9
12	$Cl_2Pt(PPh_3)_2$	dppp	39	25	41	67
13	$Cl_2Pt(PPh_3)_2$	dppb	36	30	71	34
14	$Cl_2Pt(PPh_3)_2$	dpppen	35	36	71	34
15	$Cl_2Pt(PPh_3)_2$	dpphex	36	33	64	46
16	Pd_2dba_3	dppe	36	61	94	6
17	$Cl_2Pt(PPh_3)_2$	dppe	39	34	15	88
18	Pd_2dba_3	xantphos: Cy_2PhP	16	37	111	0
19	Pd_2dba_3	xantphos: BIPHEP	42	69	74	7
20	Pd_2dba_3	xantphos: Cy_2PhP	0	0	196	0
21	$Cl_2Ni(PPh_3)_2$	xantphos	28	41	110	0

[a]Ratio of L_n:cat is 4:1 for monodentate ligands and 2:1 for bidentate ligands. [b]Base is Et_3N, except entries 18 and 19, DMAP; entry 20, 1-Adamantanamine. [c]All yields are crude ^{31}P NMR percentages, calculated from the integration of all phosphorus peaks (sum ≈ [# eq. P x 100%)]. See page 38 for structures of **13-16.**

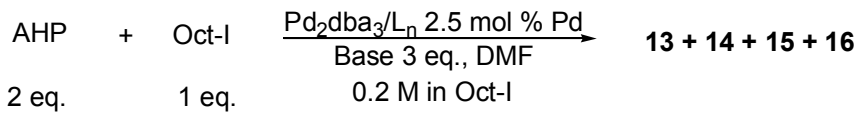
Product distribution throughout the bidentate diphenylphosphinoalkane series dppp **(8)** to dpphex **(11)** is steady (40% to 90% for **13, 14** and **15**) whether platinum or palladium is used (Table 2.1, entries 8-15). Dppe **(7)** yields different results. In the presence of palladium and **7**, formation of **13** is steady at approximately 35%, while **14** nearly doubles from 34% to 61% from platinum to palladium. The greatest difference occurs in **15** and the formation of **16**. With palladium, 94% of **15** remains unreacted, and 6% of **16** forms. With platinum, only 15% of starting material **15** remains and **16** is formed in 88% yield (entries 16, 17). Distribution of **13-16** with other ligands in Chart 2.1 was similar to that provided by ligands **8-11**.

Different palladium sources (entries 1-6) gave similar byproduct distribution. Results with platinum (entry 7) were similar.

A 1:1 mixture of ligands, xantphos:PCy_2Ph and xantphos:BIPHEP, was used in attempt to reduce both transfer hydrogenation and β-hydride elimination (entries 18-20).[64] Results were similar to using a single ligand.

Variation of base yielded interesting results (Table 2.2). The primary *t*-$BuNH_2$ yielded 24% of oxidation product **14**, with the starting material composing the remaining portion (entry 6). Pyridine quantitatively yielded **14** (entry 10). 1-Adamantanamine formed the insoluble adamantanaminium hypophosphite, which remained unreactive throughout the reaction (entry 12).

Table 2.2 Effect of base on cross-coupling product distribution



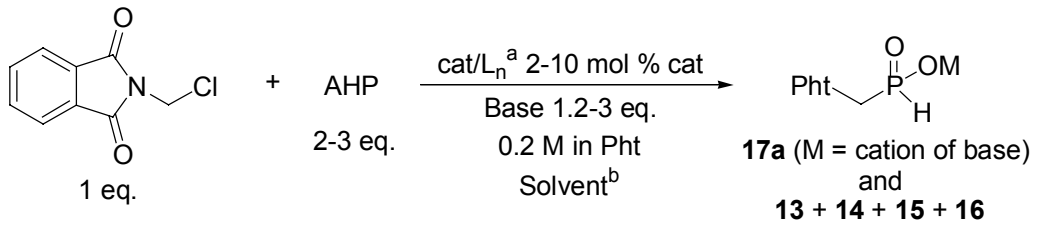
Entry	Base	Ligand[a]	13[c] (%)	14[c] (%)	15[c] (%)	16[c] (%)
1	N-Methylmorpholine	xantphos	25	91	65	7
2	N-Methylpiperidine	xantphos	20	78	77	7
3	DMAP	xantphos	31	26	139	0
4	DIEA	xantphos	45	52	91	0
5	DBU	xantphos	43	41	75	35
6	*t*-$BuNH_2$	xantphos	0	24	180	0
7	Imidazole	xantphos	25	69	38	63
8	1,1,3,3-Tetramethylguanidine	xantphos	35	25	133	0
9	N,N-Diethylamine	xantphos	26	131	27	6
10	Pyridine	xantphos	0	quant	0	0
11	Aniline	xantphos	15	137	33	10
12	1-Adamantanamine	xantphos	23	154	0	0
13	DIEA	PCy_2Ph	31	45	121	0
14	DBU	PCy_2Ph	30	31	109	10
15	N-Methylpiperidine	PCy_2Ph	25	81	73	9
16	N-Methylmorpholine	PCy_2Ph	32	77	10	64
17	Cs_2CO_3[b]	PCy_2Ph	quant	0	0	0
18	DMAP	PCy_2Ph	29	31	97	17
19	*t*-$BuNH_2$	PCy_2Ph	16	12	156	0

[a]Ratio of L_n:cat is 4:1 for monodentate ligands and 2:1 for bidentate ligands. [b]Cs_2CO_3 is 2 eq. [c]All yields are crude ^{31}P NMR percentages, calculated from the integration of all phosphorus peaks [sum ≈ (# eq. P x 100%)]. See page 38 for structures of **13-16.**

2.2 Cross-coupling of halomethylphthalimide with anilinium hypophosphite

After many failed attempts at coupling AHP and iodooctane, halomethylphthalimide became the model substrate because it has no β-hydrogens (Table 2.3). Coupling occurred under various conditions in yields around 30%, but the NMR yield never exceeded about 40%. Inexpensive CuBr with ligand L-proline provided 20% NMR yield (entry 1).[65] Hypophosphorous salts are known to be insoluble in toluene, thereby providing falsely high NMR yields (entry 3); after acidic workup, ^{31}P NMR detected no product. PEG (M_n = 4600) was used as a solvent (entry 5) and co-solvent (entry 4), but reaction mixtures were black, viscous and difficult to handle.[66] Furthermore, more practical conditions provided comparable or better yields (entries 6-15), so PEG was abandoned. $Pd_2dba_3/Cy_3P\text{-}HBF_4$ was identified as the best catalyst system (entry 12), requiring no base or additives. A mixture of solvents, either THF:NMP or THF:DMF, worked quite well, consistently providing results between 25% and 38% NMR yield (Table 2.3, entries 6-15) and (Table 2.4, entries 1, 4-6).[67,68] DMF and NMP worked well individually, too (entries 2, 3). NMP severely interfered with the ^1H NMR, making the identification of product peaks very difficult. Interestingly, reducing the palladium load to 0.1 mol % inverted the yield of byproducts **14** and **16** (Table 2.4, entry 5 vs. entry 6). However, product yield remained steady.

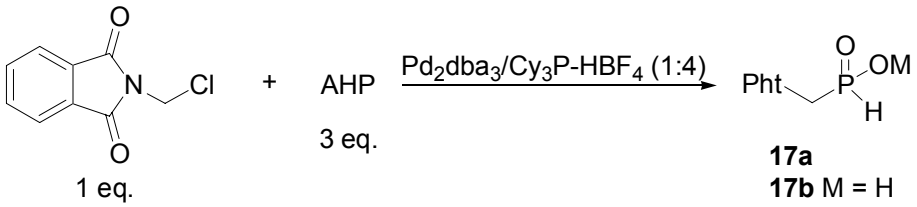
Table 2.3 Cross-coupling of chloromethylphthalimide with anilinium hypophosphite



Entry	Catalyst	Ligand	Base	13[c] (%)	14[c] (%)	15[c] (%)	16[c] (%)	17a[c] (%)
1	CuBr	L-Proline	Pyridine	38	70	70	0	19
2	$Cl_2Ni(PPh_3)_2$	Xantphos	Et_3N	0	66	44	82	4
3	$Pd(PPh_3)_4$	-	Et_3N	46	17	0	0	89
4	Pd_2dba_3	-	Et_3N	27	43	82	8	27
5	Pd_2dba_3	Ph_3As	Et_3N	21	50	91	0	16
6	Pd_2dba_3	Cy_2PhP-HBF_4	N-BuIm	0	131	35	7	23
7	Pd_2dba_3	Ph_3As	N-BuIm	0	148	24	0	27
8	Pd_2dba_3	*t*-Bu_3P-HBF_4	N-BuIm	0	85	82	3	25
9	Pd_2dba_3	*t*-Bu_2MeP-HBF_4	N-BuIm	0	148	8	15	22
10	Pd_2dba_3	Cy_3P-HBF_4	N-BuIm	0	134	10	16	32
11	Pd_2dba_3	Cy_3P-HBF_4	N-BuIm	0	194	68	0	38
12	Pd_2dba_3	Cy_3P-HBF_4	-	0	105	43	0	34
13	$Pd(OAc)_2$	Cy_3P-HBF_4	-	0	173	85	0	30
14	$PdCl_2$	Cy_3P-HBF_4	-	0	217	46	0	30
15	$Pd(PCy_3)_2$	-	-	0	193	62	0	35
16	$Cl_2Pd(PPh_3)_2$	-	TBAF	0	204	0	0	0

[a]Ratio of L_n:cat is 4:1 for monodentate ligands and 2:1 for bidentate ligands. [b]Solvents are: Entries 1-2 DMF, entry 3 toluene, entry 4 THF:PEG [1eq. PEG (M_n = 4600) with respect to Pht], entry 5 PEG (M_n = 4600), entries 6-12 THF:NMP (2:1) v/v, entries 13-15 THF:DMF (2:1) v/v, entry 16 THF. [c]All yields are crude ^{31}P NMR percentages, calculated from the integration of all phosphorus peaks.

Table 2.4 Variation of solvent and catalyst loading for cross-coupling



Entry	mol % Pd	Solvent[a]	13[b] (%)	14[b] (%)	15[b] (%)	16[b] (%)	17a[b] (%)
1	2	THF:NMP (2:1)	0	105	43	0	34
2	2	NMP	0	163	99	0	35
3	2	THF	0	86	168	8	28
4	2	THF:DMF (2:1)	0	203	64	0	36
5	5	THF:DMF (2:1)	0	222	20	7	27
6	0.1	THF:DMF (2:1)	0	79	194	0	24
7[c]	2.5	THF:PEG[d]	27	43	82	8	27

[a]Solvent ratio is (2:1) v/v. [b]All yields are crude ^{31}P NMR percentages, calculated from the integration of all phosphorus peaks. [c]Base is 3 eq. Et_3N. [d]PEG (M_n = 4600) is 1 eq. with respect to Pht.

The product, (phthalimidomethyl)phosphonous acid **17b**, was never cleanly isolated through acidic workup. Rather, mass spectroscopy combined with characteristic NMR peaks confirmed presence of the H-phosphinic acid. An authentic sample was prepared using a published procedure.[69]

2.3 Experimental

General chemistry: Anilinium hypophosphite was prepared as previously described.[38] Anhydrous solvents were used unless otherwise noted and were prepared as follows: Et_3N and DIEA were distilled from CaH_2 and stored under N_2 over activated 4Å molecular sieves; tetrahydrofuran (THF) was distilled under N_2 from sodium benzophenone ketyl, and used immediately; CH_2Cl_2 and CH_3CN were distilled from CaH_2 and used immediately. Anhydrous DMF and NMP were stored over activated 3Å molecular sieves, under N_2. Unless otherwise noted, all chemicals were used as received from the manufacturer without further purification. ^1H NMR spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts for ^1H NMR spectra are reported (in parts per million) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ ($\delta = 77.0$ ppm). ^{31}P NMR spectra were recorded at 121 MHz on a Varian Mercury-300 spectrometer, and chemical shifts are reported (in parts per million) relative to external 85% phosphoric acid ($\delta = 1.0$ ppm). Silica gel (200-300 mesh, Natland International Corporation) was used for flash chromatography. Ethyl acetate/hexanes mixtures were used as the eluent for chromatographic purifications. Radial chromatography was carried out with a Harrison Associates chromatotron using 1, 2, or 4 mm layers of silica gel 60 PF_{254} containing gypsum (E. Merck). TLC plates were visualized by immersion in anisaldehyde stain (by volume: 93% ethanol, 3.5% sulfuric acid, 1% acetic acid and 2.5% anisaldehyde) followed by heating. The Mass Spectrometry Facility of the University of South Carolina provided mass spectrometry.

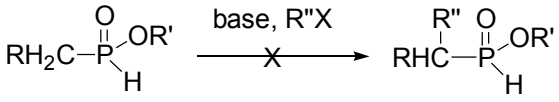
(Table 2.3, entry 13), Representative procedure: Anilinium hypophosphite (0.943 g, 6.1 mmol) and chloromethylphthalimide (0.405 g, 2.07 mmol) were weighed into an oven-dried flask. A 2:1 v/v mixture of THF:DMF (12 mL) was added via syringe. Palladium (II) acetate (0.009 g, 0.038 mmol) and PCy_3-HBF_4 (0.017 g, 0.046 mmol) were added, and the reaction was heated to 80 ºC for 18h. The crude reaction mixture was concentrated in vacuo, made basic with saturated aqueous $NaHCO_3$, and washed with ether (2x). The aqueous phase was acidified with $NaHSO_4$ and extracted with EtOAc (2x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford the title compound (see page 44; **17b** never cleanly isolated).

(Phthalimidomethyl)phosphonous acid (17):[69] A mixture of ammonium hypophosphite (0.414 g, 4.99 mmol) and HMDS (0.815 g, 5.03 mmol) was stirred and heated to 120 ºC for 2h under dry N_2. After being cooled to room temperature, CH_2Cl_2 (4 mL) was added, and the reaction was chilled in an ice bath. A solution of bromomethylphthalimide (0.307 g, 1.28 mmol) in dry CH_2Cl_2 (2 mL) was added. The mixture was stirred at 0 ºC for 1h and then at room temperature for 12h. The mixture was filtered through a layer of Celite into a mixture of MeOH (10 mL) and CH_2Cl_2 (30 mL), and the filtrate was washed with 6 N aqueous HCl (6 mL). The aqueous layer was separated and back-extracted with CH_2Cl_2 (2 x 12 mL). The combined organic solution was then dried over $MgSO_4$, filtered and concentrated in vacuo to afford the pure compound.

^{1}H NMR (D_2O, 300 MHz): δ = 7.70 – 7.84 (m, 4 H), 7.17 (d, J_{PH} = 580 Hz, H), 3.83 (d, J = 11 Hz, 2 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 20.7 (d, J_{PH} = 573 Hz). ^{13}C NMR (D_2O, 75.5 MHz) δ = 166.8, 134.4, 134.3, 131.2, 123.0, 38.2 (d, J_{PC} = 97 Hz).

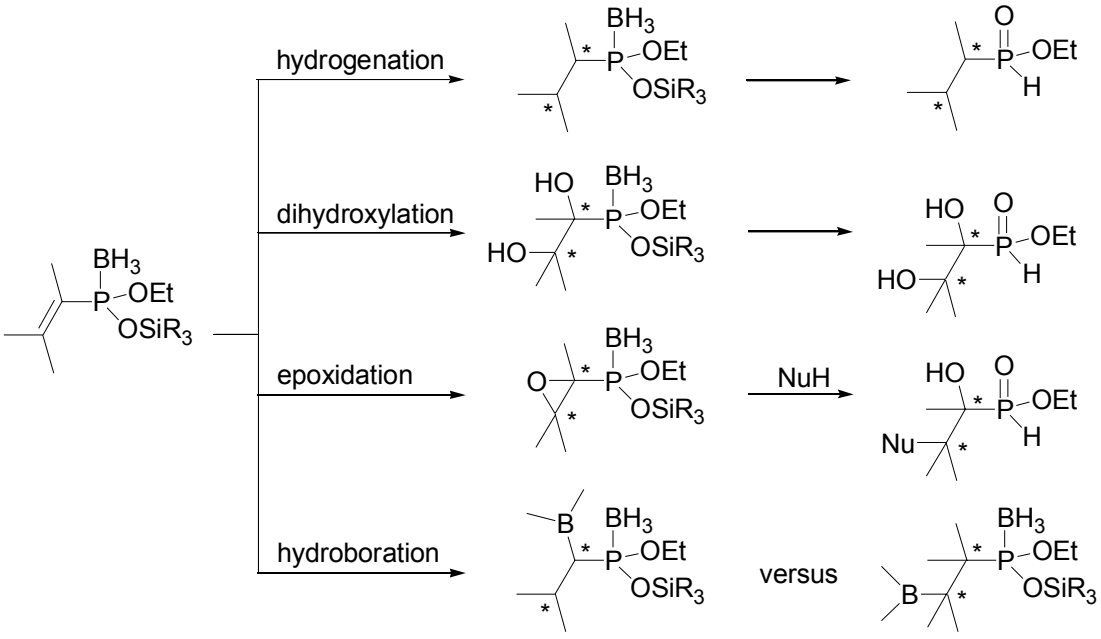
<u>Chapter Three:</u> Phosphine-borane complexes mask the phosphinylidene (P(O)H) functionality

The Montchamp group has developed new synthetic methods for the synthesis of H-phosphinates (RPO_2H_2 and RP(O)(OR')H) (Chapter 1), but obstacles still exist. The easily oxidized P-H bond prevents the synthesis of highly functionalized H-phosphinates, for example (Equation 3.1), and the use of asymmetric reactions (Scheme 3.1). Additionally, hydrogenolysis, epoxidation, cyclopropanation, cross-metathesis and others are unsuccessful on substrates with the unprotected P(O)H moiety.



(Equation 3.1)

Scheme 3.1 Proposed asymmetric reactions of protected H-phosphinates

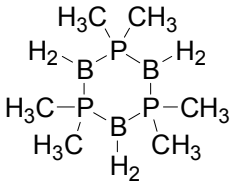


The scope of this project is quite broad: Any reaction of H-phosphinates that was problematic could, in theory, work with a protected P(O)H.

3.1 Phosphine-boranes in the literature

BH_3 is used as a protecting group for the phosphorus center, as are oxygen in the form of phosphine oxides ($P(O)R_3$) and sulfur in the form of phosphine sulfides ($P(S)R_3$). They also find broad application as nucleophiles under various organic reaction conditions.[70] These complexes are quite easy to prepare and are air-stable; they can be purified by column chromatography and have long shelf lives. Use of the borane protecting group allows chemical manipulation of the phosphorus compound while maintaining phosphorus in the "III" oxidation state.

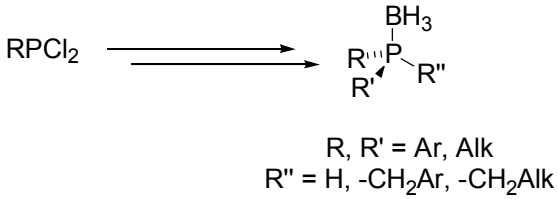
Burg and Wagner first reported phosphine-boron complexes in 1953.[71] Dimethylphosphine was reacted with diborane to form an adduct with the molecular formula $(CH_3)_2PH{\cdot}BH_3$. The trimer, along with some tetramer and a trace of higher polymer, of this monomer were formed upon heating. At the time of publication, the structure of the polymers had not been determined by physical methods, but the formation of a dimethylphosphinic acid, $(CH_3)_2P(O)OH$, from hydrolysis confirmed the presence of $(CH_3)_2PH$ and BH_3 moieties. The polymers were very unreactive toward air, acids, bases and water, hydrolyzing very slowly in the presence of HCl at 300 $^{\circ}$C. The proposed trimer structure is that of a hexatomic ring **18**, which is significantly stronger than the easily dissociable dimer of $(CH_3)_2N{\cdot}BH_2$.



18

The unexpected strength of the trimer can be explained by the presence of bulky methyl groups on the phosphorus atom. A more probable contributor is weak B-P π-bonding in which the B-H bonding electrons enter hybrid orbitals involving the 3d and perhaps the 4s orbitals of phosphorus, which are not available on the nitrogen atom. Electron density on the hydrogen would be lower, and density on phosphorus would be higher, thereby increasing the strength of the P-B σ-bond.

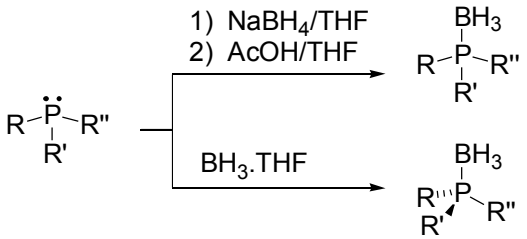
Recent methods available for formation of phosphine-boranes vary slightly but generally require the aryl- or alkyldichlorophosphine as the precursor for the borane complex (Equation 3.2).[72-74] Availability of these phosphines is sometimes limited.



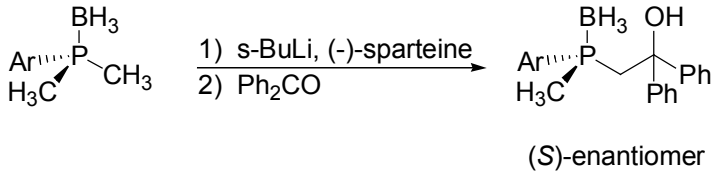
(Equation 3.2)

Alternatively, the free phosphine can be complexed directly (Scheme 3.2).[75,76]

Scheme 3.2 Formation of the phosphine-borane complex directly from the free phosphine[75,76]



Chiral complexes have been awarded much of the interest over the past several years, due to their potential as intermediates in the formation of ligands used in asymmetric homogeneous catalysis.[77] In 1995, Muci and coworkers published a protocol for enantioselective deprotonation using a lithium base in conjunction with (-)-sparteine (Equation 3.3).[75] The resulting anion was trapped with benzophenone. While the enantiomeric excesses were fair (79% to 87%), the methodology has since been used with greater success.

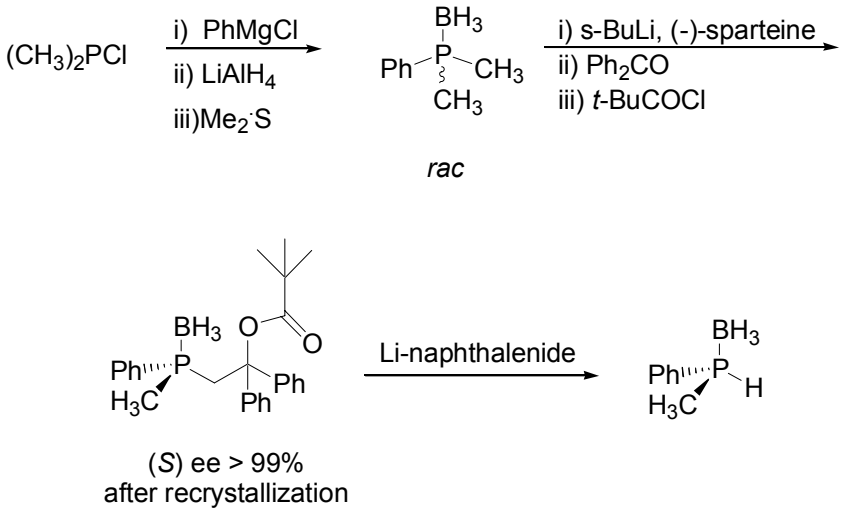


Ar (yield%, ee%) = phenyl (88%, 79%), o-anisyl (81%, 83%)
o-tolyl (84%, 87%), 1-naphthyl (86%, 82%).

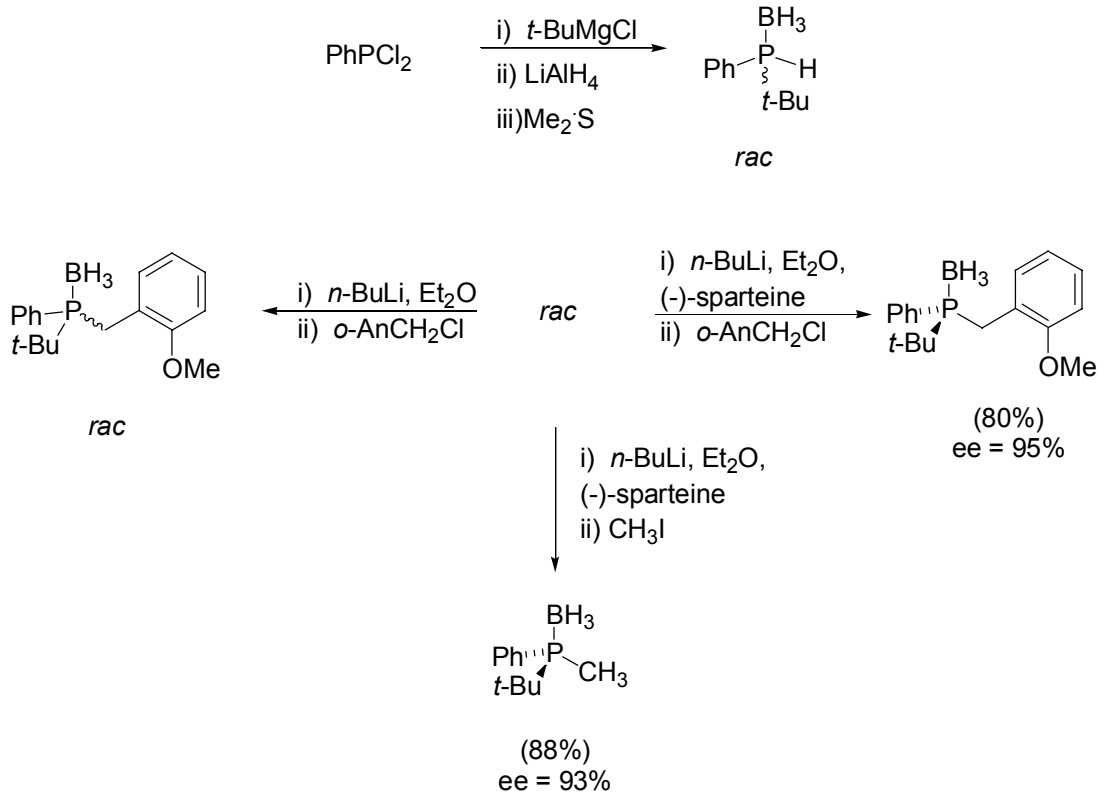
(Equation 3.3)

Secondary (Scheme 3.3) or tertiary (Scheme 3.4) *P*-chiral phosphine-boranes have been formed with the lithium base/(-)-sparteine approach.[73,78]

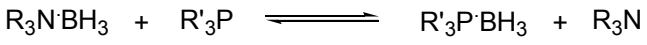
Scheme 3.3 Formation of secondary P-Chiral phosphine-borane via enantioselective deprotonation[73]



Scheme 3.4 Direct synthesis of P-Chiral phosphine-boranes via dynamic resolution with (-)-sparteine[78]



It is important to highlight Zhou and McNulty's method for the formation of tertiary phosphine-borane complexes directly from the free phosphine (Scheme 3.2 upper).[72] Others have used $NaBH_4$ as a BH_3 source, but these methods require the use of a hydride acceptor such as acetone or acetic acid in the presence of an amine base, which results in an amine-borane complex in situ. The amine-borane complex and the phosphine establish an equilibrium in which the phosphine displaces the amine, which is then removed by distillation to displace the equilibrium and drive the reaction to completion. (Equation 3.4).[70]

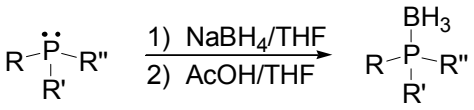


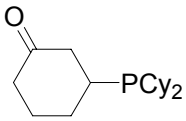
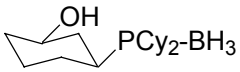
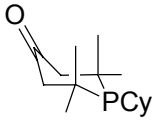
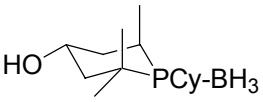
(Equation 3.4)

The phosphine-boranes are not formed directly via $NaBH_4$. Prior to the publication of Zhou's and McNulty's method in 2004, only one direct synthesis of phosphine-boranes from the borohydride was reported: A process by Imamoto that required a stoichiometric amount of cerium trichloride was published in 1985.[79] Zhou and McNulty use $NaBH_4$ with acetic acid in a tetrahydrofuran solution as a proton source.[76]

In industry, which typically requires large-scale, cost-effective synthesis, the inexpensive $NaBH_4$ is much more practical on a cost-per-mole comparison with the $BH_3 \cdot THF$ or $BH_3 \cdot Me_2S$ complexes that are commonly used as alternate borane sources. In addition, there is no need to remove the residual dimethylsulfide. Aside from the environmental effects, sulfur poisons catalysts, thereby diminishing the phosphine-borane's usefulness in further reactions where a transition metal catalyst might be employed. Whereas complexes formed with the $BH_3 \cdot THF$ or $BH_3 \cdot Me_2S$ need to be purified by column chromatography or preparative HPLC, those formed using $NaBH_4$ need no further purification and can be used directly in alkylation or addition processes. Furthermore, the use of $NaBH_4$ allows for reduction of carbonyls in a one-pot process (Table 3.1, entries 5 and 6), allowing potential for polymer-linkage, while simultaneously forming the phosphine-borane complex.[76] The following table lists six of the authors' twelve entries. A variety of secondary and tertiary phosphines is complexed successfully, with isolated yields ranging from 80% to 100%.

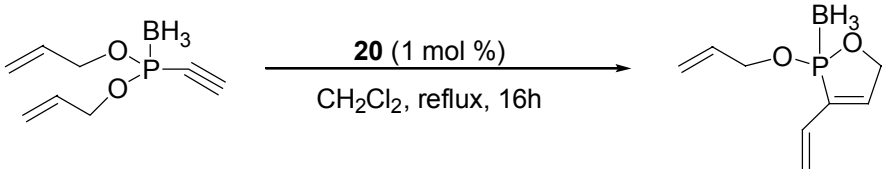
Table 3.1 Formation of phosphine-borane complexes from $NaBH_4$[76]



Entry	Phosphine	Phosphine-borane	Isolated Yield (%)
1	Bu_2PH	Bu_2PH-BH_3	99
2	Cy_3P	Cy_3P-BH_3	95
3	Ph_2PH	Ph_2PH-BH_3	95
4	*i*-BuPhPH	*i*-BuPhPH-BH_3	100
5			84
6			80

Phosphine-borane complexes are useful in organic synthesis and have applications in a variety of areas, including the formation of biologically relevant compounds, anti-HIV analogues and chiral ligands for asymmetric catalysis. Their use as nucleophiles in various reactions is quite broad.

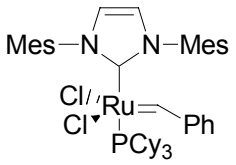
Timmer and coworkers found that compound **19** (Equation 3.5) underwent enyne metathesis in the presence of Grubb's second-generation catalyst **20** to form a heterocyclicphosphine-borane in high yields under mild conditions.[80]



19

99%

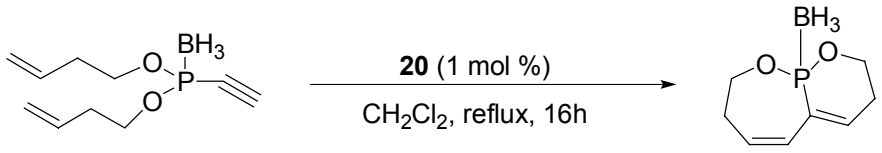
(Equation 3.5)



Ru gen-2

20

Bicyclic compound **21** was also formed via tandem ring-closing metathesis onto a phosphonoalkyne (Equation 3.6).[80] These compounds may have potential as biologically active phosphorus heterocycles or as ligands for asymmetric catalysis.



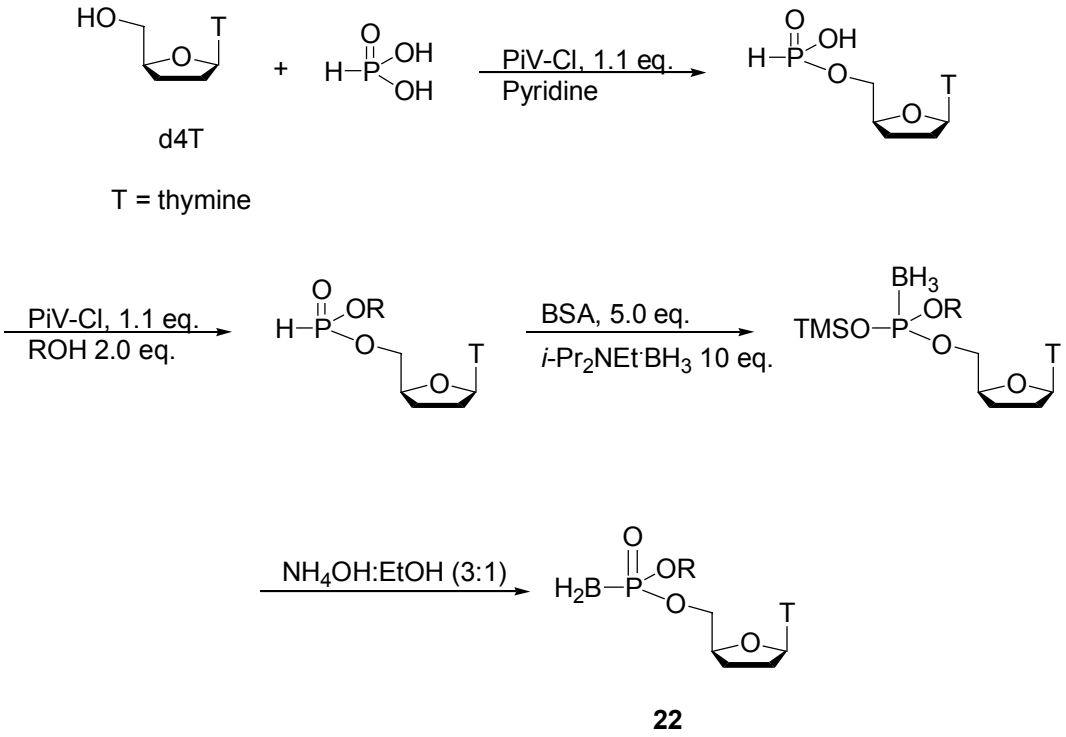
74%

21

(Equation 3.6)

Lin used boranophosphates, the oxidized P(V) form phosphine-boranes, as AZT/d4T pro-drugs **(22)** (Scheme 3.5).[81] Boranophosphates' application in DNA sequencing, therapeutic applications and boron neutron capture therapy has been studied.[82-85]

Scheme 3.5 Boranophosphates as anti-HIV pro-drugs[81]

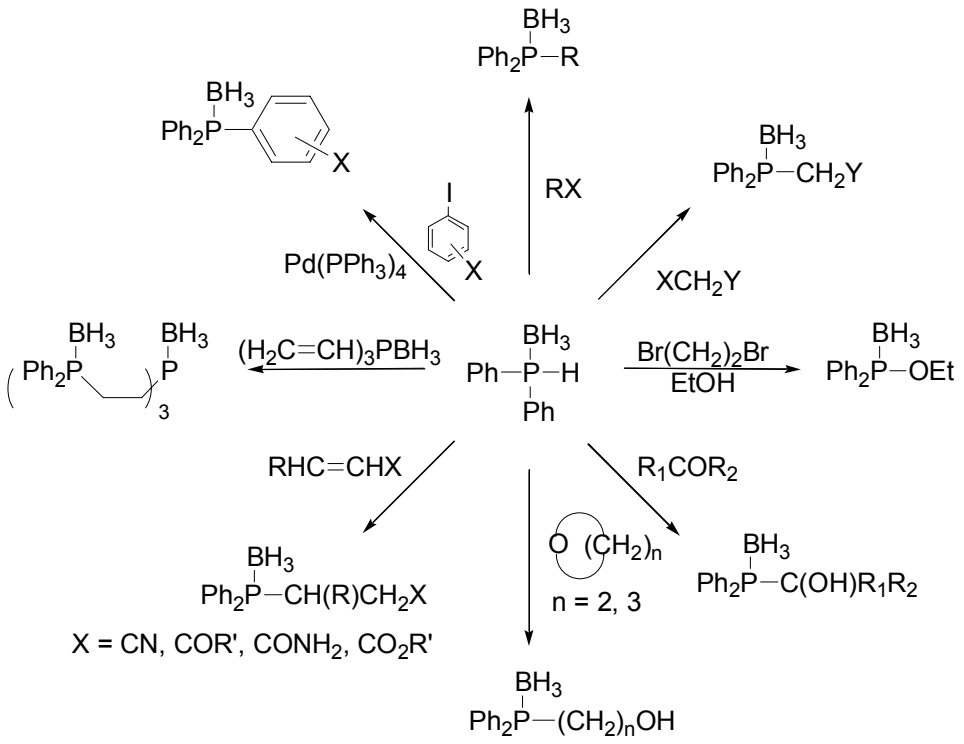


Subsequent esterifications were performed on phosphonic acid using pivaloyl chloride (trimethyl acetylchloride) in pyridine. Silylation and borane complexation was then accomplished with BSA and BH_3·DIEA complex. From this point, the TMS group was oxidatively cleaved with concentrated ammonia and ethanol to form the boranophosphate

in moderate yields (60%). While the phosphine-borane intermediate was neither tested directly nor isolated, this methodology proved useful in the formation of the final pro-drug product.

Not only does the BH_3 protect the phosphorus center, it activates the phosphine toward deprotonation. Phosphine-boranes form excellent nucleophiles and are valuable substrates in various organic reactions (Scheme 3.6).[70]

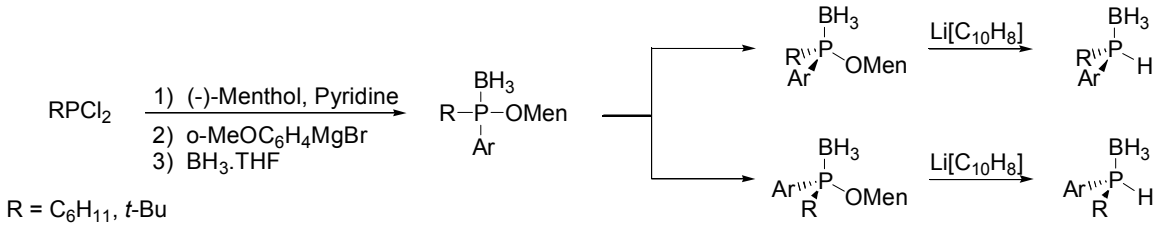
Scheme 3.6 Diphenylphosphine-borane as a nucleophile[70]



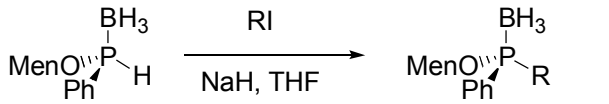
Imamoto has contributed several items to the field of phosphine-boranes, some of which are listed in Scheme 3.6. Specifically, he formed P-chiral boranophosphinates from dichlorophenylphosphine, whose diastereoisomers were separated through

successive recrystallizations. The P-OR bond was then cleaved with lithium naphthalenide to form P-chiral boranophosphines (Scheme 3.7).[70]

Scheme 3.7 Formation of chiral boranophosphinates and borano-H-phosphines from $RPCl_2$[70]



Enantiomerically pure P-chiral borano-H-phosphinates successfully underwent alkylation with NaH as the base. The use of a chiral base such as (-)-sparteine was not required, as the enantiomers had already been separated, and stereochemistry was retained through the alkylation, with 100% de (Equation 3.7).[70]

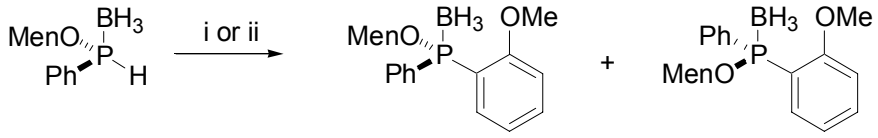


R = Me, $MeO(CH_2)_2$
de = 100%

(Equation 3.7)

Phosphine-boranes proved useful to bypass the difficulties encountered when using some phosphines for palladium-mediated cross-coupling.[86] $(S)_P$- and $(R)_P$-menthyloxyphenylphosphine-boranes were successfully cross-coupled with *o*-

iodoanisole, and the configuration was able to be controlled by adjusting reaction conditions. Acetonitrile provided solely **24**, and THF yielded **25** in 92% ee (4:96/S:R) (Equation 3.8).



$(P)_S$-**23** $(P)_S$-**24** $(P)_R$-**25**

i) 2 eq. *o*-iodoanisole, 5 mol % $Pd(PPh_3)_4$, 2 eq. K_2CO_3, CH_3CN, 50 ºC, 16h, 96%, (P)S-23:(P)R-24 = 100:0; ii) same as in i) but in THF, 50 ºC, 48h, 76%, (P)S-23:(P)R-24 = 4:96.

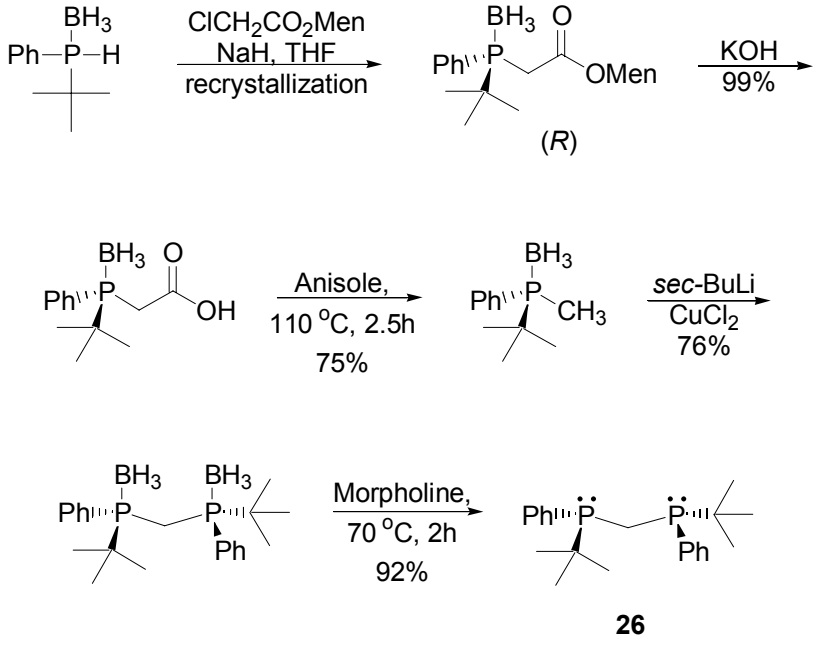
(Equation 3.8)

While the observed retention of configuration was expected, it was quite uncommon to see the inverted product. Proposedly, the effect of the solvent's polarity is expressed during the transmetallation step and is responsible for the stereochemical outcome. Proton abstraction by K_2CO_3 in polar CH_3CN occurs readily, leaving the naked phosphine anion to transmetallate with stereochemical retention. In nonpolar THF the attack on palladium and proton abstraction occur simultaneously, leading to an inversion of stereochemistry.[86]

Phosphine-borane chemistry has also proven useful in the synthesis of chiral ligands. (*R,R*)-1,2-Bis(*tert*-butylphenylphosphino)ethane **(26)**, a homologue of (*R,R*)-1,2-bis[(*o*-anisyl)phenylphosphino]ethane [(*R,R*)-DIPAMP] was synthesized (Scheme 3.8).[87] (*R,R*)-DIPAMP gained attention in the 1970s and 1980s as a ligand for catalytic

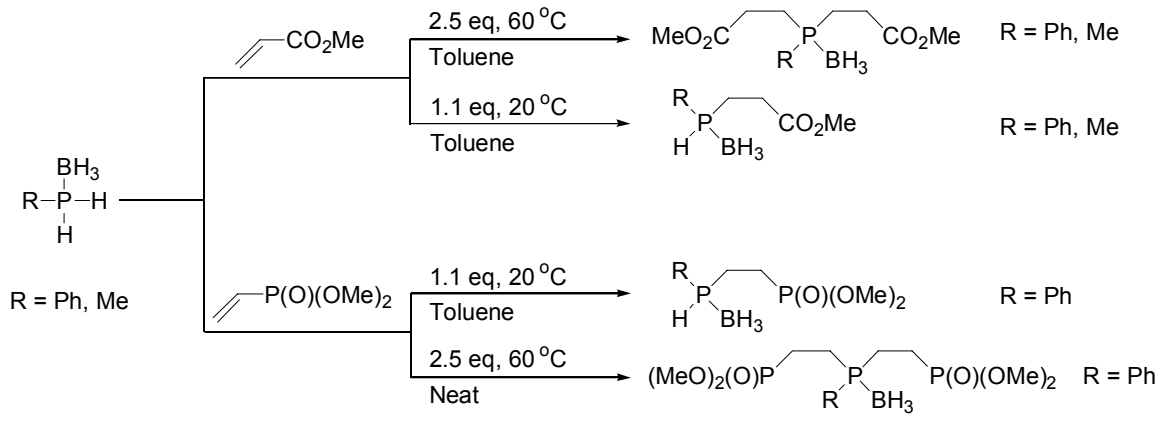
hydrogenation, with 95% ee. It was developed by Monsanto and used in the synthesis of Alzheimer drug precursor L-DOPA.

Scheme 3.8 Formation of (*R,R*)-1,2-Bis(*tert*-butylphenylphosphino)ethane[87]

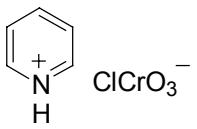


Primary phosphine-boranes undergo uncatalyzed hydrophosphination of acrylic esters, which allows access to mono-adducts and to symmetrical and unsymmetrical bis-adducts (Scheme 3.9).[88]

Scheme 3.9 Uncatalyzed hydrophosphination of vinylic esters[88]

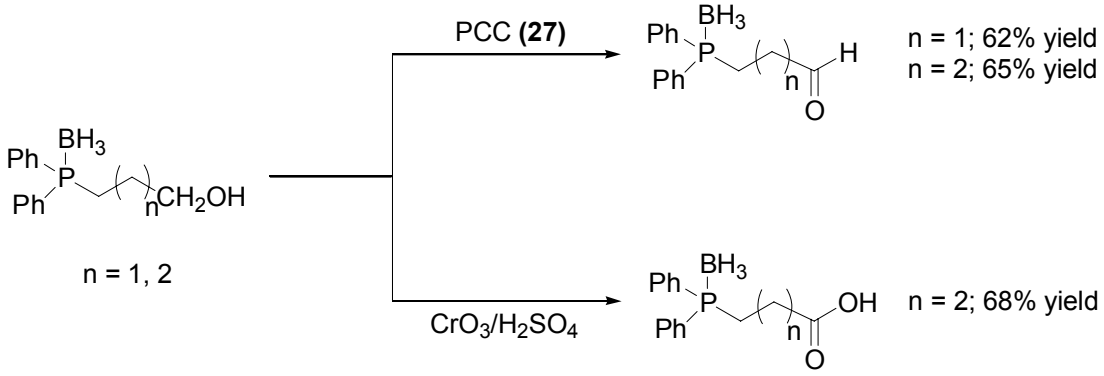


As mentioned above, BH_3 protects the phosphorus-center from unwanted oxidation. Its presence allows exposure to the oxidative conditions necessary for the formation of carbonyl- or carboxyphosphine-boranes. Primary or secondary hydroxy functionalities in the complex are oxidized to the ketone, or aldehyde and carboxylic acid with Jones' or Corey's **(27)** reagents, respectively (Scheme 3.10).[89,70]



27

Scheme 3.10 Oxidation of alcohols to corresponding aldehydes or carboxylic acids[89,70]



Decomplexation of the borane moiety is typically accomplished with a secondary amine such as diethylamine or morpholine, or with a strong acid. Recall that there is an equilibrium established between the free phosphine and borane-amine complex and the phosphine-borane and the free amine (Equation 3.4). This non-oxidative deprotection is useful for the formation of phosphines; those that will likely be used as ligands. When oxidative decomplexation is desired, mCPBA, for instance, may be used.

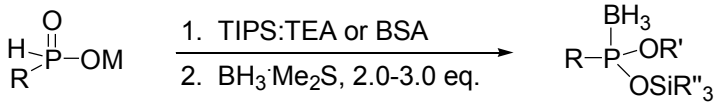
While the above methodologies are quite useful for certain applications, it is desirable to form phosphinoboranes directly from an inexpensive, readily available, stable hypophosphorous derivative. This would alleviate the need to handle air-sensitive, structurally limited and potentially expensive phosphines.

3.2 Formation and stability of phosphine-borane complexes

Phosphine-borane complex formation is straightforward and accomplished on a variety of hypophosphorous derivatives (Table 3.2). AHP, hypophosphorous acid,

phenyl butyl-H-phosphinate and alkyl phosphinates all undergo one-pot silylation-complexation in good to excellent crude yields (65-100%).

Table 3.2 Silylation-complexation of various hypophosphorous derivatives



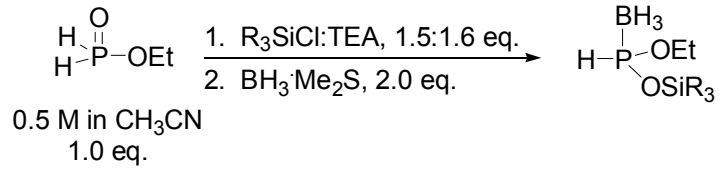
M = NH_3Ph, H, Et, Bu
R = H, Ph, CH=CH(Hex)

R' = TIPS, TMS, Et, Bu
SiR''_3 = TIPS, TMS

Entry	M =	R =	Solvent, (conc, M)	Silylating agent (eq)[a]	^{31}P NMR (isolated) %
1	NH_3Ph	H	CH_2Cl_2, (0.2)	TIPSCl (2.0)	96 (68)
2	H	H	CH_3CN, (0.5)	BSA (3.0)	67 (--)
3	Et	H	CH_3CN, (0.5)	TIPSCl (1.5)	91 (87)
4	Bu	H	CH_3CN, (0.5)	BSA (1.5)	65 (--)
5	Bu	Ph	CH_2Cl_2, (0.2)	BSA (1.5)	96 (--)
6	Et	CH=CH(Hex)	CH_2Cl_2, (0.2)	TIPSCl (1.5)	72[b] (34)
7	Et	BOCHN-allyl	CH_2Cl_2, (0.2)	TIPSCl (1.5)	100 (37)

[a]All BSA reactions were conducted at room temperature. TIPSCl:TEA were pre-mixed at 0 °C before addition to a 0 °C phosphorus solution and allowed to warm to room temperature. [b]Trans:Cis (5.7:1).

Before examining the reactivity of the phosphine-borane complex, it was important to choose the proper silylating agent: one that offered stability, high yields and clean silylation. A readily available stock solution of ethyl hypophosphite (0.5 M in CH_3CN) was chosen to probe the effect of silylating agents. The order of relative stability of -$OSiR_3$ for acid hydrolysis is: trimethylsilyl (TMS), 1 < triethylsilyl (TES), 64 < *tert*-butylsilyl (TBS), 20,000 < triisopropylsilyl (TIPS), 700,000 < *tert*-butyldiphenylchlorosilane(TBDPS), 5,000,000. In basic media, the relative stability is: TMS 1 < TES 10-100 < TBS~TBDPS 20,000 < TIPS 100,000. As noted, TIPS is more stable than TBDPS under basic conditions and relatively quite stable in acidic media, which makes TIPS the more generally resistant. We examined trimethyl-, triethyl-, *tert*-butyldiphenylmethyl-, diphenylmethyl-, *tert*-butyldimethyl- and triisopropylchlorosilanes and confirmed that TIPSCl would be the best silylating agent, for both its stability and its reactivity with the hypophosphite (Equation 3.9).



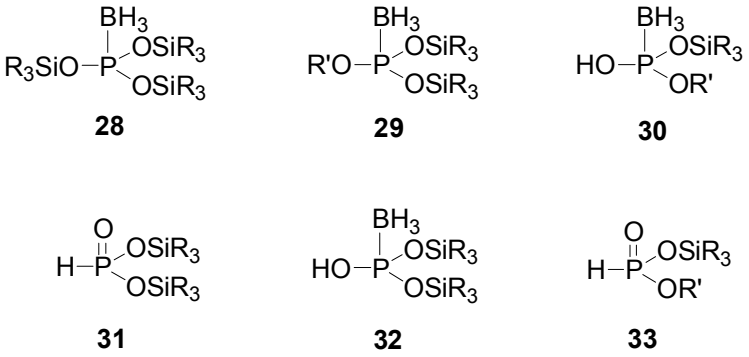
R_3Si (^{31}P NMR yield): TBDMS (59%); TES (38%); TBDPS (36%); DPMS (55%); TIPS (91%); TMS (96%). Trimethylsilyl via BSA on butyl phenyl-H-phosphinate, 0.2 M in CH_2Cl_2.

(Equation 3.9)

Various oxidation products **28-33** formed in the cases of TBDMS, TES, TBDPS and DPMS (Chart 3.1). While the trimethylsilylated butyl phenyl-H-phosphinate (Table

3.2, entry 5) formed in good yield, its hydrolyzed product was of little synthetic value, so it was abandoned. The use of an alkyl hypophosphite would provide the most synthetically useful product because of the P-H bond available for further manipulation.

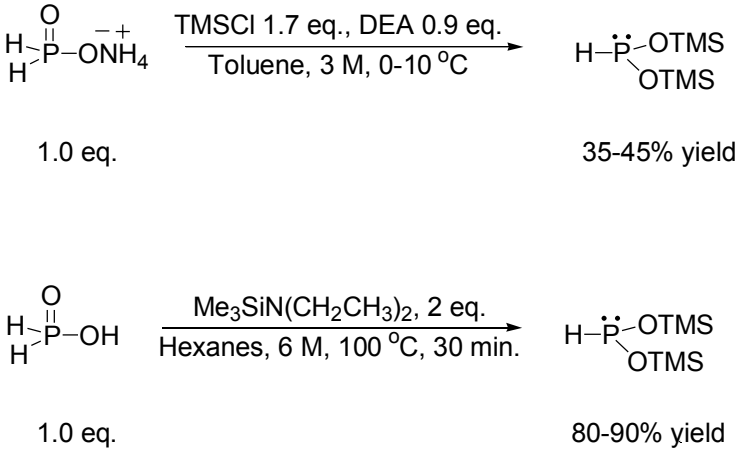
Chart 3.1 Oxidation products from screening of -SiR_3Cl



As mentioned above, TIPS offers great stability to both acidic and basic conditions, but the purification of its P-B complexes can be difficult, due to the very bulky, non-polar silyl group. The use of 100% hexanes for column chromatography only improved the purity of the crude reaction mixture by a little. A petroleum ether/hexanes mixture was tried, but the column was simply too long and too much solvent was used, defeating the practicality of the purification. Luckily, crude reaction mixtures did not contain many phosphorus nuclei, and purification with 100% hexanes usually yielded 90% or better purity in phosphorus.

Bis(trimethylsilyl) hypophosphite [$(Me_3SiO)_2PH$] is pyrophoric, as reported in the literature (Scheme 3.11).[90] Interestingly, in this work no pyrophoric activity occurred during the open-air manipulation of the phosphine intermediates.

Scheme 3.11 Literature formation of the pyrophoric bis-trimethylsilylated phosphine[90]

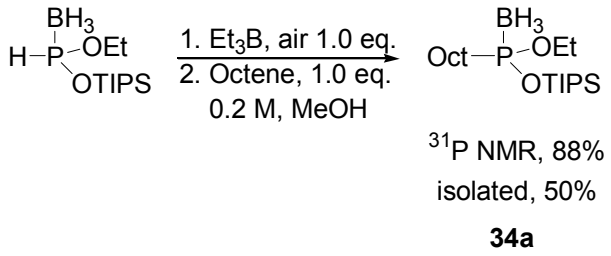


In conclusion, the phosphine-borane derived from ethyl hypophosphite and TIPSCl (Table 3.2, entry 3) yielded the best overall results and is used in the reactivity investigations.

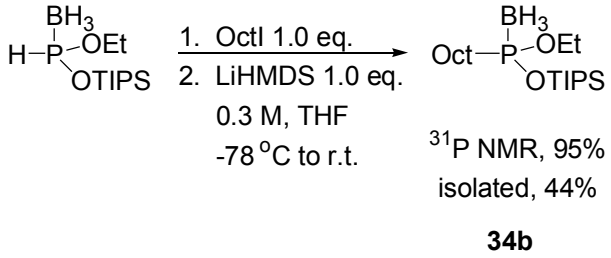
3.3 Reactivity

This project has been under investigation for only a short period. Thus far, investigations have been limited to mainly the methodology listed in Chapter 1. Triethylborane/oxygen-initiated radical addition (Equation 3.10) and P-C bond formation with LiHMDS work well (Equation 3.11), while palladium-catalyzed cross-coupling (Equation 3.12) and hydrophosphinylation (Equation 3.13) yielded no product. These two reactions, however, do provide insight into the thermal stability of the phosphine-borane starting material. Neither AIBN radical addition nor $NiCl_2$-catalyzed hydrophosphinylation were attempted. Reduction of the vinyl-phosphine-borane

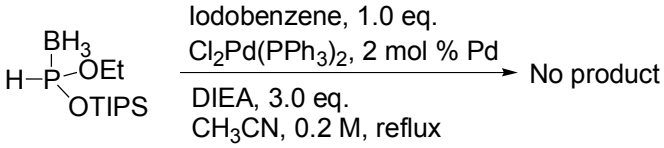
complex by hydrogenation was unsuccessful (Equation 3.14). The complex added to a carbonyl with interesting results (Scheme 3.12).



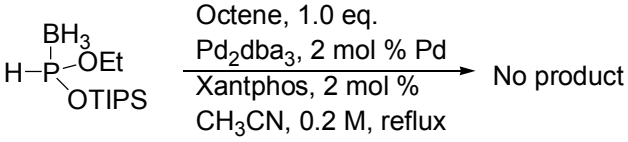
(Equation 3.10)



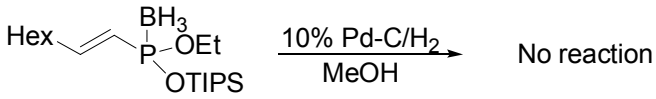
(Equation 3.11)



(Equation 3.12)



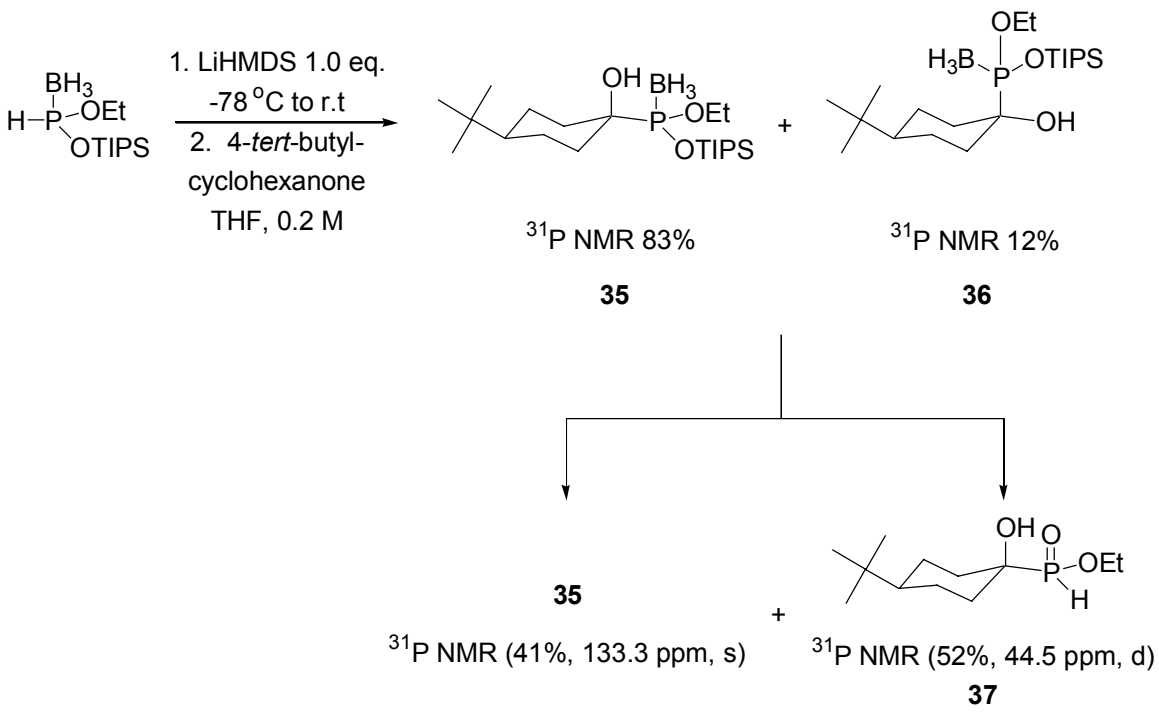
(Equation 3.13)



(Equation 3.14)

Scheme 3.11 shows the addition of the complex to a carbonyl, a bulky ketone (4-*tert*-butylcyclohexanone), chosen out of convenience. The reaction mixture was prepared according to standard alkylation procedures for P-C bond formation (Chapter 1.4) and yields interesting results. The reaction worked quite well, according to the crude ^{31}P spectra. Two main phosphorus peaks were observed (83%, 131.4 ppm, s) and (12%, 110.9-113.4 ppm, s), consistent with compounds **35** and **36**, respectively, in Scheme 3.12. As expected, the bulky phosphine-borane attacked equatorially (from the underside of the carbonyl) and in higher frequency than the axial attack. Work-up included solvent evaporation, acidification with $NaHSO_4$, extraction and drying over $MgSO_4$. Gas evolved from the sample after removal from the rotary evaporator, and the immiscible liquid present was removed with $MgSO_4$. After purification by column chromatography, the product was stored, in solution, in the refrigerator for two days. Upon removal, there was additional immiscible liquid in the flask. After solvent evaporation, the pure product was again treated with $MgSO_4$ before NMR. Phosphorus NMR revealed two major signals; intact product (133.3 ppm, s, 42%) **35** and decomplexed, hydrolyzed (44.5 ppm, 52%, d) **37** (Scheme 3.12). It is thought that the hydroxy group caused the decomplexation through a sort of neighboring group participation. Note that the percentages of **35** and **37** indicate a ratio, not isolated yield.

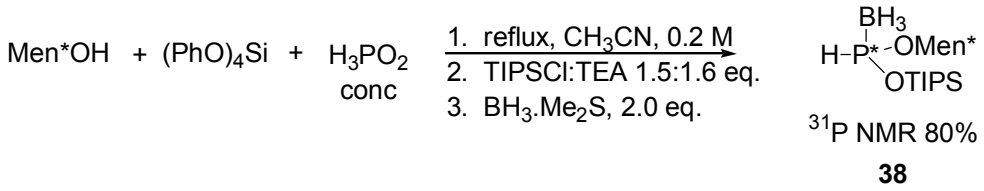
Scheme 3.12 Addition to a carbonyl via deprotonation with LiHMDS



The reactions are straightforward, using the same procedures from Chapter 1. The only additional precautions were using flame-dried glassware and mild reactant deoxygenation in order to avoid oxidation of the uncomplexed intermediate. Isolation of the pure product was challenging because of the non-polar nature of the products; hexanes were used for column chromatography. The phosphine-borane starting material seemed to be quite stable both in air and under thermal conditions. Under cross-coupling conditions (Equation 3.12), 68% of the starting material remained, and 32% oxidation product, the phosphite oxide [$(RO)_3P(O)$], formed. Under hydrophosphinylation conditions (Equation 3.13), 95% of the starting material remained, while the H-phosphonate oxidation product formed in 5% yield.

Synthesis of a P-chiral phosphine-borane complex **38** occurs in good crude ^{31}P yield (80%) via in situ transesterification with tetraphenoxysilane and menthol (Equation

3.15). However, diastereomeric separation has not been accomplished. In principle, isolation of diastereoisomers would provide a nice path to the synthesis of P-chiral synthons for catalysis as well as P-chiral compounds of biological interest.



(Equation 3.15)

Although preliminary, these results are promising and pave the way to a broad, methodologically and synthetically useful project.

3.4 Experimental

General Chemistry: Refer to Chapter 2.3.

General: All reactions were conducted under nitrogen in flame-dried glassware. Lithium hexamethyldisilazane (1 M in THF), triethylborane (1 M in THF), butyl lithium (1.6 M in hexanes), borane-methyl sulfide complex (1 M in CH_2Cl_2 and 2 M in THF), borane-tetrahydrofuran complex (1 M in THF) and aqueous hypophosphorous acid (50 wt. %) were obtained from Aldrich and used as received. Concentrated hypophosphorous acid was obtained by concentrating the 50 wt. % aqueous solution in vacuo on a rotary evaporator at room temperature for 20-30 minutes before the reaction.

Ethyl triisopropylsilyl phosphonoborane (Table 3.2, entry 3), Representative Procedure: Triisopropylchlorosilane (TIPSCl) (2.89 g, 15.0 mmol) was added by weight into a flame-dried two-neck round bottom flask. The flask was cooled to 0 ˚C, with stirring, and Et_3N (1.62 g, 16.0 mmol) was added. The mixture was allowed to stir for approximately 10 minutes at 0 ˚C. In a separate flame-dried multi-neck flask, a solution of ethyl hypophosphite (0.5 M in CH_3CN) (20 mL, 10 mmol) was cooled to 0 ˚C. The entire volume of the TIPSCl:Et_3N mixture was added by syringe to the 0 ˚C hypophosphite solution, at a rate that minimized the visible formation of gas. The reaction mixture was maintained at 0 ˚C for 10-15 minutes, at which time the bath was removed, and the reaction was allowed to proceed under N_2 overnight. The reaction mixture was quenched with $BH_3{\cdot}Me_2S$ (2.0 M in THF) (10 mL, 20 mmol), by drop-wise addition at room temperature. After no less than 45 minutes the reaction mixture was concentrated in vacuo and extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the crude compound, which was purified by column chromatography (100% v/v Hexanes) to yield the title compound as a near-colorless oil (2.30 g, 87% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20 (d, J_{PH} = 430 Hz, 1 H), 4.03 – 4.20 (m, 2 H), 3.75 (q, J_{HB} = 6.7 Hz, 1 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.06 – 1.31 (m, 21 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 113.5 – 115.4 (dq, J_{PH} = 201.1 Hz, J_{PB} = 66.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 65.0 (d, JPOC = 7.49 Hz), 17.6, 16.6 (d, JPOCC = 6.05 Hz), 12.6. HRMS-FAB (*m/z*): $[M + NH_4]^+$ calc for $C_{11}H_{30}BO_2PSi_2$, 282.2190; found, 282.2196.

Bis-triisopropylsilyl phosphonoborane (Table 3.2, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48 (d, J_{PH} = 419 Hz, 1 H), 0.756 – 1.32 (m, 42 H), 0.597 (bq, J_{BH} = 80.0 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 99.8 – 101.9 (dq, J_{PH} = 170 Hz, J_{PB} = 72.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 17.7, 12.6.

Ethyl triisopropylsilyl oct-1-enyl-phoshonoborane (Table 3.2, entry 6): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.64 – 6.80 (m, 1 H), 5.77 – 5.86 (m, 1 H), 3.96 – 4.11 (m, 2 H), 3.62 – 3.77 (m, 2 H), 2.75 – 2.83 (q, J = 7.33 Hz, 2 H), 2.16 – 2.32 (m, 2 H), 0.620 – 1.70 (m, 31 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 118.7 – 120.1. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 17.9, 12.5.

Ethyl triisopropylsilyl (3-tert-butoxycarbonylamino-propenyl)-phosphonoborane (Table 3.2, entry 7): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.61 – 6.73 (m, 1 H), 5.97 – 6.01 (m, 1 H), 3.98 – 4.08 (m, 2 H), 1.4 (s, 9 H), 0.829 – 1.40 (m, 23 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 118.4 – 119.3. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 155.5, 146.8 (d, J_{PC} = 14.7 Hz), 124.2 (d, J_{PCC} = 75.1 Hz), 62.6 (d, J_{POC} = 4.03 Hz), 42.6 (d, J_{PCCC} = 16.7 Hz), 28.3, 17.5, 16.5 (d, J_{POCC} = 6.62 Hz), 12.5.

Ethyl triisopropylsilyl octylphosphonoborane (Compounds 34a, 34b):

(Equation 3.7, compound 34a): To 10 mL of MeOH was added ethyl triisopropylsilyl phosphonoborane (0.574 g, 2.17 mmol) and 1-octene (0.3195 g, 2.85 mmol) at room temperature. Triethylborane (1 M in THF) (2 mL, 2 mmol) was added in one portion, and the reaction was allowed to stir open to air for 2 h. The reaction mixture was

concentrated in vacuo, and $KHSO_4$ and EtOAc were added. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine. Drying and concentration afforded the crude title compound, which was purified by column chromatography (100% v/v Hexanes) to yield (0.379 g, 50% yield).

(Equation 3.8, compound 34b): Ethyl triisopropylsilyl phosphonoborane (0.438 g, 1.66 mmol) and iodooctane (0.412 g, 1.72 mmol) were placed in a flask under vacuum for 10 minutes. THF (7 mL) was added, and the temperature was reduced to –78 ºC. The reaction mixture was returned to vacuum for an additional 10 minutes. LiHMDS (1.7 mL, 1.7 mmol) was added drop-wise to the mixture at –78 ºC. After addition, the ice bath was removed, the reaction mixture reached room temperature and was concentrated in vacuo. The crude mixture was extracted with EtOAc (2x), washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (100% v/v Hexanes) yielded the title compound (0.275 g, 44% yield).

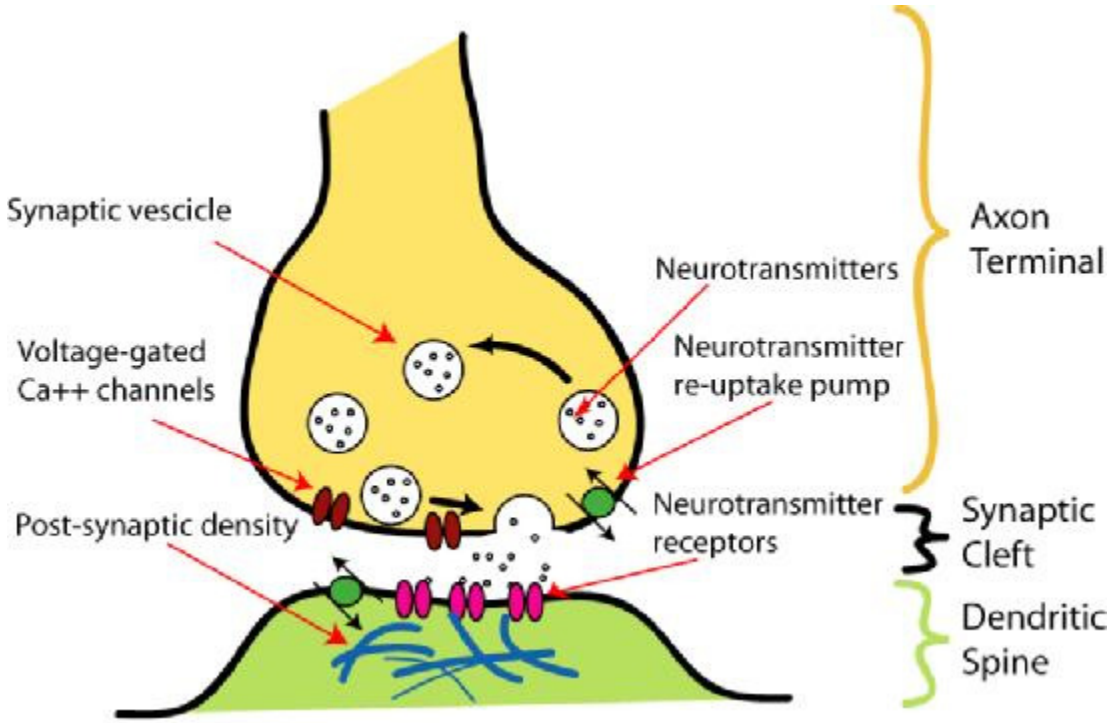
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.83 – 4.18 (m, 2 H), 1.66 – 1.71 (m, 2 H), 1.56 – 1.58 (m, 2 H), 0.858 – 1.35 (m, 37 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 134.6 – 136.6. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 63.0 (d, J_{POC} = 2.88 Hz), 33.1 (d, J_{PC} = 53.6 Hz), 32.1, 31.0 (d, J_{POCC} = 14.1 Hz), 29.9, 29.3 (d, J_{PCCCC} = 2.59 Hz), 22.4 (d, J_{PCC} = 62.5 Hz), 18.4, 17.7, 16.7 (d, J_{PCCC} = 6.33 Hz), 14.2, 12.8.

Chapter Four: Synthesis and biological evaluation of GABA analogues

4.1 Brief introduction of cell signaling

Cellular communication is an important and involved sequence of events, controlled in part by various neurotransmitters, or chemicals used to relay, amplify and modulate electrical signals between cells. Synapses, or junctions through which communication occurs, are composed of axons and dendrites (Scheme 4.1).[91] In simplified terms, cellular signaling is initiated in the axon and travels across the synaptic cleft to the dendrite.

Figure 4.1 Synapse detailing cell signaling[91]



Neurotransmitters can be roughly segregated into three categories: monoamines, peptides, and amino acids. Monoamines include norepinephrine, dopamine, serotonin

and acetylcholine. Peptides include vasopressin, somatostatin, neurotensin and others. Aspartic acid, glycine and the major central nervous system (CNS) neurotransmitters glutamic acid and γ-aminobutyric acid (GABA) comprise the amino acid category of neurotransmitters**.**

Small-molecule neurotransmitters, such as GABA and glutamic acid, are packaged inside vesicles within the cells. When an action potential, or nerve impulse, travels to the synapse, calcium ion channels open. Calcium ions prompt vesicles to travel to the cell membrane, where the two fuse. Neurotransmitters are released in a process called exocytosis and travel across the synaptic cleft by diffusion. In the post-synaptic cell they bind with receptors, which in turn open ion-channels to allow for the influx or efflux of ions. After neurotransmitter release, uptake pumps remove excess compound in order to avoid desensitization of the synapse and to ensure the subsequent nerve firings have the same potential as the previous event.

The excitatory post-synaptic potential (EPSP) is defined as the temporary increase in the post-synaptic cell potential caused by the influx of positively charged ions into the post-synaptic cell or the efflux of negatively charged ions. The increase in positive charge in the post-synaptic cell increases the ability of a nerve fiber to fire a signal. Glutamic acid is the major excitatory neurotransmitter. Negatively charged ions flowing into the post-synaptic cell defines an inhibitory post-synaptic potential (IPSP); GABA is the major inhibitory neurotransmitter.[92]

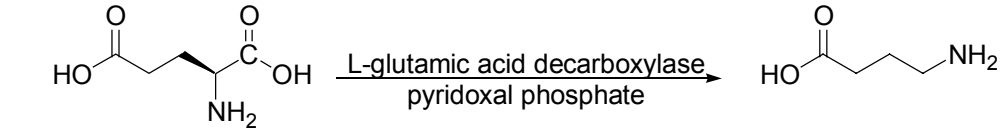
There are two types of transmembrane receptors, ionotropic and metabotropic. Ionotropic receptors contain a central pore that functions as a ligand-gated ion channel, while metabotropic receptors affect the ion channels indirectly, through a cascade of

transductions. Ionotropic receptors are activated quickly and remain open for a few milliseconds. Metabotropic receptors, because of the series of activations required to open the ion channel, take longer to open but remain open for a much longer period of time, from seconds to minutes. As the name implies, transmembrane receptors are embedded in the lipid bilayer of the cell and have cellular interior and cellular exterior moieties. The N-terminus is contained in the cellular exterior while the C-terminus is in the interior. A receptor's function is inherent in its design, while the role of ligands that bind to the receptor are secondary and depend upon the type of receptor to which they bind.[92]

4.2 GABA is the chief inhibitory neurotransmitter

γ-Aminobutyric acid, a small, non-complex amino acid, affects many areas of human physiology. It is the chief inhibitory neurotransmitter in the developed brain, but it has also been shown to play an immensely important role in the growth of new neurons in the developing brain, where it acts as an excitatory neurotransmitter.[93] GABA and its receptors affect brain function and mediate a variety of neurological and physiological responses and are involved in disorders and diseases. Analgesia, anxiety, epilepsy, schizophrenia, Alzheimer's disease and Huntington's disease are all, at least in part, manifestations of the GABA system. As such, much regard has been given to the delineation and understanding of its mechanism of action in order to address physiological problems that might arise from the malfunction of any of a number of processes involved in neurotransmission.

GABA **(39)** is an endogenous ligand, synthesized in GABAergic neurons through the decarboxylation of glutamic acid **(40)** via L-glutamic acid decarboxylase (GAD) and its cofactor pyridoxal-5'-phosphate (PLP) (Equation 4.1). It is degraded by gamma-aminobutyric acid transaminase (GABA-T) or removed by uptake receptors.



(2S)-2-aminopentanedioic acid
(glutamic acid)

39

γ-aminobutyric acid
(GABA)

40

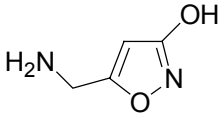
(Equation 4.1)

Three types of GABA receptors have been identified: $GABA_A$, $GABA_B$ and $GABA_C$.[94] $GABA_A$ receptors are ligand-gated chloride channels that mainly function as postsynaptic receptors and mediate fast synaptic inhibition. They contain multiple allosteric binding sites for benzodiazepines, picrotoxin, barbiturates, centrally active steroids, avermectin and propofol.[95] $GABA_B$ receptors are metabotropic and are located mainly on nerve terminals, where they mediate slow synaptic inhibition. A major function of $GABA_B$ receptors is to modulate the release of several neurotransmitters, such as glutamate[96], dopamine[97], noradrenaline[97], serotonin[97], substance P[98], cholecystokinin[99] and somatostatin[100] via presynaptic $GABA_B$ binding sites[13]. $GABA_C$ receptors are ligand-gated chloride ion channels and are only located in neurons of the retina, where they mediate slow and sustained responses.[94]

Compounds that influence the activity of GABA receptors and the cell-signaling system have the potential to mediate various CNS diseases and provide scientists with a better understanding of the architecture and specific functioning of GABA receptors. These analogues are divided into two categories, agonist and antagonists. Agonists are chemicals that mock the endogenous GABA and interact with the receptor(s) in the same manner as GABA, while antagonists compete with or block GABA or agonist binding. There are also compounds, named uptake inhibitors, which mediate the uptake of GABAergicchemicals.

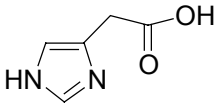
GABA receptors are identified and characterized by their interactions with certain agonists and antagonists (Chart 4.1). $GABA_B$ receptors are insensitive to the specific $GABA_A$ agonists 1,2,3,6-tetrahydropyridin-4-yl-carboxylic acid (isoguvacine) **49** and 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP) **46**, the $GABA_A$ antagonist bicuculline **44** and by their specific affinity for the muscle relaxant (R)-4-amino-3-(4-chlorophenyl)butyric acid [(R)-baclofen] **47**.[94] $GABA_C$ receptors are activated by *cis*-aminocrotonic acid (CACA) **48**, which is not recognized by $GABA_A$ or $GABA_B$. They are not blocked by bicuculline and are blocked by picrotoxin, which also blocks $GABA_A$ receptors.[101]

Chart 4.1 Some GABA agonists and antagonists



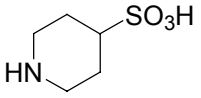
Muscimol $GABA_A$ agonist

41



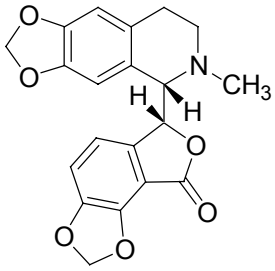
IAA $GABA_A$ partial agonist
$GABA_C$ antagonist

42



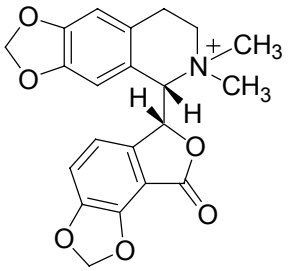
IAA $GABA_A$ partial agonist

43



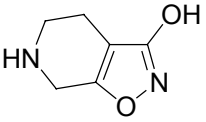
Bicuculline $GABA_A$ antagonist

44



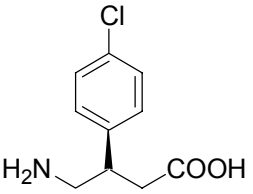
BMC $GABA_A$ antagonist

45



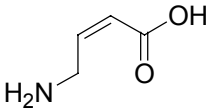
THIP $GABA_A$ partial agonist

46



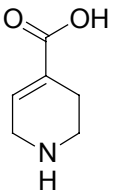
(R)-Baclofen $GABA_B$ agonist

47



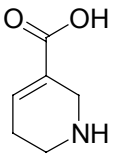
CACA $GABA_C$ agonist

48



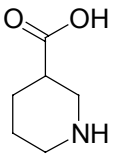
Isoguvacine
$GABA_A$ agonist

49



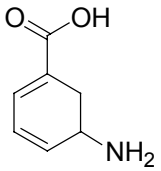
Guvacine
Uptake inhibitor

50



Nipecotic acid
Uptake inhibitor

51



Gabaculine
GABA metabolism

52

Each of $GABA_A$, $GABA_B$ and $GABA_C$ contains combinations of three primary classes of protein subsets, which themselves contain numerous isoforms.[102] Three primary classes, α, β and γ, have been identified through cDNA cloning and expression studies. Six alpha subunits (α_1-α_6), three beta subunits (β_1-β_3) and three gamma subunits (γ_1-γ_3) are present in the brain. Consequently, numerous heteromeric $GABA_A$, $GABA_B$ and $GABA_C$ receptors exist.

Different subunit isomeric combinations are responsible for drug recognition. For instance, if the α_1 subunit of the most common $GABA_A$ receptor is replaced with α_4 or α_6, the receptor fails to recognize benzodiazepine.[103,104] This is due to a single amino acid substitution: an arginine residue in α_4 and α_6 replaces histidine 101, which is present in α_1, α_2, α_3 and α_5 subunits. Receptors containing α_1, α_2, α_3 and α_5 combined with a β and γ subunit are all recognized by classic benzodiazepines. Some benzodiazepines are able to distinguish among different subunit isoforms and are therefore only sensitive to certain receptors. Triazolopyridazine (CL218,872)[105], the hypnotic Zaleplon and certain β-carboline-3-carboxylic acid esters can differentiate among the isoforms[106]. This phenomenon enables the specific targeting of GABA receptors.

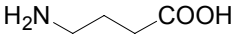
4.3 Phosphinic acids as GABA analogues

Because GABA and its receptors are so prevalent in the CNS, it is important to be as specific as possible when designing analogues in order to avoid side effects. As noted above, understanding the exact isoform composition of each receptor and subsequent formulation of the proper analogue will aid in this. However, much is still unknown about the exact composition of each receptor. Furthermore, while there are some

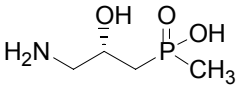
structural characteristics associated with analogue activity in certain receptors, there is no rule. New analogues are necessary in order to continue the structural probe of each receptor and to learn how to specifically target the desired receptor.

Phosphinic acids have become appealing targets in the search for biologically active GABA analogues, because they serve as bioisosteres of the carboxylic acid functionality in GABA.[107] In fact, the derivatives of aminopropyl phosphinic acids are the most potent $GABA_B$ agonists and antagonists known, and **59** is the first selective antagonist for the $GABA_C$ receptors.[101] Several other phosphorus containing GABA analogues have been synthesized since the mid-1990s, with much of the work coming from the Froestl group at Novartis (Chart 4.2).[13,14,108-112] Overman[101,113], Krogsgaard-Larsen[114,115] and Chebib[116] have synthesized other analogues (Chart 4.2).

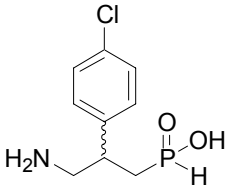
Chart 4.2 Phosphinic acid GABA analogues



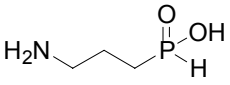
GABA



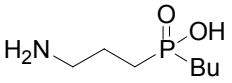
55 CGP 44532 $GABA_B$ agonist



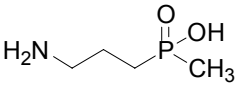
58 CGP 35832 $GABA_B$ agonist



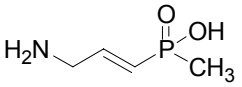
53 CGP 27492 $GABA_B$ agonist



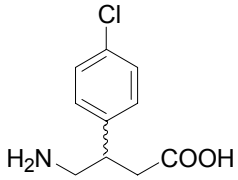
56 CGP 36742 $GABA_B$ antagonist



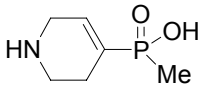
54 CGP 35024 $GABA_B$ agonist



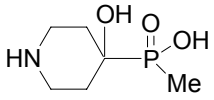
57 CGP 44530 $GABA_C$ agonist



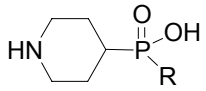
Baclofen
$GABA_B$ agonist



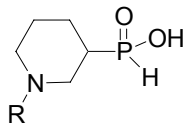
59 TPMPA
$GABA_C$ antagonist



63 $GABA_A$ antagonist



60 R = H $GABA_A$ partial agonist
61 R = OH $GABA_A$ antagonist
62 R = Me $GABA_A$ antagonist



64 R = H
65 R = $CH_2CH_2CH{=}CPh_2$
GABA uptake inhibitors

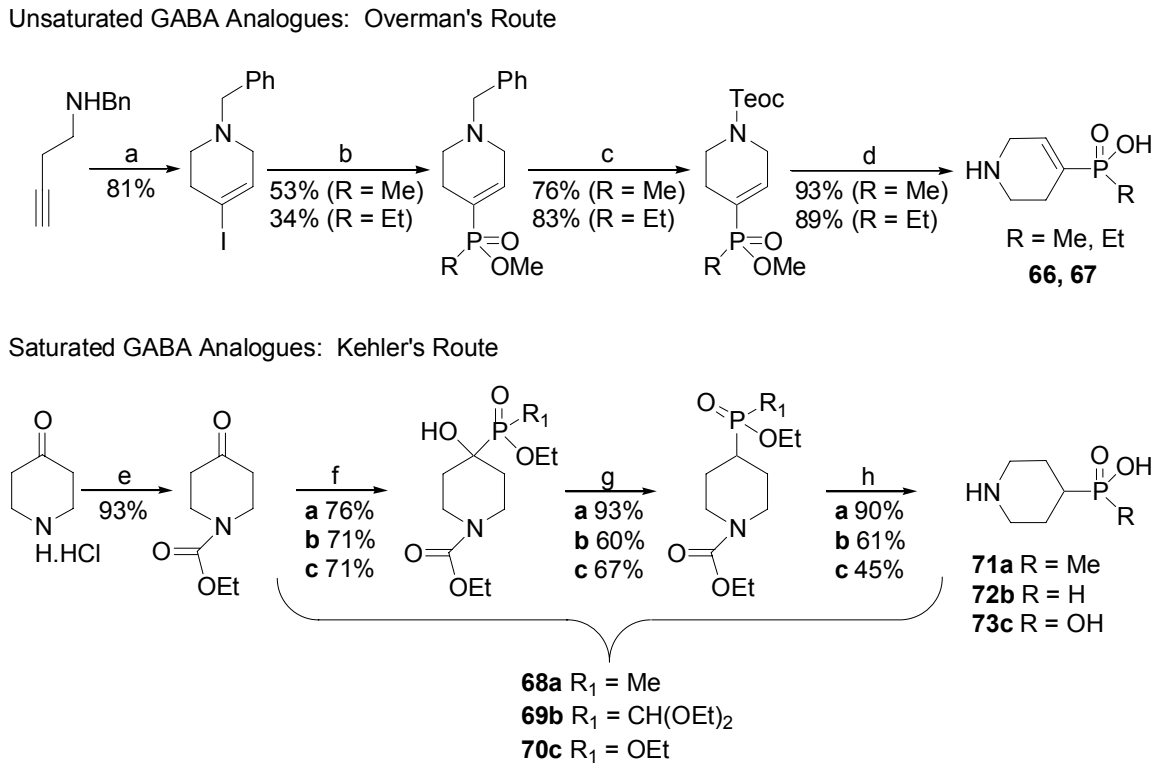
Compound **53** is the simplest phosphinic acid GABA analogue and the most potent $GABA_B$ agonist in vitro. In vivo, however, it has mild antagonistic effect, presumably due to the in vivo oxidation of the P-H bond to the phosphonic acid.[117] Subcutaneous administration of compound **58**, the phosphinic acid analogue of the

$GABA_B$ agonist baclofen, yields equipotent agonistic effect but is orally inactive, again because of in vivo oxidation to the mild antagonistic phosphonic acid (phaclofen).[13,117] This has been generally observed on phosphinic acid analogues containing a P-H bond. Consequently, analogues containing the phosphinic P-C bond were investigated. Analogue **54** displays high potency without the problems associated with **53**. It acts agonistically in both pre- and post-synaptic receptors. Compound **55** is more potent than baclofen and does not cause sedation or other side effects that are associated with baclofen, such as vertigo, nausea and vomiting. It has been selected for further drug development. The butyl phosphinic acid analogue **56** is capable of penetrating the blood-brain barrier and is orally active as an antagonist, blocking the effects of baclofen. It has been shown to improve different aspects of learning and memory in experimental animals and has been selected as a development compound for the treatment of cognition deficits.[14] The exact pharmacological profile of $GABA_C$ receptors has not yet been developed. The discovery of $GABA_C$-specific antagonist TPMPA **59** has given some insight into these receptors. Piperidine-based compounds **60-63** display affinity for $GABA_A$. Uptake inhibitors **64** and **65** have potential as pain, anxiety and epilepsy medications.[107]

4.4 Synthesis of GABA analogues

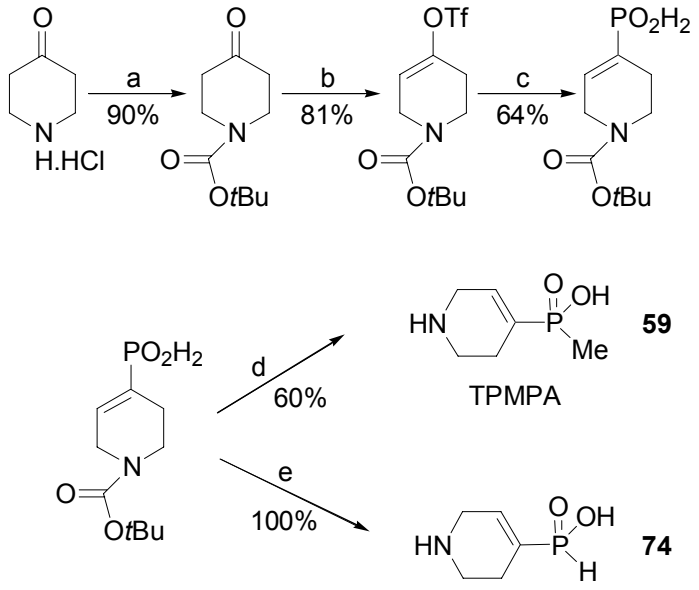
Synthesis of GABA analogues has been an ongoing project within the Montchamp group. Some of the group methodology is a manifestation of the need to develop novel biologically active or medicinally interesting compounds containing functionalities that may have been sensitive under previously reported conditions (Chapter 1), (Scheme 4.1, 4.2). Our methodology provides a more-direct synthetic route to known GABA analogue **59** (Chapter 1).[31] Overman prepared the unsaturated analogues via cross-coupling of the alkyl H-phosphinate and the iodoalkene in the presence of $Pd(PPh_3)_4$.[101,113] Kehler prepared the saturated analogues, the piperidin-4-ylphosphinates, through carbonyl addition of the phosphinates followed by deoxygenation (Scheme 4.1).[107,115,118] Dumond and Montchamp published the divergent synthesis of both **59** and its H-phosphinic acid homologue via the cross-coupling of anilinium hypophosphite followed by methylation (Scheme 4.2).[31] A simple deprotection of the nitrogen formed the isoguvacine-related H-phosphinic acid directly **74**. In Kehler's route, formation of the H-phosphinic acid **72b** required the deprotection of the Ciba-Geigy intermediate **69b** (Scheme 4.1).

Scheme 4.1 Literature syntheses of tetrahydropyridin-4-ylphosphinic acids and piperidin-4-ylphosphinic acids[101,107,113,115,118]



(a) CH_2O, NaI, RSO_3H, H_2O. (b) RP(O)(OMe)H, $Pd(PPh_3)_4$, DABCO, toluene, 85 ºC. (c) $TMSCH_2CH_2OC(O)Cl$, toluene, r.t. (d) (i) 48% HBr, AcOH, 95 ºC; (ii) Dowex 50 H^+. (e) EtOC(O)Cl, NaOH, Et_2O, H_2O. (f) $R_1P(O)(OEt)H$, Et_3N, 100 ºC. (g) (i) MeOC(O)C(O)Cl, DMAP, CH_3CN, r.t.; (ii) Bu_3SnH, AIBN, toluene, 90 ºC. (h) Conc HCl, reflux.

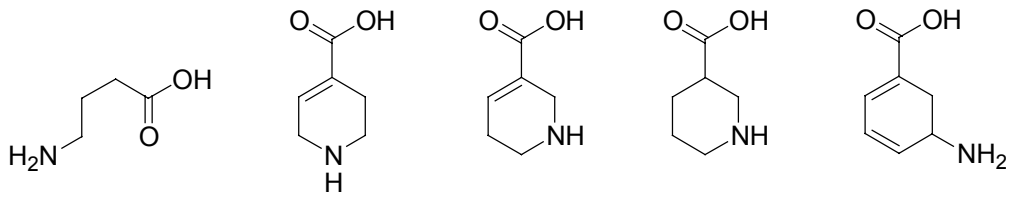
Scheme 4.2 Synthetic approach to phosphinyl GABA analogues[31]



(a) BOC_2O, Et_3N, DMF, r.t. (Ref. [120]). (b) (i) LDA, THF, -78 ºC; (ii) $PhNTf_2$, -78 to 0 ºC (Ref. [121]). (c) AHP, $Pd(OAc)_2$, dppp, Et_3N, C_6H_6, reflux. (d) (i)DBU, MeI, TMSCl, -78 ºC to r.t.; (ii) Dowex $50H^+$. (e) Conc HCl, reflux.

GABA is a simple compound and conformationally flexible. In order to be received by a particular receptor, a particular conformer must be achieved. Binding affinity and receptor-selectivity could be increased through the use of conformationally-restricted analogues. Examples of phosphorus analogues are listed in Chart 4.2: **57**, **59-65**, and some non-phosphorus analogues are listed below (Chart 4.3). In addition to increased selectivity and binding affinity, conformational space of the receptors may be mapped with restricted analogues.

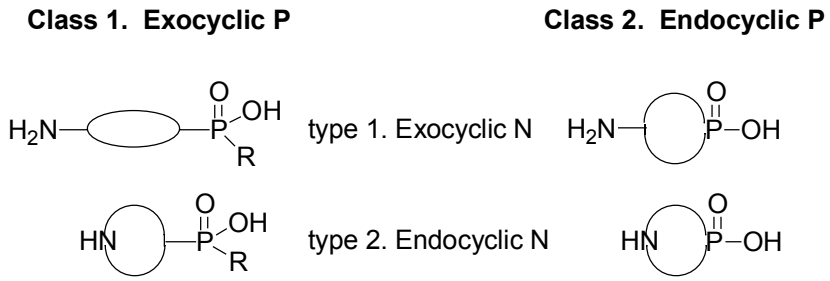
Chart 4.3 Conformationally-restricted GABA analogues



GABA Isoguvacine Guvacine Nipecotic acid Gabaculine

New classes of conformationally-restricted phosphorus analogues were proposed: phosphorus, nitrogen or both atoms would be bound within a cyclic system (Chart 4.4).

Chart 4.4 Proposed structural classes of phosphinyl GABA analogues[123]

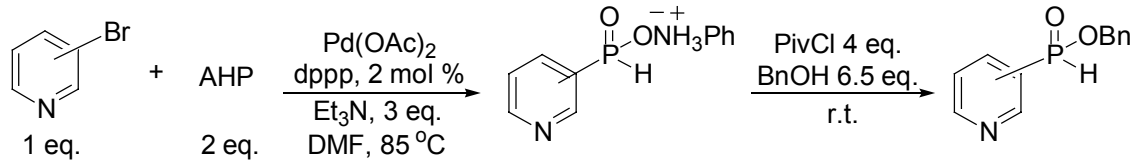


The focus of the following work is on Class 1 analogues.

4.4.1 Palladium-catalyzed cross-coupling

Initial investigations into the synthesis of GABA analogues involved the cross-coupling of bromopyridines followed by the esterification of the anilinium salt with benzyl alcohol in the presence of pivaloyl chloride (Scheme 4.3).

Scheme 4.3 Cross-coupling of 2- and 3-bromopyridine with AHP followed by esterification

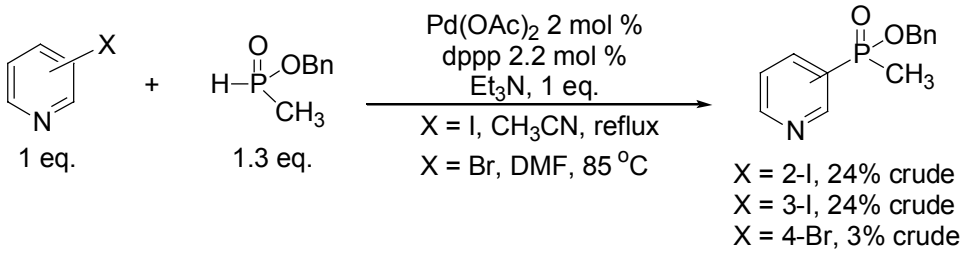


While 3-bromopyridine underwent coupling and esterification very well (nearly quantitative for each step), 2-bromopyridine did not couple in acceptable yield (about 10% crude yield). This low yield is due to electronic effects of the nitrogen. 4-bromopyridine.hydrochloride underwent cross-coupling in 46% crude ^{31}P NMR yield and 30% crude esterification yield in the presence of 3 equivalents of Et_3N, whereas 4 equivalents should have been used because of the presence of the hydrochloride salt. Work-up and purification on the 2- and 4-bromopyridines were not attempted due to lower crude yields. Note that because these reaction mixtures were heterogeneous, crude ^{31}P NMR yields are qualitative, not quantitative. The purification of the H-phosphinate benzyl ester proved quite difficult. After several failed purification attempts, it was determined that the benzyl ester was hydrolytically unstable.

Contemporaneous with this work was the development of Chapter 1.4 and the formation of benzyl methyl-H-phosphinate.[48] This compound proved useful in the cross-

coupling reactions and appropriate for the synthesis of GABA analogues, as the P-CH_3 would not oxidize in vivo as the P-H does.

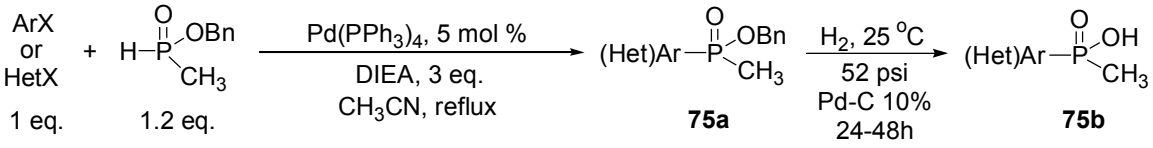
Initial cross-coupling conditions are listed (Equation 4.2). Substituted pyridines were used as model compounds. Unlike the coupling of the heterocycles with AHP**,** these preliminary results were not acceptable (3-24% crude yields). Refluxing toluene or additional equivalents of base did not yield better results. As a more hindered and therefore less nucleophilic base than Et_3N, DIEA was not expected to be as harsh on the sensitive benzyl methyl-H-phosphinate. After a brief investigation, $Pd(PPh_3)_4$ (5 mol %), DIEA (3 eq.) in refluxing acetonitrile was chosen as the best system (Table 4.1).[122]

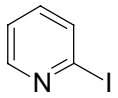
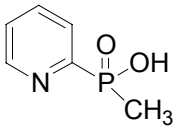
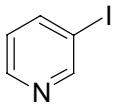
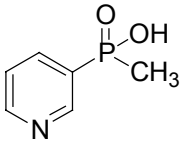
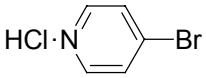
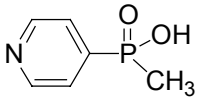
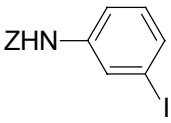
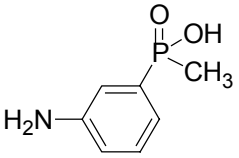
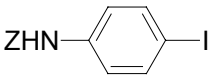
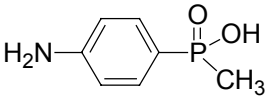
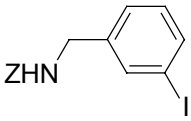
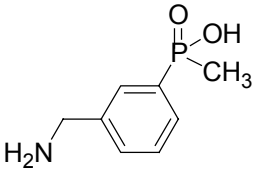


(Equation 4.2)

Products were purified by column chromatography, and the benzyl ester and protecting group, if present (**75a**), were subsequently cleaved via hydrogenolysis. This sequence provided several GABA analogues of type **75b** (Table 4.1). Alternatively, butyl methyl-H-phosphinate was used (Table 4.1, entry 4) and deprotected by refluxing in concentrated HCl overnight, followed by treatment with propylene oxide to remove the salt.

Table 4.1 Synthesis of aryl and heteroaryl phosphinic acids as GABA analogues

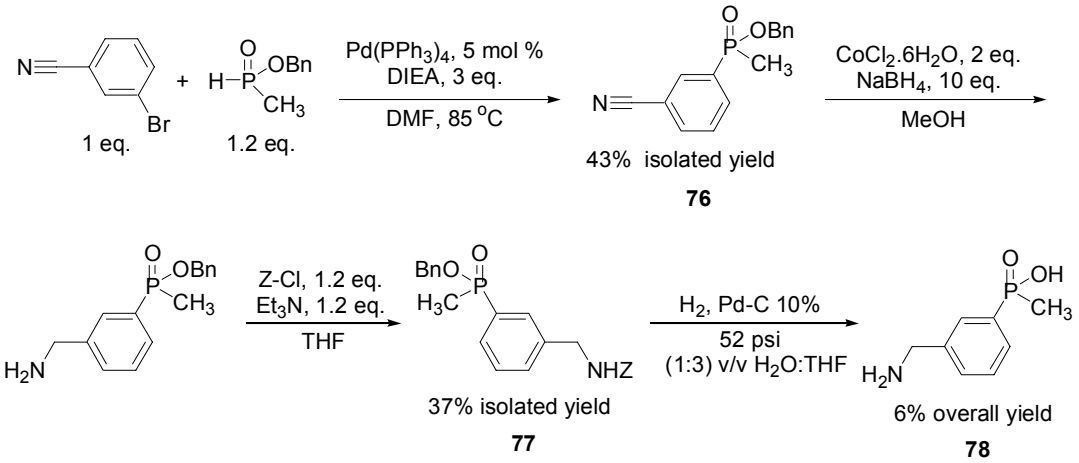


Entry	ArX or HetX	GABA analogue	Time[b], h	Yield (Isolated)[c] %	Overall Yield[d,h] %
1			21	37 (31)	31
2			17	51 (43)	36
3[a]			21	51 (27)	23
4[e]			4	99 (81)	70[f]
5			2.25	62 (54)	52
6			23	96 (20)[g]	18

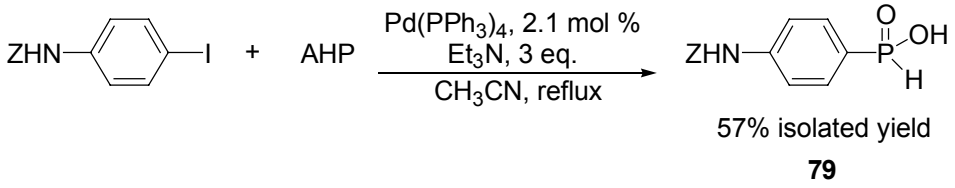
[a]Four eq. of DIEA. [b]Cross-coupling reaction time. [c]Cross-coupling ^{31}P NMR yield. Isolated yield in parentheses. [d]Overall isolated yield after deprotection. [e]Phosphorus source is butyl methyl-H-phosphinate, 1.2 eq. [f]Deprotection via reflux in conc. HCl followed by treatment with propylene oxide. [g]Isolated yield after three chromatography columns. Product was incredibly polar, and there were three phosphorus products that co-eluted, requiring multiple purifications. [h]Hydrogenolysis solvents were either (1:2) v/v H_2O:THF or (1:3) v/v H_2O:THF.

In attempt to use more cost-effective starting materials, Table 4.1, entry 6 (**76)** was also formed from the nitrile (Scheme 4.4).[124]

Scheme 4.4 Synthesis of a GABA analogue via reduction of a nitrile



Multiple attempts were made to hydrogenolyze the CBZ protecting group of H-phosphinic acids, as discussed below (Equation 4.3) and shown in Scheme 4.5. However, formation of the H-phosphinic acid GABA analogues of type **75b** was never achieved; hydrogenolysis fails on P-H containing compounds. Cross-coupling with AHP and the heterocycle followed by acidification (Equation 4.3) provided a fair isolated yield (57%). Titration with NaOH and solubilization in DMSO followed. Although the salt was soluble in DMSO, sulfur poisons catalysts, so the subsequent attempt at hydrogenolysis of the CBZ (Z) protecting group failed.



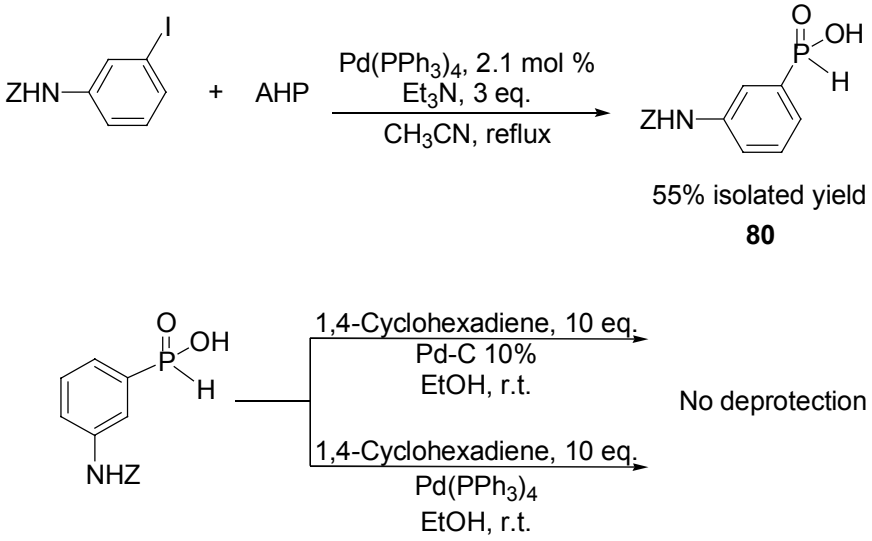
57% isolated yield

79

(Equation 4.3)

In other attempts, transfer hydrogenation of the P-H bond-containing analogues was attempted with 1,4-cyclohexadiene, a known hydrogen donor (Scheme 4.5).[125,126] These reactions, too, were unsuccessful.

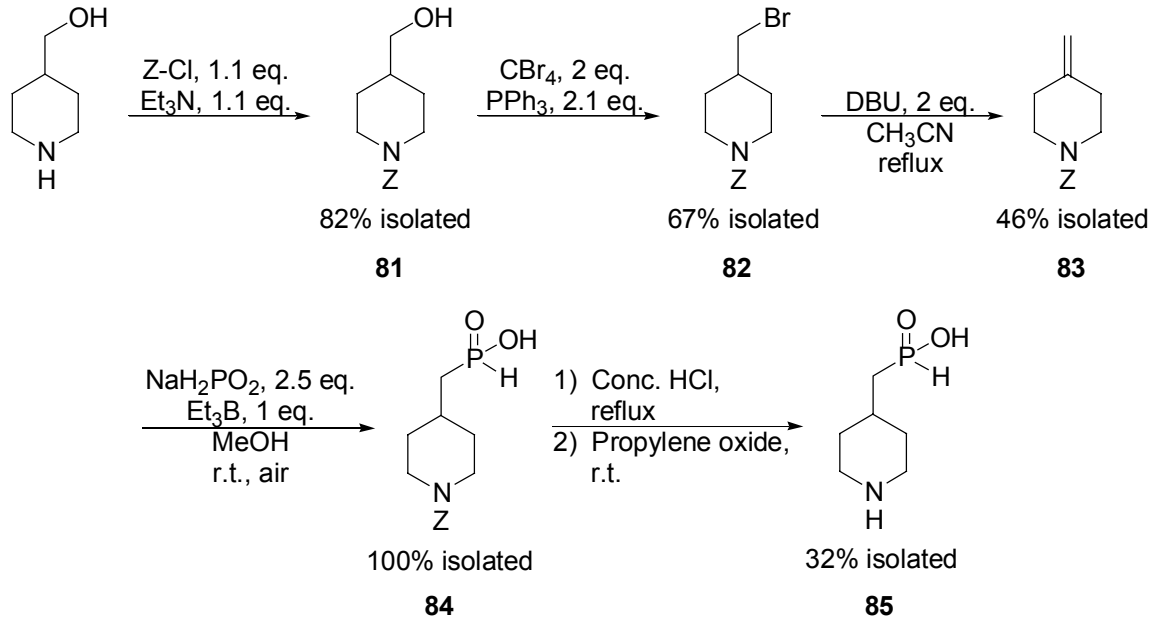
Scheme 4.5 Attempted hydrogenolysis of Z-protecting group using 1,4-cyclohexadiene in the presence of palladium



4.4.2 Triethylborane-initiated radical addition

A piperidine-based analogue was formed from 4-piperidine methanol using the triethylborane/oxygen-initiated radical addition, as discussed in Chapter 1.2. The overall yield was fair and was accomplished through a sequence of reactions (Scheme 4.6).

Scheme 4.6 Synthesis of an H-phosphinic acid GABA analogue from 4-piperidine methanol



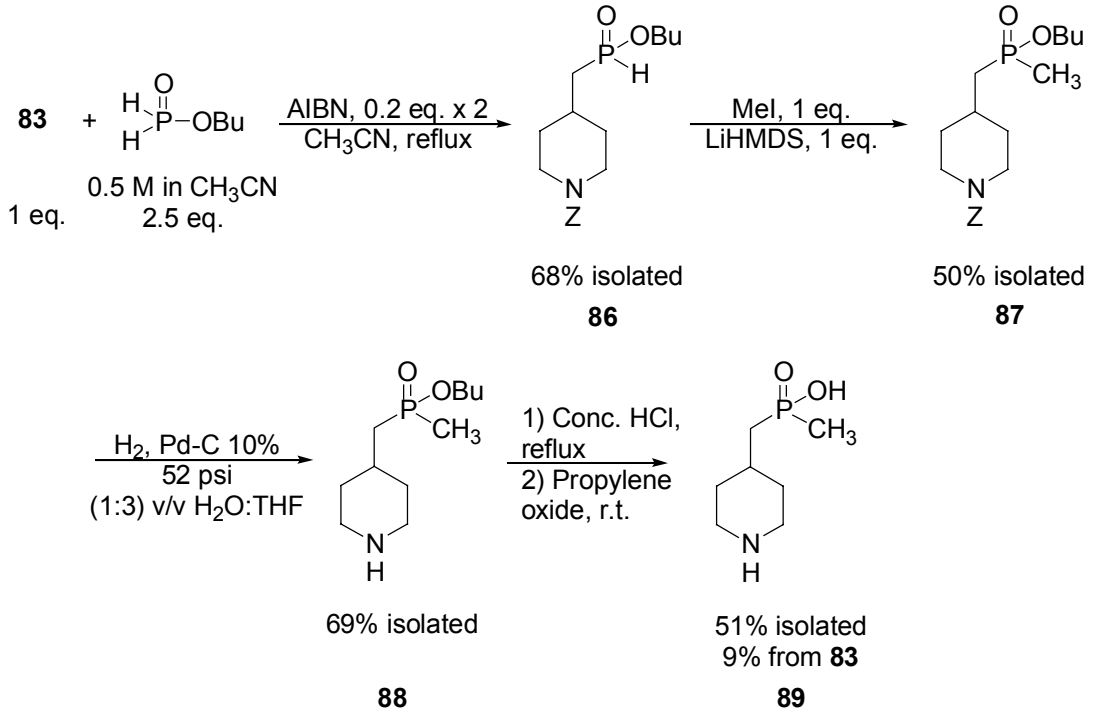
Protection of the free amine was accomplished via benzyl chloroformate, followed by the conversion of the alcohol to the bromide with bromoform and triphenylphosphine. Base-promoted elimination provided the alkene. Radical-initiated addition of sodium hypophosphite in methanol followed by an acidic workup provided the H-phosphinic acid. Deprotection of the CBZ-protecting group afforded **85** in 32% yield.

The low yield (32%) from the deprotection step can be attributed to the work-up of this 100 mg scale (of the HCl salt) reaction. The deprotection conditions work well, but losing more than half of the molecular weight drastically reduces the working scale, and losses are noticed multi-fold.

4.4.3 AIBN addition followed by alkylation with LiHMDS

The P-CH_3 analogue **89** is synthesized (Scheme 4.7) by combining two methodologies that were developed in the Montchamp group recently, AIBN-initiated addition and P-C bond formation (Chapter 1.2.2 and 1.4).[40,48]

Scheme 4.7 Synthesis of a GABA analogue via AIBN radical addition and alkylation



To the alkene, butyl hypophosphite in 0.5 M CH_3CN solution is added through AIBN-initiated addition in good isolated yield to form **86**. Alkylation using iodomethane is accomplished in 100% crude (50% isolated) yield **(87)**. Deoxygenation, using conditions described in Chapter 1.4, was used for the alkylation step, although probably not necessary in the presence of the highly reactive alkyl iodide. Hydrogenolysis to form **88** was attempted via hydrogen in the presence of palladium. Unfortunately, there was

liquid, presumably water, in the hydrogenator's vacuum/nitrogen line, and it entered the sample tube during purging and displaced an unknown amount of sample. The liquid's composition is unknown, but if it was water from the main water aspirator line, certainly it contained dissolved minerals. If it contained any amount of a previous sample, this would bias the biological testing. According to spectra, it appears that the contamination was not another substrate, but rather minerals that complexed with the product. The protected ester appears at 54.2 ppm as a singlet. Two phosphorus nuclei are present after hydrogenolysis [(78%, 63.6 ppm, s), (22%, 64.3 ppm, s)]. The proton spectrum indicates some degree of incomplete hydrogenolysis. The resulting mixture was refluxed in concentrated HCl to cleave the ester, providing two phosphorus nuclei [(80%, 56.1 ppm, s), (20%, 55.8 ppm, s)]. Any remaining CBZ-protecting group would have been cleaved during this step, as well. The proton spectrum is consistent with this. Two phosphorus nuclei [(77%, 46.1 ppm, s), (21%, 45.7 ppm, s)] are present after the propylene oxide step, but the proton spectrum is consistent with a singular phosphorus compound having one P-CH_3 moiety. This indicates there remains complexation with the nitrogen as the phosphinate cation.

4.5 Biological evaluation of GABA analogues

Several GABA analogues (**85** and Table 4.1, entries 1, 2, 3, 5) were submitted to Dr. Wolfgang Froestl at Novartis Pharmaceuticals for testing of activity toward $GABA_B$ receptors. None showed activity except for Table 4.1, entry 3. It has weak antagonistic properties (>40 μM) in $GABA_B$ receptors.

4.6 Experimental

General Chemistry: Refer to Chapter 2.3

Methyl-pyridin-2-yl-phosphinic acid benzyl ester (Table 4.1, entry 1, type 75a), Representative Procedure: 2-Iodopyridine (1.024 g, 5.00 mmol) and benzyl methyl-H-phosphinate (0.955 g, 6.02 mmol) were solubilized in CH_3CN (25 mL). DIEA (1.94 g, 15.0 mmol) was added to the flask, followed by $Pd(PPh_3)_4$ (0.289 g, 0.25 mmol). The reaction refluxed for 21 hours, and after cooling to room temperature it was concentrated in vacuo, washed with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The mixture was purified using radial chromatography (100% v/v EtOAc to 90% EtOAc: 10% MeOH v/v) to afford the title compound (0.368 g, 31% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.761 (d, J = 4.69, 1 H), 8.06 (tt, J = 4.69, J = 1.17, 1 H), 7.77 – 7.85 (m, 1 H), 7.38 – 7.43 (m, 1 H), 7.27 – 7.31 (m, 5 H), 5.045 – 5.11 (m, 1 H), 4.78 – 4.85 (m, 1 H), 1.82 (d, J = 14.4 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 42.0. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 155.7, 153.8, 150.7 (d, J_{PC} = 20.4 Hz), 136.5, 136.3 (d, J_{PCC} = 9.79), 128.7, 128.5, 128.2, 128.1, 127.8, 126.2 (d, J_{PCCC} = 3.16 Hz), 66.6 (d, J_{POC} = 6.05 Hz), 13.8 (d, J_{PC} = 103.35 Hz).

Methyl-pyridin-3-yl-phosphinic acid benzyl ester (Table 4.1, entry 2, type 75a): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.93 – 8.96 (m, 1 H), 8.75 – 8.78 (m, 1 H), 8.06 – 8.14 (m, 1 H), 7.34 – 7.40 (m, 1 H), 7.29 – 7.32 (m, 5 H), 5.07 – 5.14 (m, 1 H), 4.79 – 4.85 (m, 1 H), 1.74 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 41.6. ^{13}C NMR

($CDCl_3$, 75.5 MHz) δ = 153.2, 152.1 (d, J_{PCC} = 12.4 Hz), 139.5 (d, J_{PCC} = 8.35), 128.9, 128.8, 128.3, 123.8 (d, J_{PC} = 9.2 Hz), 66.7 (d, J_{POC} = 5.8 Hz), 16.6 (d, J_{PC} = 103.6 Hz).

Methyl-pyridin-4-yl-phosphinic acid benzyl ester (Table 4.1, entry 3, type 75a): ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.68 – 8.72 (m, 2 H), 7.56 – 7.62 (m, 2 H), 7.24 – 7.26 (m, 5 H), 5.01 – 5.08 (m, 1 H), 4.73 – 4.79 (m, 1 H), 1.66 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 41.0. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 150.3, 150.2, 135.9, 135.8, 128.9, 128.8, 128.4, 125.3, 125.1, 66.9 (d, J_{POC} = 5.8 Hz), 15.9 (d, J_{PC} = 103.1 Hz).

(3-Benzyloxycarbonylamino-phenyl)-methyl-phosphinic acid butyl ester (Table 4.1, entry 4, type 75a): ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.6 (s, 1 H), 7.27 – 8.01 (m, 9 H), 5.21 (s, 2 H), 3.88 – 3.95 (m, 1 H), 3.64 – 3.74 (m, 1 H), 1.60 (d, J_{PH} = 14.7 Hz, 3 H), 1.50 – 1.55 (m, 2 H), 1.23 – 1.35 (m, 2 H), 0.831 – 0.880 (t, J = 7.3 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 43.3. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 154.0, 139.8, 139.6, 136.3, 132.5, 132.0, 130.8, 129.6, 129.4, 128.5, 128.1, 124.5, 124.4, 122.0, 66.6, 64.4 (d, J_{POC} = 6.3 Hz), 18.7, 15.4 (d, J_{PC} = 103.1 Hz), 13.6.

[4-(Benzyloxycarbonylamino-phenyl]-methyl-phosphinic acid benzyl ester (Table 4.1, entry 5, type 75a): ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 – 7.82 (m, 14 H), 5.21 (s, 2 H), 5.01 – 5.07 (m, 1 H), 4.68 – 4.74 (m, 1 H), 1.68 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 44.6.

[3-(Benzyloxycarbonylamino-methyl)-phenyl]-methyl-phosphinic acid benzyl ester (Table 4.1, entry 6, type 75a) and (Compound 77): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 - 7.73 (m, 14 H), 5.30 (s, 1 H), 5.14 (s, 2 H), 5.02 – 5.08 (m, 1 H), 4.71 – 4.77 (m, 1 H), 4.41 - 4.43 (d, J = 5.9 Hz, 2 H), 1.69 (d, J_{PH} = 14.7 Hz, 3H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 44.3. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 156.8, 139.8, 139.6, 136.9, 136.5, 136.4, 132.9, 131.8, 131.2, 130.5, 130.4, 130.3, 129.4, 129.2, 128.8, 128.6, 128.4, 128.2, 67.1, 66.2 (d, J_{POC} = 5.8 Hz), 44.9, 16.2 (d, J_{PC} = 102.5 Hz).

Methyl-pyridin-2-yl-phosphinic acid (Table 4.1, entry 1), Representative procedure: Methyl-pyridin-2-yl-phosphinic acid benzyl ester (0.147 g, 0.625 mmol) in a solvent mixture of H_2O:THF (1:3) v/v was hydrogenolyzed in the presence of 10 mol % Pd-C (0.079 g) and H_2 for 24h**.** The suspension was filtered through Celite and extracted with EtOAc (2x). The aqueous layer was concentrated in vacuo, followed by a deuterium-exchange with D_2O (3x). This afforded the title compound as light yellow oil (0.090 g, 100% hydrogenolysis yield).

^{1}H NMR (D_2O, 300 MHz): δ = 7.89 – 8.64 (m, 4 H), 1.42 (d, J_{PH} = 15.0 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 23.6. ^{13}C NMR (D_2O, 75.5 MHz) δ = 152.4, 146.4 (d, J_{PC} = 7.2 Hz), 142.5, 129.3 (d, J_{PCC} = 10.7 Hz), 128.3, 16.4 (d, J_{PC} = 105.4 Hz).

Methyl-pyridin-3-yl-phosphinic acid (Table 4.1, entry 2): ^{1}H NMR (D_2O, 300 MHz): δ = 8.51 – 8.72 (m, 3 H), 7.86 – 7.90 (m, 1 H), 1.32 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 26.8. ^{13}C NMR (D_2O, 75.5 MHz) δ = 147.8, 147.7, 143.2, 143.1, 142.9, 16.9 (d, J_{PC} = 103.7 Hz).

Methyl-pyridin-2-yl-phosphinic acid (Table 4.1, entry 3): ^{1}H NMR (D_2O, 300 MHz): δ = 8.75 – 9.15 (m, 2 H), 8.23 – 8.28 (m, 2 H), 1.62 (d, J_{PH} = 14.4 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 28.1. ^{13}C NMR (D_2O, 75.5 MHz) δ = 142.1, 127.6, 15.9 (d, J_{PC} = 102.5 Hz).

(4-Amino-phenyl)-methyl-phosphinic acid (Table 4.1, entry 5): ^{1}H NMR (D_2O, 300 MHz): δ = 7.24 – 7.66 (m, 4 H), 1.31 (d, J_{PH} = 14.1 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 33.9. ^{13}C NMR (D_2O, 75.5 MHz) δ = 138.1, 131.7, 131.5, 130.0, 128.7, 123.6.

(3-Aminomethyl-phenyl)-methyl-phosphinic acid (Table 4.1, entry 6) and (Compound 78): ^{1}H NMR (D_2O, 300 MHz): δ = 7.35 - 7.37 (m, 4 H), 4.03 (s, 2 H), 1.27 (d, J_{PH} = 13.8 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 32.9. ^{13}C NMR (D_2O, 75.5 MHz) δ = 139.8, 132.8, 131.3, 130.6, 130.1, 129.3, 43.1, 16.8 (d, J_{PC} = 98.8 Hz).

(3-Amino-phenyl)-methyl-phosphinic acid (Table 4.1, entry 4): (3-Benzyloxycarbonylamino-phenyl)-methyl-phosphinic acid butyl ester (0.128 g, 0.353 mmol) was refluxed for 7h in conc HCl (1.8 mL). The resulting solution was washed with EtOAc and concentrated in vacuo. The salt was dissolved in MeOH (2 mL), and propylene oxide (110 μL) was added. The solution was stirred at room temperature for 24h. After concentration, the acid was dissolved in hot absolute EtOH, precipitated with Et_2O and collected by filtration to yield the title compound (0.0519 g, 86% yield).

^{1}H NMR (D_2O, 300 MHz): δ = 7.40 – 7.69 (m, 4 H), 1.47 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 32.2.

(3-Cyano-phenyl)-methyl-phosphinic acid benzyl ester (Compound 76): 3-Bromobenzonitrile (2.23 g, 12.2 mmol) and benzyl methyl-H-phosphinate (2.31 g, 14.7 mmol) were solubilized in DMF (60 mL). DIEA (4.78 g, 37.0 mmol) was added to the flask, followed by $Pd(PPh_3)_4$ (0.691 g, 0.598 mmol). The reaction proceeded for 24h at 85 ºC, after which it was treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The mixture was purified using radial chromatography (50% EtOAc: 50% Hexanes v/v) to afford the title compound (0.979 g, 43% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 - 8.06 (m, 9 H), 5.07 – 5.14 (m, 1 H), 4.79 – 4.86 (m, 1 H), 1.73 (d, J_{PH} = 14.7 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 41.4.

(4-Amino-phenyl)-phosphinic acid (Compound 79), Representative procedure: Et_3N (0.607g, 6.00 mmol) and CH_3CN (10 mL) are added to a mixture of 4-(iodo-phenyl)-carbamic acid benzyl ester (0.706 g, 1.99 mmol), AHP (0.802, 5.20 mmol) and $Pd(PPh_3)_4$ (0.0482g, 0.042 mmol). The reaction was heated to reflux and proceeds for 6h. After cooling to room temperature, the mixture was concentrated in vacuo, and the crude mixture was extracted with Et_2O and acidified with 3 N aqueous HCl. The aqueous layer was concentrated in vacuo to yield the target compound (0.832 g, 57% yield).

^{1}H NMR (DMSO-d6, 300 MHz): δ = 10.1 (s, 1 H), 7.34 – 7.63 (m, 9 H), 7.42 (d, J_{PH} = 545, 1 H), 5.16 (s, 2 H). ^{31}P NMR (DMSO-d6, 121.5 MHz): δ = 17.2 (d, J_{PH} = 545 Hz).

(3-Amino-phenyl)-phosphinic acid (Compound 80): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.3 (s, 1 H), 7.39 (d, J_{PH} = 578 Hz, 1 H), 7.21 – 7.71 (m, 9 H), 5.12 (s, 2 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 23.4 (d, J_{PH} = 577 Hz).

4-Bromomethyl-piperidine-1-carboxylic acid benzyl ester (Scheme 4.11, Compound 82): Compound **81** (9.0 g, 36.1 mmol), CBr_4 (26.7 g, 80.4 mmol) and PPh_3 (22.1 g, 84.2 mmol) were solubilized in THF (250 mL), and the reaction proceeded at room temperature for 24h. The resulting suspension was filtered, concentrated and purified. Column chromatography (5% EtOAc: 95% Hexanes v/v to 10% EtOAc: 90% Hexanes v/v) afforded the title compound (7.6 g, 67% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26 – 7.36 (m, 5 H), 5.13 (s, 2 H), 4.23 (m, 2 H), 3.29 – 3.30 (m, 2 H), 2.79 (m, 2 H), 1.24 – 1.83 (m, 5 H).

4-Methylene-piperidine-1-carboxylic acid benzyl ester (Scheme 4.11, Compound 83): Compound **82** was solubilized in CH_3CN (100 mL), and DBU (2.93 g, 19.2 mmol) was added to the solution. The reaction mixture was refluxed for 24h. After cooling to room temperature, the mixture was concentrated in vacuo and purified by column chromatography (20% EtOAc: 80% Hexanes v/v to 80% EtOAc: 20% Hexanes v/v) to afford the title compound as a yellow oil (2.22 g, 28% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31 – 7.37 (m, 5 H), 5.14 (s, 2 H), 4.76 (s, 2 H), 3.51 (t, J = 5.57 Hz), 2.20 (s, 4 H).

4-Hydroxyphosphinoylmethyl-piperidine-1-carboxylic acid benzyl ester (Scheme 4.11, Compound 84): Compound **83** (0.470 g, 2.03 mmol) and NaH_2PO_2 (0.454 g, 5.16 mmol) were solubilized in MeOH (10 mL). Et_3B (2 mL, 2 mmol) was added in one portion, and the reaction proceeded at room temperature in open air for 2h. The reaction mixture was concentrated in vacuo. It was then acidified with 20% $NaHSO_4$, extracted with EtOAc (2x), dried over $MgSO_4$ and concentrated to yield the title compound (0.603 g, 100% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36 (s, 5 H), 7.28 (d, J_{PH} = 544 Hz, 1 H), 5.12 (s, 2 H), 4.11 – 4.16 (m, 2 H), 2.81 (m, 2 H), 1.96 – 2.18 (m, 3 H), 1.65 – 1.85 (m, 4 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 37.4 (d, J_{PH} = 546 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 155.4, 128.7, 128.2, 128.1, 67.3, 44.1, 36.4 (d, J_{PC} = 90.6 Hz), 31.2, 30.2.

Piperidin-4-yl-methyl-phosphinic acid (Compound 85): See procedure for (Table 4.1, entry 4). Procedure yielded title compound (0.0911 g, 32% yield).

^{1}H NMR (D_2O, 300 MHz): δ = 6.84 (d, J_{PH} = 504 Hz, 1 H), 3.18 – 3.2 (m, 2 H), 2.77 – 2.86 (m, 2 H), 1.76 – 1.87 (m, 3 H), 1.26 – 1.41 (m, 4 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 27.3 (d, J_{PH} = 508 Hz). ^{13}C NMR (D_2O, 75.5 MHz) δ = 43.9, 37.6 (d, J_{PC} = 88.7 Hz), 29.68 (d, J_{PCCC} = 10.1 Hz), 28.3.

4-Butoxyphosphinoylmethyl-piperidine-1-carboxylic acid benzyl ester (Scheme 4.12, Compound 86): A solution of Compound **83** (0.975 g, 4.21 mmol) and BuOP(O)H2 (0.5 M in CH_3CN, 21.1 mL, 10.5 mmol) was heated to reflux. AIBN (0.133 g, 0.812 mmol) was then added, and the mixture was heated under N_2. After 6h at reflux, another portion

of AIBN (0.138 g, 0.843 mmol) was added, and the reaction refluxed overnight. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and washed with saturated aqueous $NaHSO_4$. The aqueous phase was then extracted with EtOAc, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine. Drying over $MgSO_4$ and concentration afforded the crude compound, which was purified by column chromatography (30% EtOAc: 70% Hexanes v/v to 10% MeOH: 90% EtOAc v/v) to yield the title compound (1.02 g , 68% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.29 – 7.40 (m, 5 H), 7.19 (d, J_{PH} = 529 Hz, 1 H), 5.12 (s, 2 H), 4.08 – 4.18 (m, 2 H), 3.93 – 4.04 (m, 2 H), 2.78 – 2.82 (m, 2 H), 1.96 – 2.03 (m, 1 H), 1.16 – 1.86 (m, 10 H), 0.945 (t, J = 7.33 Hz, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 37.0 (d, J_{PH} = 532 Hz).

4-(Butoxy-methyl-phosphinoylmethyl)-piperidine-1-carboxylic acid benzyl ester (Scheme 4.12, Compound 87): Compound **86** (0.983 g, 2.78 mmol) was treated in vacuo for 5 minutes before THF (9 mL) was added. The temperature of the solution was reduced to –78 ºC, and vacuum was pulled on the solution for 10 minutes. LiHMDS (2.65 mL, 2.65 mmol) was added drop-wise at –78 ºC. After 10 minutes, iodomethane (0.375 g, 2.64 mmol) was added in one portion. The temperature was maintained at –78 ºC for 15 minutes, and then the ice bath was removed. When the reaction mixture reached room temperature, it was concentrated in vacuo. The residue was taken up in EtOAc and washed with brine. The aqueous layer was extracted with EtOAc (2x). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. Column

chromatography (70% EtOAc: 30% Hexanes v/v to 10% MeOH: 90% EtOAc v/v) afforded the title compound (0.508 g, 50 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 – 7.42 (m, 5 H), 5.12 (s, 2 H), 4.11 – 4.16 (m, 2 H), 3.89 – 4.09 (m, 2 H), 2.82 – 2.86 (m, 2 H), 1.15 – 2.00 (m, 11 H), 1.46 (d, J_{PH} = 13.5 Hz, 3 H), 0.937 (t, J = 7.6, 3 H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 54.2. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 128.5, 128.0, 127.9, 67.0, 63.9, 43.9, 36.5 (d, JPC = 91.0 Hz), 33.5, 32.7, 30.6, 18.9, 13.7.

Methyl-piperidin-4-ylmethyl-phosphinic acid butyl ester (Scheme 4.12, Compound 88): See procedure for (Table 4.1, entry 1). Procedure yielded title compound (0.221 g, 69% yield).

^{1}H NMR (D_2O, 300 MHz): δ = 3.79 – 3.88 (m, 2 H), 3.02 – 3.06 (m, 2 H), 2.59 – 2.68 (m, 2 H), 1.14 – 2.03 (m, 11), 1.41 (d, J_{PH} = 13.8 Hz, 3 H), 0.721 (t, J = 7.33 Hz, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 63.4.

Methyl-piperidin-4-ylmethyl-phosphinic acid (Scheme 4.12, Compound 89): See procedure for (Table 4.1, entry 4). Procedure yielded title compound (0.0692 g, 51% yield).

^{1}H NMR (D_2O, 300 MHz): δ = 3.23 – 3.27 (m, 2 H), 2.82 – 2.94 (m, 2 H), 1.66 – 2.00 (m, 7 H), 1.36 (d, J_{PH} = 14.1, 3 H). ^{31}P NMR (D_2O, 121.5 MHz): δ = 46.1. ^{13}C NMR (D_2O, 75.5 MHz) δ = 44.0, 32.0, 30.1, 28.4, 18.4, 12.9.

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VITA

The author was born January 22, 1980 on Dover AFB, Delaware, as the third daughter to Michael and Kathryn McClellan. In 1998, she graduated from Wesclin High School in Trenton, Illinois. The author completed her BS in Chemistry with a specialization in Forensic Chemistry, *cum laude*, in 2002 from Southern Illinois University at Carbondale.

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She married Stephen Tellez in the summer of 2005.

ABSTRACT

METHODOLOGY AND SYNTHESIS USING HYPOPHOSPHOROUS DERIVATIVES: PHOSPHORUS-CARBON BOND FORMATION AND GABA ANALOGUES

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The focus of this work lies on the exploitation of hypophosphorous derivatives in order to develop new methodologies for P-C bond formation as well as synthesizing biologically relevant phosphorus compounds.

A review of the work published to date from the Montchamp group is provided in Chapter 1: Much of the methodology is applied in the remainder of the thesis in reactions such as radical addition, base-promoted alkylation and cross-coupling of anilinium hypophosphite. The following chapter describes initial results of the transition-metal catalyzed cross-coupling in the presence of β-hydrogens and with chloromethylphthalimide. The application of phosphine-borane chemistry as a phosphinylidene protecting group is discussed in Chapter 3. An in-depth literature review provides the background for the new methodology. Novel γ-aminobutyric acid analogues are synthesized using methods developed within the Montchamp group. Their synthesis and biological evaluation are discussed in the final chapter.