DEVELOPMENT AND REACTIVITY OF NOVEL BENZO-FUSED PHOSPHORUS-CONTAINING HETEROCYCLES

by

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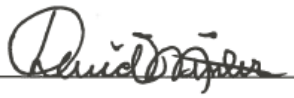

For The College of Science and Engineering

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LIST OF ABBREVIATIONS & ACRONYMS

AcOCs	Cesium acetate
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
bs	Broad singlet
Cy	Cyclohexyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Cy_2NMe	*N*,*N*-dicyclohexylmethylamine
d	Doublet
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DCC	*N,N'*-dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet
DIC	*N,N'*-diisopropylcarbodiimide
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMCDA	Trans-*N,N*′-dimethylcyclohexane-1,2-diamine

DME	1,2-dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
DOPO	9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dq	Doublet of quartet
EDC.HCl	*N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride
equiv.	Equivalents
EWG	Electron-withdrawing group
EDC.HCl	*N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride
equiv.	Equivalents
FRAC	Fungicide resistance action committee
ha	Hectares
HetAr	Heteroaryl
i-Pr	Isopropyl
IRAC	Insecticide resistance action committee
LiHMDS	Lithium hexamethyldisilazane
logP	Lipophilicity
m	Multiplet
n-BuLi	*n*-butyl lithium
NBS	*N*-bromosuccinimide

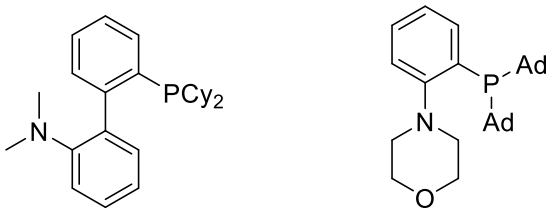
n.d.	Not detected
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
Np	Naphthyl
NPhth	*N*-Phthalimide
N.R.	No reaction
p-TsOMe	Methyl *para*-toluenesulfonate
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
pH	Potentiel hydrogen
PivCl	Pivaloyl chloride
PivOCs	Cesium pivalate
quant.	Quantitative
RDP	Resorcinol bis(diphenyl phosphate)
r.t.	Room temperature
s	Singlet
S_N2	Nucleophilic substitution 2
SPINOL	1,1'-spirobiindane-7,7'-diol
sat.	Saturated
t	Tons or triplet (for experimental part)
TBAF	Tetra-*n*-butylammonium fluoride
t-BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TEA	Triethylamine
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter I: Background on phosphorus-containing heterocycles

I.1. A brief history on organophosphorus chemistry

Phosphorus was discovered in 1669 by German alchemist Hennig Brand as he distilled urine.[1] The name "phosphorus", meaning light-bearing, came from the fact that the substance he obtained glowed in the dark and its ability to spontaneously catch on fire when exposed to air. By the end of the 19th century, phosphorus compounds -mainly inorganic phosphorus compounds- already had many applications ranging from uses as fertilizers to key ingredient in safety matches.[2] The emergence of organophosphorus chemistry started at the end of the 19th century in Russia with August Michaelis and Aleksandr Arbuzov. They are considered to be the founders of organophosphorus chemistry and synthesized various phosphorus-and-carbon-containing compounds via the famous Michaelis-Arbuzov reaction.[3] Since then, organophosphorus compounds have been extensively studied in organic synthesis. A simple search query on SciFinder® with "phosphine-catalyzed" keywords leads to 1,201 research articles involving various reactions such as the Morita-Baylis-Hillman reaction, the Mannich reaction, their variations, and multiple annulation reactions.[4] Moreover, tertiary phosphines represent the most significant class of ligands for metal-catalyzed cross-couplings (Figure 1.1).[5] DavePhos (**1.1**), developed by Buchwald *et al.*, is the first reported ligand from the Buchwald-Hartwig ligand family and is used in Buchwald-Hartwig couplings as well as in Suzuki-Miyaura couplings[6] and Mor-DalPhos (**1.2**), developed by Stradiotto *et al*, allowed for unprecedented Pd-catalyzed C-N and C-C bond formation (Figure 1.1).[7]



DavePhos (**1.1**) Mor-DalPhos (**1.2**)

Figure 1.1 Structures of DavePhos and Mor-DalPhos

Another striking example of organophosphorus compounds versatility is the Wittig reaction, which got awarded the Nobel prize in 1979, and the related reactions, which constitute one of the most powerful tools for the formation of C-C bonds and have found numerous applications in the total synthesis of natural products.[8] Applications of phosphorus compounds go far beyond their organic synthetic utility. For example, azametiphos (**1.3**) is an acetylcholine esterase inhibitors used as an insecticide in aquaculture,[9] glyphosate (**1.4**) is a total herbicide,[10] fosfomycin (**1.5**) is a natural phosphonate with antibiotic properties[11] and brigatinib (**1.6**) is an anticancer drug containing a phosphine oxide moiety that greatly improves its potency as well as its water solubility.[12] Apart from biologically activity, organophosphorus compounds were found to have applications in other distant fields such as corrosion inhibition with etidronic acid (**1.7**),[13] uranium extraction with di-(2-ethylhexyl)phosphoric acid (**1.8**),[14] or flame retardancy with Fyroflex® RDP (**1.9**)[15] and DOPO (**1.10**), produced on a very large scale (>10,000 t/year), mainly used in epoxy resins in the electrical and electronics industry as well as in the aerospace industry (Figure 1.2).[16]

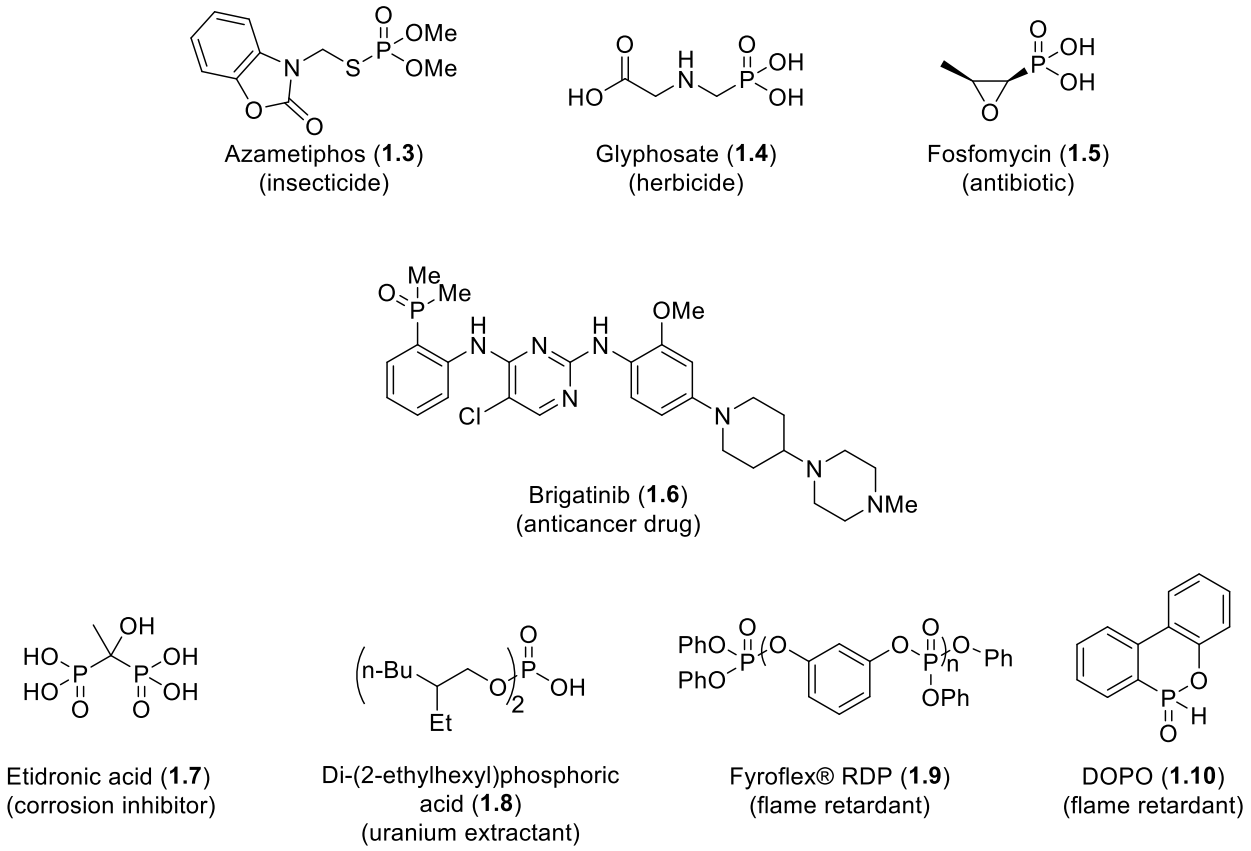


Figure 1.2 Structure of selected industrially relevant organophosphorus compounds

Among all the phosphorus compounds, phosphorus-containing heterocycles (noted *P*-heterocycles), such as DOPO **1.10** are part of a subclass of special importance to organic chemists.

I.2. Benzo-fused phosphorus-containing heterocycles

P-heterocycles are, as their non-cyclic analogs, used in a wide range of applications from organic synthesis to industrially relevant fields such as pharmaceuticals or flame-retardants. For example, acids **1.11** and **1.12** (Figure 1.3) are part of the C_2-symetrical chiral phosphoric acids (CPAs) which have been extensively studied in the last 10 years and are capable of catalyzing a wide range of reactions under mild and environmentally friendly conditions, such as reductive amination, Pictet-Spengler reactions, aza-Diels–Alder addition reactions, cascade reactions, amination

reaction, Friedel-Crafts reactions, N–H insertion reaction and many others.[17] The significance of CPAs in the field of asymmetric catalysis resulted in the 2021 Nobel Prize being awarded to Benjamin List for is work his work on developing powerful asymmetric organo-catalysts, including CPAs.[18] Another *P*-heterocycle relevant to organic synthesis is Lawesson's reagent **1.13**, which is a powerful thionation reagent of C=O and P=O bonds.[19] *P*-heterocycles can also be found in industrially relevant fields. Ifosfamide (**1.14**) is a chemotherapy drug from the nitrogen mustards family and is used in the treatment of a number of types of cancers.[20] Salithion (**1.15**) is a acetycholine esterase inhibitor used as an insecticide.[21] DOPO (**1.10**), presented previously, is an industrially relevant flame-retardant.

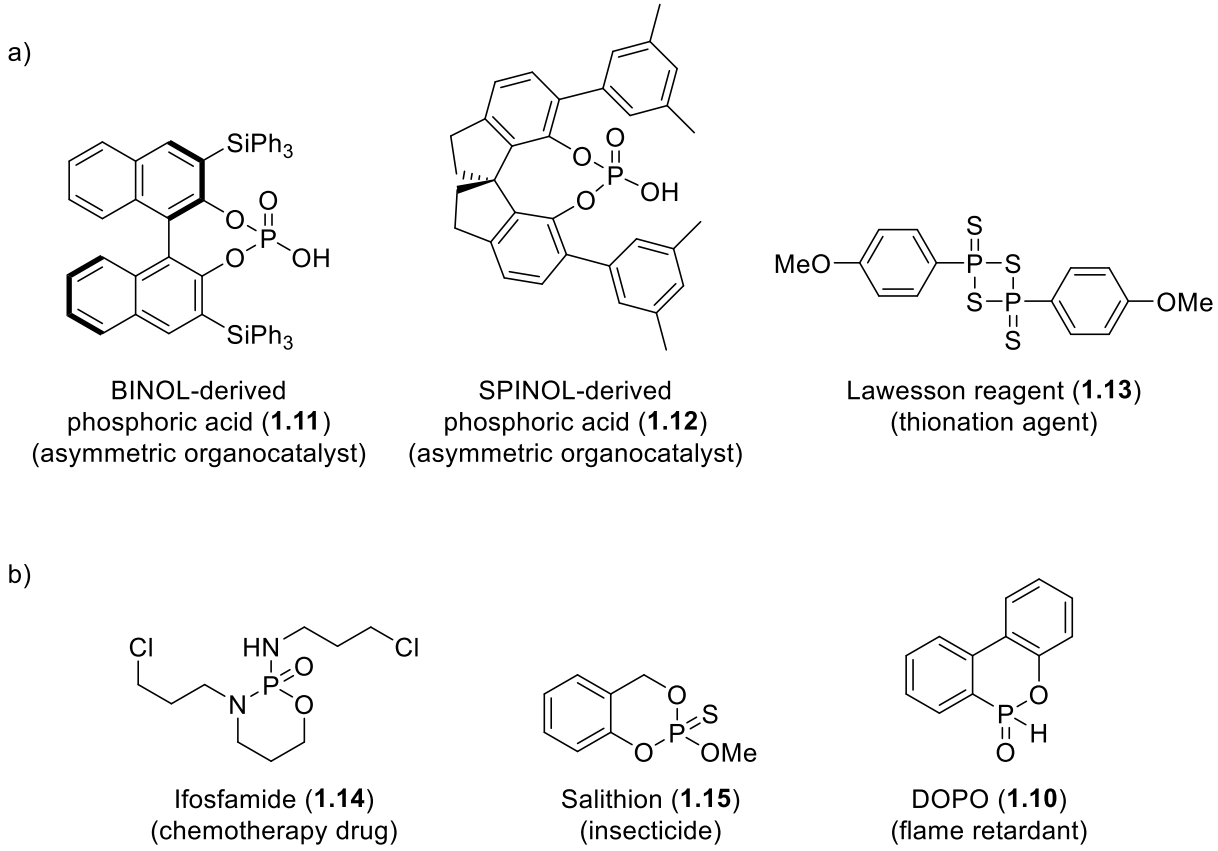


Figure 1.3 Examples of *P*-heterocycles relevant to a) organic synthesis. b) industry

The focus of this thesis is on 5- and 6-membered benzo-fused *P*-heterocycles, *i.e.*, a phenyl ring which is fused with another ring which contains at least one phosphoryl moiety (Figure 1.4). The

other members of the ring can be carbon-, nitrogen- or oxygen-based. Surprisingly, these types of structures have been relatively underexplored.

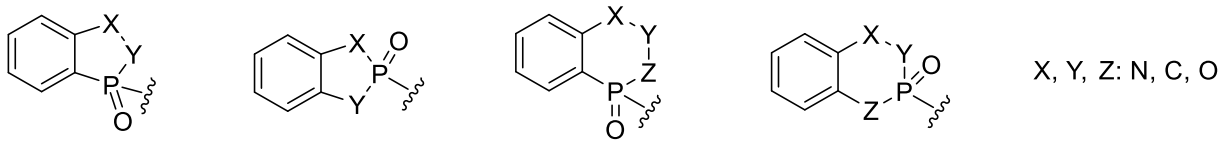
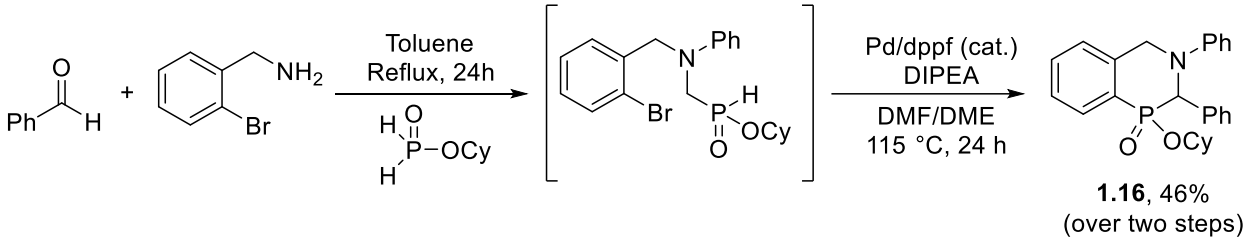


Figure 1.4 General structure of benzofused phosphorus heterocycles of interest to this thesis

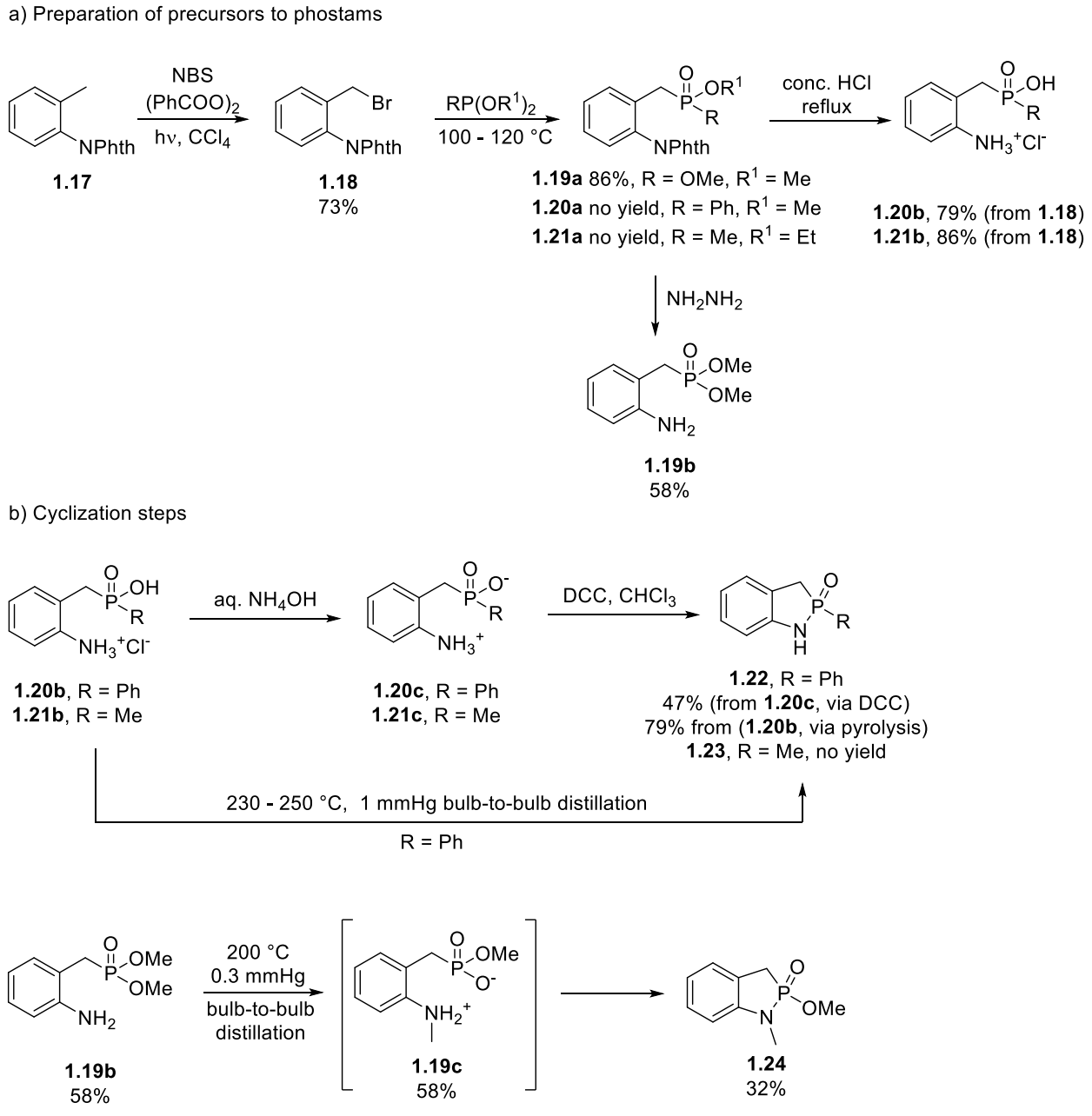
We focused first on *P,N*-heterocycles: phosphorus heterocycles also containing a nitrogen atom in the ring (either distant or adjacent to the phosphorus center). In this category there is only one example reported in the literature for the phosphorus analogue of dihydroisoquinolinones, which are the key pharmacophore of some phosphoinositide 3-kinase inhibitor used in the treatment of some cancers.[22] The synthesis of phosphorus analogue **1.16** was reported by Montchamp *et al*. and synthesized via a tandem Kabachnik-Fields/Hirao coupling (Scheme 1.1).[23]



Scheme 1.1 Synthesis of phosphorus-containing heterocycle **1.16** via a one-pot Kabachnik-Fields/Hirao coupling [23]

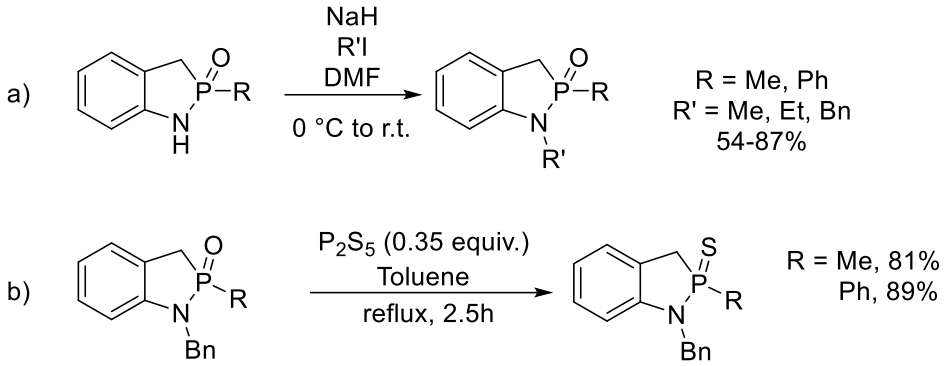
Next our attention turned towards 5- and 6-membered benzo-fused phostams (*P*-heterocycles containing a P(O)N moiety) (Figure 1.). The 6-membered phostams are not known in the literature while several examples of 5-membered phostams can be found in the literature. Collins and coworkers did pioneering work on the synthesis of 5-membered phostams in the early 1980's.[24] They synthesized a series of phostams starting from phthalimide-protected *o*-toluidine **1.17** which was brominated via a radical pathway into benzyl bromide derivative **1.18** in good yield (Scheme

1.2, a). Then, Michaelis-Arbuzov reaction with various phosphites and phosphonites afforded the corresponding phosphonate **1.19a** and phosphinates **1.20a** and **1.21a**. Hydrazonolysis of the phthalimide group of phosphonate **19a** afforded aminophosphonate **1.19b** in good yield. Hydrolysis of phosphinate **1.20a** and **1.21**a under acidic conditions delivered phosphinic acids **1.20b** and **1.21b** in 79% and 86% yields respectively.



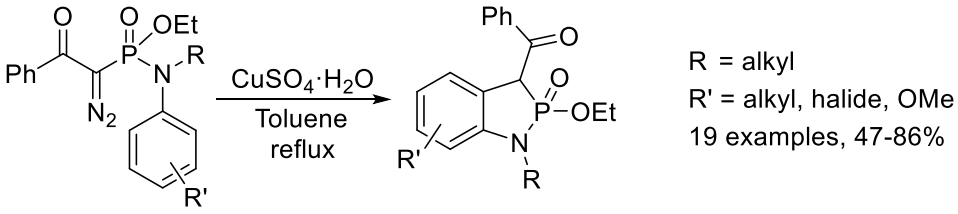
Scheme 1.2 Summary of the work of Collins *et al.* on access to benzophostams (early 1980's) [24]

Collins, Drygala and Swan also performed some derivatization on the obtained phostams, such as N-alkylation of benzophostams **1.22** and **1.23** (Scheme 1.3, a) and some *P*-sulfuration experiments (Scheme 1.3, b)



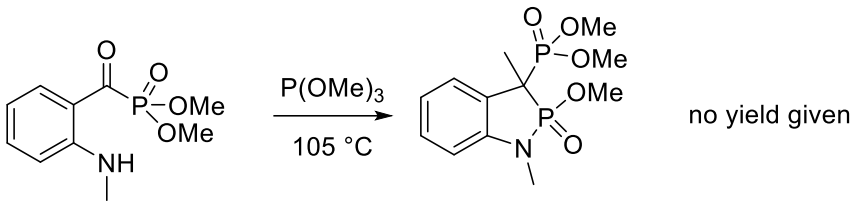
Scheme 1.3 Derivatization of phostams by Collins and coworkers: a) *N*-Alkylation. b) *P*-Sulfuration [24c]

Huan and Xu synthesized a series of α-benzoylated phostams through a copper-catalyzed reaction involving a carbenoid intermediate (Scheme 1.4).[25] The described methodology requires *N*-alkyl compounds and the substituents on the aromatic ring are limited to alkyl groups, methoxy and halogens (F, Cl, Br).



Scheme 1.4 Benzoylated phostams synthesis by Huan and Xu [25]

On a more anecdotal note, Griffiths *et al.* described the synthesis of a α-methyl-α-phophonylated phostam by reacting a benzoylphosphonate with trimethyl phosphite at high temperature (Scheme 1.5).[26]



Scheme 1.5 Griffiths *et al.* synthesis of a phostam [26]

This thesis will present the various methods developed during this Ph.D. project to access novel *P*-heterocyclic scaffolds and to expand the toolbox of strategies to access already known *P*-heterocycles. Beforehand, a new and useful concept to evaluate academic methodologies on a cost aspect, invented in the Montchamp group, will also be discussed and applied.

Chapter II: On the cost of academic methodologies

Research interests in the Montchamp group include the development of *P*-stereogenic compounds as well as *H*-phosphinate chemistry. Thus, chiral phosphoric acids (noted CPAs) and transition metals have always been of interest to our laboratory. We noticed that their cost was extremely high in certain cases; however, this is rarely -if ever- addressed in the literature. On the contrary, it even came to our attention that, sometimes, on the account of novelty or yield improvement, this aspect was completed disregarded. Although improving and discovering catalytic systems and expanding scopes of methodologies is of the utmost importance in academic research, the price of chemicals is also a non-negligible factor that should be considered to evaluate or compare methodologies, particularly if the application range is broad. Indeed, costs of chemicals represent a significant portion of any grant proposal budget. Thus, Montchamp and coworkers decided to tackle this gap in academic methodology and decided to provide the scientific community with tools that would easily allow to compare and evaluate methodologies on a cost basis.[27]

II.1. The cost of chemicals

This journey started in 2018 with the establishment of the concept of cost of chemicals. Of course, this is not properly speaking a new concept; however, all references to the cost of chemicals were made in $/g. From the point of view of organic chemists, it is not the most adequate measurement as the standard measurement of quantity is the mole. Thus, Monchtamp *et al.* decided to use the $/mol as a more appropriate unit of measurement.[27] Moreover using $/g can be very deceptive in some cases where molecular weights can be of great difference. For example, if one were to compare gold(III) chloride ($AuCl_3$) with palladium(II) chloride ($PdCl_2$), it would appear that $AuCl_3$ is 3.5 times more expensive than $PdCl_2$ if one looks at the price per weight (88.4 $/g for $AuCl_3$ versus 25.2 $/g for $PdCl_2$); while in reality, when looking at the price per mole, $AuCl_3$ is actually

6.0 times more expensive than $PdCl_2$ (26,200 $/mol versus 4,470 $/mol). This example is not innocent as we decided to start with the comparison of the price of metals, and especially of transition metals; the reason for that is that many literature accounts in transition metal catalysis are filled with general statement on the price of different approaches being more or less expensive than others without actually providing the proofs or calculations.

II.1.1. The cost of metal chlorides

Comparing metals price became an obvious start in the project of developing a tool to compare methodologies and chemicals on a cost basis. We chose to compare metal chlorides and some metalloid chlorides since metal catalysts that are of value to synthetic methodologies are often prepared from the chloride instead of other salts or metal oxides. In the vast majority of cases, the chloride derivative is the cheapest source of an element. Thus, it would be a good place to start to compare methodologies based on metal catalysis. To do so, the prices of compounds were compiled from all the major US suppliers (Sigma-Aldrich, Fisher Scientific, Acros Organics, Alfa Aesar, TCI, Strem, Oakwood Chemical) and for each compound the lowest price among all suppliers was selected. If both the hydrate and the anhydrous forms were available, the latter was chosen for the study. The results are summarized in the form of a color-coded periodic Table 2.1. The metal and metalloid chlorides were separated into five color-coded cost categories, from very inexpensive (light green) to extremely expensive (red), defined on the basis of the *molar cost of the most readily available chloride compound.* In other words, the chosen cost is for the least expensive oxidation state of a particular element in its chloride form. For example in the case of iron, two oxidation states are available: iron(II) chloride and iron(III) chloride with $FeCl_2$ (201 $/mol) being significantly more expensive than $FeCl_3$ (~1 $/mol). Thus, the reported value is the one of $FeCl_3$. This example illustrates once more the issues with methodologies marketed as

"inexpensive" just because one element can be very cheap in a certain oxidation state even though the actual oxidation state required can be significantly more expensive.

Table 2.1 Cost of the cheapest metal chlorides in their most common oxidation state in $/mol (calculated in 2018) [27]

Very inexpensive < 100 $/mol	Inexpensive 101-300 $/mol	Expensive 301-1,000 $/mol	Very expensive 1,001-10,000 $/mol	Extremely expensive > 10,000 $/mol

H																	He
Li 4	Be 145											B	C	N	O	F	Ne
Na 0	Mg 3											Al 5	Si	P	S	Cl	Ar
K 1	Ca 1	Sc 19,970	Ti 33	V 245	Cr 130	Mn 3	Fe 1	Co 71	Ni 70	Cu 5	Zn 5	Ga 505	Ge	As	Se	Br	Kr
Rb 700	Sr 525	Y 705	Zr 86	Nb 210	Mo 375	Tc	Ru 4,480	Rh 39,300	Pd 4,470	Ag 250	Cd 105	In 395	Sn 10	Sb	Te	I	Xe
Cs 100	Ba 52	La	Hf 595	Ta 1,025	W 610	Re 33,590	Os 19,070	Ir 19,590	Pt 13,780	Au 26,810	Hg 65	Tl 965	Pb 25	Bi 115	Po	At	Rn
Fr	Ra																
		La 690	Ce 120	Pr 1,365	Nd 1,015	Pm	Sm 1,365	Eu 6,510	Gd 1,605	Tb 8,065	Dy 1,280	Ho 2,755	Er 1,220	Tm 17,180	Yb 3.820	Lu 15,980	

It can clearly be seen that some elements including scandium, rhodium, osmium, iridium, platinum and gold are extremely expensive (> 10,000 $, in red) and that a few elements including ruthenium, palladium and indium are in the very expensive category (between 1,000 and 10,000 $/mol). The molar cost of elements correlates mostly to their abundance in the Earth's crust.[28] For example, the most abundant metals are aluminum (8.2% by weight) and iron (5.6% by weight) and they both belong to the very inexpensive category of elements ($AlCl_3$ is recorded at 7 $/mol and $FeCl_3$ at 1 $/mol) while rhodium which is present only at 7.10^{-8} % by weight is the most expensive element reported in Table 2.1 (39,300 $/mol). However, some elements, such as scandium, do not follow this trend. Scandium (19,970 $/mol), which belongs to the extremely expensive category is actually as abundant (0.0022% by weight) than very inexpensive elements such as lithium (0.02% by weight and a molar cost of 4 $/mol) and lead (0.0014% by weight and a molar cost 25 $/mol).

This is due to the difficulty of purification of scandium ores as it is often mixed with other rare earth elements like thorium.[29] Radioactive elements, such as actinides, were not tabulated as their use in organic synthetic methodology is essentially non-existent. Table 2.1 is a useful tool to quickly get an idea of which elements would be economically more interesting to use in a reaction. For example, developing a reaction using $NiCl_2$ (70 $/mol) instead of $PdCl_2$ (4,470 $/mol) would cost 64 times less for the same loading. This can be interpreted in two ways: to be competitive, a reaction developed with $PdCl_2$ in the place of $NiCl_2$ would require: 1) a loading 64 times lower, with the same yield or 2) a yield 64 times higher, with the same loading. However, one has to be careful by using the results shown in Table 2.1 to not fall into the trap of generalities and false claims by affirming that certain catalysts are always cheaper than others just based on the elements it is made of, as it was shown previously in the case of $FeCl_2$ and $FeCl_3$. Another example where general claims made can be very misleading is nickel catalysis. Methodologies using nickel-based catalysts are often labeled as more cost-effective compared to palladium-catalysis. However, bis(1,5-cyclooactadiene)nickel(0) ($Ni(cod)_2$, 7,370 $/mol), which requires a glovebox, is actually two orders of magnitude more expensive than anhydrous nickel(II) chloride (70 $/mol) and 1.3 times more expensive than palladium(II) acetate (5,735 $/mol). Thus, a methodology using $Ni(cod)_2$ in lieu of $Pd(OAc)_2$ is actually going backwards both in terms of cost and practicality.

A first version of the molar cost of transition metals was established by Montchamp in 2009 (Table 2.2).[27] Compared to Table 2.1, the only differences are: 1) VCl_3 moved from the expensive (yellow, 520 $/mol) to inexpensive (dark green, 245 $/mol), 2) $MoCl_5$ was bumped up from inexpensive (dark green, 141 $/mol) to expensive (yellow, 375 $/mol) and 3) $TaCl_5$ was also bumped up from expensive (yellow, 860 $/mol) to very expensive (orange, 1,025 $/mol). This illustrates that,

despite the years passing and the changes in price, the relative molar costs appear to be conserved qualitatively between the elements.

Table 2.2 Cost of the cheapest oxidation state of metal chlorides in $/mol (in 2009) [27]

Sc 14,285	Ti 13	V 520	Cr 120	Mn 8	Fe 2	Co 95	Ni 48	Cu 8	Zn 18
Y 510	Zr 60	Nb 110	Mo 141	Tc	Ru 2,765	Rh 42,360	Pd 4,910	Ag 285	Cd 110
La 520-13,190	Hf 350	Ta 860	W 465	Re 35,185	Os 29,540	Ir 16,005	Pt 21,150	Au 21,720	Hg

Even though metal chlorides prices give a rough idea of which elements are more expensive than others, tabulating their prices does not give an accurate depiction of the actual cost of a catalytic system as in a lot of cases, a ligand has to be added to the metallic center to provide the desired reactivity.

II.1.2. Palladium sources and common ligands

Palladium catalysis is undoubtly one of the most powerful tools in synthetic chemistry, as proven by the 2010 Nobel Prize awarded to Heck, Negishi and Suzuki for their work on palladium-catalyzed reactions in organic synthesis.[30] Thus, we decided to tabulate the price of palladium sources and ligands commonly used in the literature (Table 2.3).

Table 2.3 Molar cost of some common palladium sources and common phosphine ligands

Entry	Compound	MW (g/mol)	Molar cost ($/mol)
1	Pd/C	106.42	9,829
2	$PdCl_2$	177.33	4,470
3	$Pd(OAc)_2$	224.51	5,735
4	$Pd(PPh_3)_4$	1155.56	9,015
5	$PdCl_2(PPh_3)_2$	701.90	5,900
6	Pd_2dba_3	915.72	13,640
7	$Pd(dba)_2$	575.00	12,673
8	$[Pd(allyl)Cl]_2$	365.89	34,338
9	Triphenylphosphine	262.29	9
10	Tri-*t*-butylphosphine	202.32	5,500
11	Dppe	398.42	235
12	Dppp	412.44	404
13	Dppf	554.38	438
14	Xantphos	578.62	984
15	Nixantphos	551.55	26,200
16	rac-BINAP	622.70	3,730
17	(S)- or (R)-BINAP	622.70	35,870
18	(S)- or (R)-SEGPHOS	610.57	41,640
19	*t*-BuDavePhos	341.47	19,465
20	XPhos	476.72	1,406
21	JackiePhos	796.66	240,396

Table 2.3 clearly shows that the cost of palladium catalysts can vary greatly depending on its source. Unsurprisingly, Pd(II) sources are generally a lot less expensive than Pd(0) sources. Palladium acetate (Table 2.3, entry 3), one of the most common and most employed pre-catalyst for palladium(0)-catalyzed reaction, costs 5,735 $/mol while $Pd(PPh_3)_4$ (Table 2.3, entry 4), most common source of active Pd(0) catalysts for cross-couplings and related reactions, is almost twice the cost of $Pd(OAc)_2$ with 9,005 $/mol. Another stable and common source of Pd(0) is Pd_2dba_3 (Table 2.3, entry 6) and, interestingly, its cost is 13,640 $/mol but it actually comes down to 6,820 $/mol per palladium since it contains two Pd atoms. Thus, it is also a more affordable source of Pd(0). On the other end of the "economic" spectra, we can find allylpalladium(II) chloride dimer (Table 2.3, entry 8) which costs a high 34,338 $/mol (17,169 $/mol of Pd). So, depending on which starting compound is employed to generate the palladium catalyst can already greatly influence the price of the reaction. In addition to that, chemists often add a ligand to tune the reactivity of their catalysts. Table 2.3 shows that ligands can clearly add up to the cost of a reaction (Table 2.3, entries 9-21). If triphenylphosphine (Table 2.3, entry 7) can be considered low-cost, it is not a ligand of choice nowadays in most palladium-based methodologies. Some other common bidentate ligands, such as dppp, dppe, dppf and xantphos (Table 2.3, entries 9-12) could be labelled as moderately expensive since they cost less than 1,000 $/mol and would, thus, not be the main economic contributor in a palladium/ligand system, especially if one wants to use a chiral ligand. For example, racemic BINAP (Table 2.3, entry 16) costs 3,730 $/mol but using one or the other enantiomers (Table 2.3, entry 17) brings up the price almost 10 times higher with 35,870 $/mol. Along the same lines, chiral SEGPHOS (Table 2.3, entry 18) is even more expensive with 41,640 $/mol. Enantiopurity of a ligand is not the only way to make its price go up. Indeed, among the achiral Buchwald ligand family, prices can be very high. If XPhos (Table 2.3, entry 20) is only

1,406 $/mol and *t*-BuDavePhos (Table 2.3, entry 19) already costs 19,465 $/mol, JackiePhos (Table 2.3, entry 21) comes down to an extremely high cost of 240,936 $/mol. Thus, one can clearly see that, when choosing a catalytic system for a reaction, the choices of the element, the source of the element as well as the ligands can have a huge impact of the price and that, sometimes, it can even be the ligand that largely contributes to the exceedingly high price of the catalyst. The concept of cost of chemicals can, of course, also be applied to other chemicals than metal catalysts and ligands.

II.1.3. The cost of phosphorus compounds

One major research interest in the Montchamp group is the synthesis of organophosphorus compounds.[31] Thus, we compiled the molar cost of some key compounds in phosphorus chemistry (Table 2.4). Table 2.4 shows that the cost of common building block for organophosphorus chemistry, except anilinium hypophosphite (AHP, Table 2.4, entry 10), diisopropylphosphite (Table 2.4, entry 16), chlorodiphenylphosphine (Table 2.4, entry 18) and diphenylphosphine oxide (Table 2.4, entry 21) are very inexpensive (< 30 $/mol). An interesting point to note is that all these phosphorus building blocks are actually prepared from elemental phosphorus P_4 which cannot be purchased from chemical suppliers. The relatively low molar costs of common phosphorus building blocks illustrate that in organophosphorus methodology, the cost of the reaction is likely to come from the catalyst and/or the ligands involved (if any) rather than from the starting material itself.

Since it is possible to quantify the molar cost of any chemical as long as it is commercially available, Montchamp *et al.* came up with a concept that would allow to quantitatively evaluate a methodology or a synthesis of a specific compound in an economical approach.[27]

Table 2.4 Molecular weight and molar cost of some common phosphorus reagents

Entry	Compound	MW (g/mol)	Molar cost ($/mol)
1	PCl_3	137.33	17
2	PCl_5	208.24	13
3	$POCl_3$	153.33	10
4	P_2O_5	141.94	4
5	H_3PO_4	98.00	0
6	H_3PO_3	82.00	5
7	H_3PO_2	66.00	5
8	$NaH_2PO_2 \cdot H_2O$	105.99	7
9	$NH_4H_2PO_2$	83.03	14
10	AHP	159.12	248
11	$P(OMe)_3$	124.08	8
12	$P(OEt)_3$	166.16	6
13	$P(OPh)_3$	310.29	14
14	$(MeO)_2P(O)H$	110.05	8
15	$(EtO)_2P(O)H$	138.10	12
16	$(i\text{-}PrO)_2P(O)H$	166.16	42
17	$(PhO)_2P(O)H$	234.19	12
18	Ph_2PCl	220.63	79
19	$PhPCl_2$	178.99	26
20	PhP(O)(OH)H	142.09	22
21	$Ph_2P(O)H$	202.20	130

II.2. Cost of academic methodologies (CAM) and aggregate molecular weight (AMW)

To be able to evaluate and compare methodologies on a cost-basis would prove relevant in organic synthesis to choose the best approach to the synthesis of the desired targets. Thus, we introduced a new and user-friendly tool allowing the evaluation of various methodologies.

II.2.1. Definitions

For a given reaction shown in equation 1, the CAM value, shown in equation 2, is defined as the sum of all the molar cost (in $/mol) for the reagents and catalysts multiplied by their number of equivalents and divided by the reaction yield (if known; otherwise it is considered to be 1) where the yield is expressed as a fraction of either isolated yield or conversion. Thus, CAM unit is also $/mol.

$$aA + bB \xrightarrow{cC} P \qquad (1)$$

A = reactants
B = reagents
C = catalysts
a, b, c = number of equivalents
P = product

$$CAM = \frac{\Sigma\ (bB + cC)\ (\$/mol)}{1 \text{ or yield}} \qquad (2)$$

One of the objectives of this new tool was to be as general as possible and also user-friendly. To do so, a few items are not included in CAM calculations:

a) cost of solvents, as it is most of the time negligible (< 1 $/mol). Moreover, in a lot of methodology papers, solvent concentration is not optimized and depends on the scale of the reaction. On very small scale, using a very low concentration might be used more for a

convenience aspect of stirring or of the reaction vessel volume more than a reactivity issue while on larger scales it becomes important to optimized the amount of solvent.

b) cost of isolation or purification because the amount of sorbents, drying and decolorizing agents, washing and/or recrystallization solutions and solvents are not routinely provided in the experimental parts of manuscripts.

c) material hazards and associated additional shipping fees.

d) reaction times, activation methods (heat, electrolysis, light, etc). Although energy consumption is an important factor in the cost estimates, this information is not available in the literature and is dependent of the geographical location and other external factors.

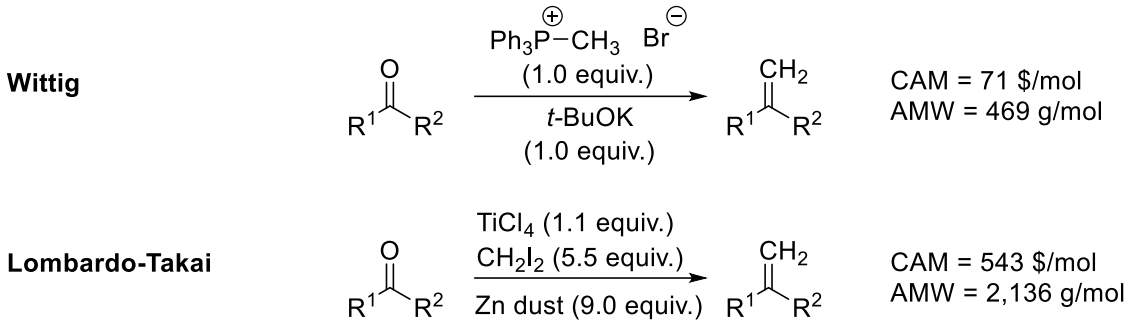
Obviously, the aforementioned list is not comprehensive, and the real cost of a chemical reaction should include cost assessments of all steps, including waste disposal. However, considering that information about waste generation and waste disposal is not provided in literature accounts, there is no meaningful possibility of including them in CAM. Furthermore, personnel cost is also a major part of any operating budget but in view of the focus of this concept (*i.e.* academic methodology) it is reasonable to consider that the adequate infrastructure and personnel are already in place to perform the desired reactions. For these reasons, CAM is restricted to the cost of chemicals required to do research, which is a measurement that can be applied on any publication.

It might be needed to remind the reader that CAM is not an accurate depiction of the exact cost of a methodology but that it is intended to be used as a relative concept, *i.e.*, by using a uniform method of price sampling, one would be able by comparing the CAM values to get an accurate and valid assessment of distinct synthetic methodologies.

To complement the CAM in assessing the efficiency of a methodology, another parameter was introduced: the *Aggregate Molecular Weight* (AMW), which is a green metric. Indeed, the amount of material introduced (reagents, catalysts, additives, etc, expressed as molecular weight in g/mol) that is used to prepare products appears like a valid criterion for the evaluation, comparison and selection of methodologies. Thus, for the same model reaction (equation 1), AMW is defined as the sum of the molecular weights of reagents and catalysts affected by their numbers of equivalents (equation 3).

$$AMW = \Sigma\ [b \times MW(B) + c \times MW(C)] \qquad (3)$$

One strength of this concept is the comparison of seemingly non-comparable methodologies without having to exactly know the structures of the starting materials and/or of the desired products. For example, if one wants to synthesize a library of 1,1-disubstituted olefins for a scope study, one will have to choose between several approaches such as Wittig reaction, Lombardo-Takai olefination, olefin methatesis, Tebbe olefination, etc.[32] Without a doubt, accessibility of starting materials and/or reagents/catalysts, experimental set-ups, prior experience, etc., do play a significant part in selecting an appropriate methodology, yet these parameters are difficult to quantify during this selection and/or evaluation process. CAM allows for a quantitative evaluation of these methodologies which can help selecting the best method on a cost aspect. As an illustration, a comparison was made between two olefination methods: the Wittig olefination[33] and the Lombardo-Takai olefination (Scheme 2.1). After calculating both CAM and AMW, the Wittig method appears a lot more interesting than the Lombardo-Takai.[34] Based on a cost approach, the Wittig olefination is clearly better. Yet, if the starting ketone is enolizable, the Lombardo-Takai might still appear as a better alternative.[34a]



Scheme 2.1 Comparison of two olefination methods using CAM and AMW

In addition to comparing methodologies without having to know the specific structure of the starting materials and/or of the final products, the CAM concept can be used in cases where one wants to make a specific product using different methodologies. Then, it becomes interesting to include the starting material(s) (or reactants) costs in the calculations. In this case, we propose to use CAM*, which, for the model reaction given in equation 1, is defined as the ratio of the sum of the molar cost of reagents, reactants and catalysts affected by their molar equivalents over the yield (equation 4).

$$\text{CAM*} = \frac{\Sigma\ (aA + bB + cC)\ (\$/\text{mol})}{\text{yield}} \qquad (4)$$

Likewise, AMW* can be defined as the sum of the molecular weights of the reactants, reagents and catalysts affected by their molar equivalents (equation 5)

$$\text{AMW*} = \Sigma\ [a \times \text{MW(A)} + b \times \text{MW(B)} + c \times \text{MW(C)}] \qquad (5)$$

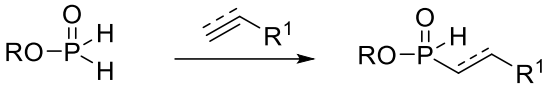
Thus, CAM and AMW were introduced as a two-point criterion in the numerical comparison of various synthetic methodologies, where the smaller values of both would be indicative of the “better" approach. It is important to remember also that CAM and AMW are only some of the several variables that may be considered when choosing a particular methodology, although

consideration of cost alone may be sufficient in some cases. In the rest of this chapter, the CAM value will be illustrated with concrete examples from Montchamp's laboratory.

II.2.2. Synthetic methodologies through the CAM lense

II.2..2.1. Hydrophosphinylation

Hydrophosphinylation, which is defined as the addition of hypophosphorous acid derivatives to carbon-carbon double- and triple-bonds (Scheme 2.2), has been one transformation at the heart of the Montchamp group and has been extensively studied.[31]



Scheme 2.2 General definition of hydrophosphinylation

Hydrophosphinylation of unactivated alkenes can take place according to two pathways: either under free-radical conditions or under transition metal-catalyzed conditions.[35] The cost of several methods has been compiled in Table 2.5. Entries 1, 2 and 3 do not correspond to hydrophosphinylation methods but to the syntheses of hypophosphorous acid derivatives $ROP(O)H_2$ with R = Et (Table 2.5, entry 1) or R = *n*-Bu (Table 2.5, entries 2 and 3) which are used in some hydrophosphinylation reactions. As expected, free-radical methods using sub-stoichiometric quantities of initiator are a lot cheaper than the method using stoichiometric amount (Table 2.5, entries 4 and 5 vs. entry 6).[35b,c] Moreover, using AIBN or triethylborane does not seem to have a huge impact on the price. Palladium-based approaches illustrate the power of transition metal catalysis. Indeed, entries 7 and 8, which have a low but classic loading of 1 mol% do not present a strategic advantage in terms of cost over free-radical methods.[35d,e] However, it was shown that very low loading of catalyst would still allow for the reaction to proceed and, thus, decrease significantly the portion of the cost due to the catalytic system (Table 2.5, entry 11),[35d] and can

even become negligible (Table 2.5, entry 12).[36] Nickel-based methods, at a loading of 3 mol%, are cheaper than free-radical approaches and are comparable in cost with lower loading of palladium (Table 2.5, entry 8 and 9).[35]

Another aspect which shows the broad application of the CAM concept is the case of recyclable catalysts. For example, the hydrophosphinylation reaction can be performed using a polymer-supported catalytic system.[35e] The cost of the Pd/PS-Nixantphos catalyst is approximately 96,200 $/mol leading to the highest CAM value by far (1,230 $/mol for a loading of 1.2 mol% of palladium) for the hydrophosphinylation reaction in the case of one run (Table 2.5, entry 13). However, it was shown that this polymer-supported catalyst could be reused for up to 5 times without loss of activity. This means that if the same resin is used multiple times, the CAM value can significantly decrease as the cost of the catalyst is only to be considered in the first run. Thus, for three runs the CAM value drops to 410 $/mol (Table 2.5, entry 14) and for 5 runs it decreases to 246 $/mol which is a net improvement over the "one run" value but is still more expensive than most of the other approaches.

Overall, hydrophosphinylation methods can be performed for a very low price (< 25$/mol) with nickel or palladium. Moreover, AMW values suggest that the palladium approach would be preferable (Table 2.5, entry 10 vs entry 11). This is mainly due to the fact that palladium-based hydrophosphinylation can be directly performed using H_3PO_2 while the nickel-based approaches require a pre-esterification step of H_3PO_2 to yield $ROP(O)H_2$ which significantly add to the AMW value. In the end, both the AMW and the CAM values point towards the palladium-catalyzed hydrophosphinylation as the method of choice.

Table 2.5 Cost comparison of various conditions for the hydrophosphinylation of alkenes

Entry	Reagents and catalysts	AMW (g/mol)	CAM [a] ($/mol)
1	2 $Me_2Si(OEt)_2$ + H_3PO_2	362.56	27
2	0.66 $Si(OBu)_4$ + H_3PO_2	277.56	73
3	2 *n*-BuOH + H_3PO_2	214.24	7
4	2.5 $EtOP(O)H_2$ + 0.2 AIBN	939.24	108
5	2 $BuOP(O)H_2$ + 0.2 Et_3B	448.08	87
6	2.5 NaH_2PO_2•H_2O + 1 Et_3B	309.98	381
7	2 $EtOP(O)H_2$ + 0.01 Pd_2dba_3 + 0.022 xantphos	747.01	212
8	1.5 H_3PO_2 + 0.01 Pd_2dba_3 + 0.022 xantphos	120.89	166
9	2 $EtOP(O)H_2$ + 0.03 $NiCl_2$ + 0.033 dppe	742.15	64
10	2 $BuOP(O)H_2$ + 0.03 $NiCl_2$ + 0.033 dppe	445.51	24
11	H_3PO_2 + 0.00125 Pd_2dba_3 + 0.00275 xantphos	68.73	25
12	H_3PO_2 + 0.00001 Pd_2dba_3 + 0.00022 xantphos	66.02	5
13	1.5 H_3PO_2 + 0.012 Pd/PS-nixantphos [b]	-	1,230
14	1.5 H_3PO_2 + 0.012 Pd/PS-nixantphos (3 runs) [b]	-	410
15	1.5 H_3PO_2 + 0.012 Pd/PS-nixantphos (5 runs) [b]	-	246

a: cost per mole of synthesized product, rounded to the nearest integer, assuming a yield of 100%. b: Polystyrene-supported Nixantphos, calculated for 0.14 mmol of Nixantphos for 2 mmol of isocyanate.

II.2.1.2. Radical arylation of phosphinylidenes

Another important contribution to the field of organophosphorus chemistry by Montchamp and coworkers is the development of a manganese(II)-catalyzed direct arylation of phosphinylidene compounds (*i.e.*, with a general structure: $R_1R_2P(O)H$).[37] It is an alternative to metal catalyzed cross-coupling. In recent years, both metal-catalyzed "C-H activation" and radical processes have been described to accomplish this transformation.[38] Table 2.6 summarizes the cost of radical-based methodologies for the arylation of phosphinylidene compounds.

Table 2.6 Cost comparison of various conditions for the arylation of phosphinylidene compounds.

Entry	Reagents and catalysts	AMW (g/mol)	CAM [a] ($/mol)
1	3 $AgNO_3$	509.61	507
2	0.1 $AgNO_3$ + 2 $Na_2S_2O_8$	493.19	27
3	3 $Mn(OAc)_3$•2 H_2O	700.26	1,288
4	0.05 $Mn(OAc)_2$ + 0.01 $Co(OAc)_2$	10.42	9
5	0.05 $Mn(OAc)_2$ + 3 MnO_2 + 3 AcONa	515.56	18
6	0.1 $Pd(OAc)_2$ + 1 *p*-benzoquinone + 2 AgOAc + 2 AcONa	628.43	1,334

a: cost per mole of synthesized product, rounded to the nearest integer, assuming a yield of 100%.

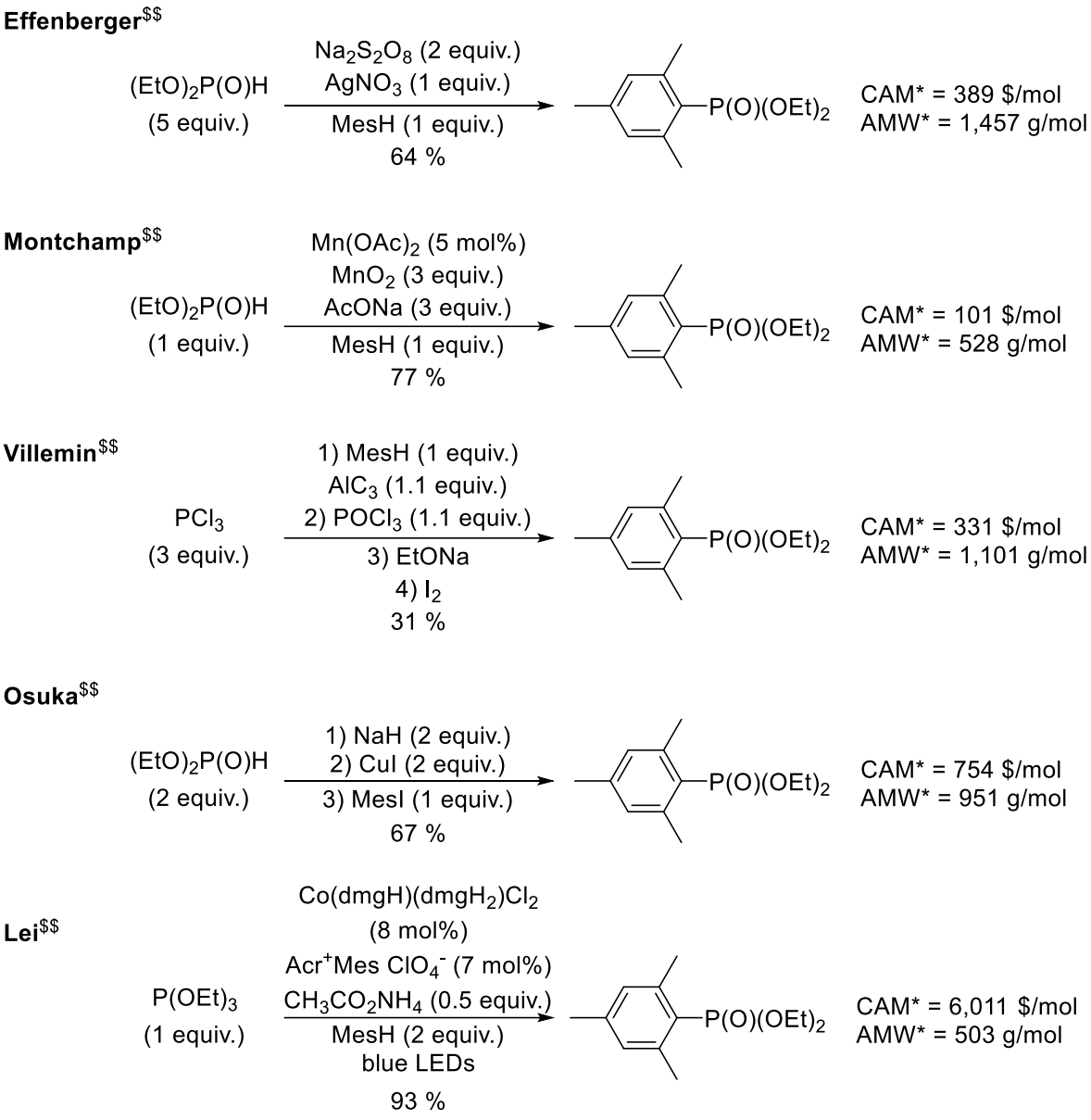
The first example of an intermolecular arylation was reported by Effenberger in 1985 using silver as the phosphorus-centered radical generator either in stoichiometric quantities or in catalytic amount with an excess of sodium persulfate as the stoichiometric reoxidizing agent.[39] Unsurprisingly, the CAM value of the stoichiometric silver reaction (Table 2.6, entry 1) is almost

20 times more expensive than its catalyzed version (Table 2.6, entry 2). Interest in managanese-promoted arylation of phosphinylidenes started in the mid-2000s, especially with the work of Zou and coworkers who contributed greatly to this area.[40] The conditions developed require a stoichiometric quantity of manganese(III) acetate but were a good improvement in terms of yields compared to most silver-based methods. This example illustrates once more the importance of oxidation state of metals when looking at the cost of an element. In table 2.6, manganese appears to be in the "very inexpensive" category while silver is only in the "inexpensive" one (3 $/mol for $MnCl_2$ vs. 250 $/mol for AgCl). However, this is calculated for $MnCl_2$ and not $MnCl_3$ and, indeed, $Mn(OAc)_3$•2 H_2O is actually much more expensive than AgOAc (respectively 643 $/mol vs. 169 $/mol). Thus, Mn(III)-promoted arylation of phosphinylidenes has a CAM value of 1,288 $/mol (Table 2.6, entry 3) which is a lot higher than any silver-promoted or silver-catalyzed arylation. Ishii and coworkers were able to by-pass the use of stoichiometric Mn(III) species by using a Mn(II)/Co(II)/O_2 system which presumably allows for the Mn(II) to be oxidized into the active Mn(III) species.[41] The catalytic system works with 5 mol% of $Mn(OAc)_2$ and 1 mol% of $Co(OAc)_2$. This leads to a CAM value of only 9 $/mol (Table 2.6, entry 4) due to the fact that: 1) the two reactive species are in catalytic quantities and 2) $Mn(OAc)_2$ is one order of magnitude cheaper than $Mn(OAc)_3$•2 H_2O (respectively 66 $/mol vs. 643 $/mol). However, it should be noted that all the yields are based on recovered material and calculated by GC, not isolated. Moreover, the method required a very specific ratio of oxygen/nitrogen of 50/50, which is not practical at all. In 2014, Montchamp and coworkers published a similar but by far more practical approach.[42] They still used $Mn(OAc)_2$ in catalytic quantity but, ingeniously, used MnO_2 as the re-oxidizing agent. This method is very practical and very cheap, with a CAM value of 18 $/mol (Table 2.6, entry 5). Finally, arylation of

phosphinylidenes can also be achieved via Pd-catalyzed C-H activation.[43] However, it does require silver acetate in stoichiometric quantities, leading to the highest CAM value, 1,334 $/mol, among the methods presented (Table 2.6, entry 6).

Except for Ishii's system (Table 2.6, entry 4), all the AMW values are relatively close (between ~500 and ~700 g/mol). Using the CAM concept, manganese(II)- and silver(I)-catalyzed arylation methodologies are all comparable and superior to the other versions.

A comparison of various methods for the preparation of diethyl mesitylphosphonate further proves the utility of CAM* and AMW* for the evaluation of several synthetic methodologies when one wishes to access one specific compound (Scheme 2.3). The classic Effenberger method[39] relies on a stoichiometric quantity of silver (1 equivalent) and a large excess of diethyl phosphite (5 equivalents) giving a CAM* of 389 $/mol and a high AMW* of 1,457 g/mol. In comparison, the Montchamp method, which is also a radical reaction, delivers the product much more efficiently in terms of cost with a CAM* of 101 $/mol as well as an AMW* of 528 g/mol. Villemin's method[44] is based on a Friedel-Crafts type reaction while Osuka's[45] proceeds through a copper coupling. Neither of these methods provide a significant improvement in terms of cost over Effenberger's methods as the CAM* value is similar in the Villemin's case (331 $/mol) and twice higher in Osuka's case. The AMW* are a little lower than Effenberger's but still in the same order of magnitude. Lastly, Lei and coworkers performed the synthesis of diethyl mesitylphosphonate via photoredox catalysis.[46] Despite having a very high yield (93%) and the lowest AMW* (503 g/mol), suggesting this method could be the most efficient, its CAM* is the highest by far (6,011 $/mol). Most of the cost comes from the acridinium catalyst which has a molar cost of 79,493 $/mol. Thus, using 7 mol% still costs 5,600 $/mol.



Scheme 2.3 CAM* and AMW* analysis of various synthesis of diethyl mesitylphosphonate

This example really showcases how powerful the CAM (and CAM*) concept can be for the comparison of drastically different methodologies. Indeed, it allows to evaluate syntheses starting from very different starting material and using a vast array of reactivity. In conclusion, CAM(*) and AMW(*) can be used as a two-criterion metric for the evaluation of seemingly non-comparable methodologies. In general, the best methods will have both low CAM and AMW values. It is important to keep in mind that CAM is aimed for academic synthetic

methodologies and that it does not represent the real cost of a reaction but that it should be used relatively to compare methodologies. It is also important to see that CAM should be used as a complement of other parameters, not as a substitute. As every concept, CAM presents limitations in its use and, thus, it is critical to always think about other aspects (such as practicality, commercial availability, reaction scale, etc.) that cannot be translated into CAM but have a significant impact in choosing a route toward a product.

Chapter III: Strategies towards the synthesis of 5- and 6-membered benzophostams

We noted that benzolactams, in particular the 2-oxindole framework, are encountered in a variety of bioactive products including several alkaloids (Figure 3.1).[47] Likewise, benzofused bicyclic sulfonamides, often referred to as benzosultams, are found in numerous pharmaceuticals as well as agricultural agents (Figure 3.1).[48]

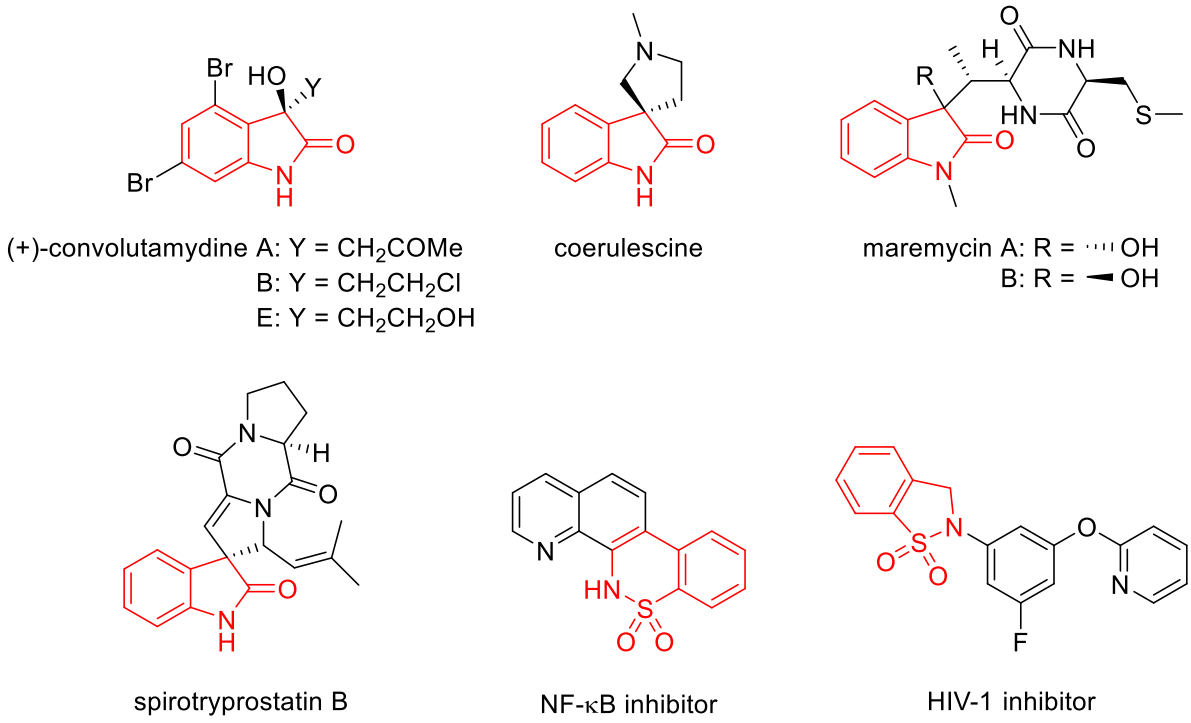


Figure 3.1 Selected examples of biologically relevant benzolactams and benzosultams

Due to the specificities of phosphorus chemistry, phosphorus-containing heterocyclic scaffolds are generally underexplored compared to their carbon analogues. In particular, cyclic phosphonamides seem to have been significantly less investigated than their carboxamide and sulfoxamide analogues. Due to the need to expand the chemical space for the discovery of novel bioactive agents, organophosphorus compounds have received renewed attention.[12a] We assessed 5- and 6-

membered benzophostams as attractive and novelty-rich heterocyclic scaffolds and focused our efforts on compounds represented in Figure 3.2.

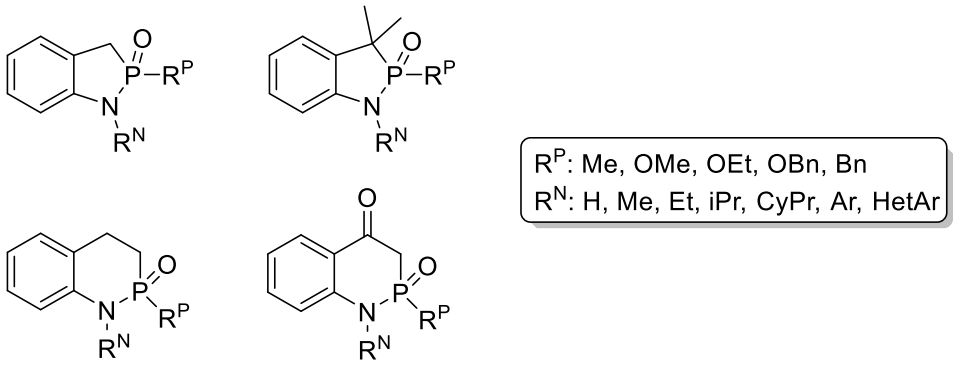
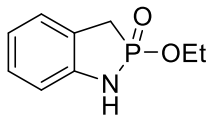


Figure 3.2 General structure of desired phostams

As presented in the introduction, 5- and 6-membered benzophostams are underexplored scaffolds in the literature (see Chapter I). Only a handful of 5-membered phostams have been synthesized by Swan, Drygala and coworkers in the 1980s and 6-membered phostams were still unknown.[24] Thus, on the chemistry part, the goal of this project was two-fold: first, the development of robust, efficient and divergent syntheses towards the target structures and, secondly the study of their functionalization at various positions, mainly at the phosphorus, the nitrogen and the benzylic carbon.

III.1. Synthetic strategies towards phostam **3.1**

The first objective was to establish routes to access the desired benzophostam scaffolds. Phostam **3.1** was chosen as the model target (Figure 3.3). The reason for this is: compound **3.1** was not known at the time, but the structure was close enough to Collins *et al.* work that their research could be used as a starting point. Moreover, we believed that developing routes towards phostam **3.1** would allow access to various other *P*-substituted phostams by small and reasonable modifications of the syntheses.



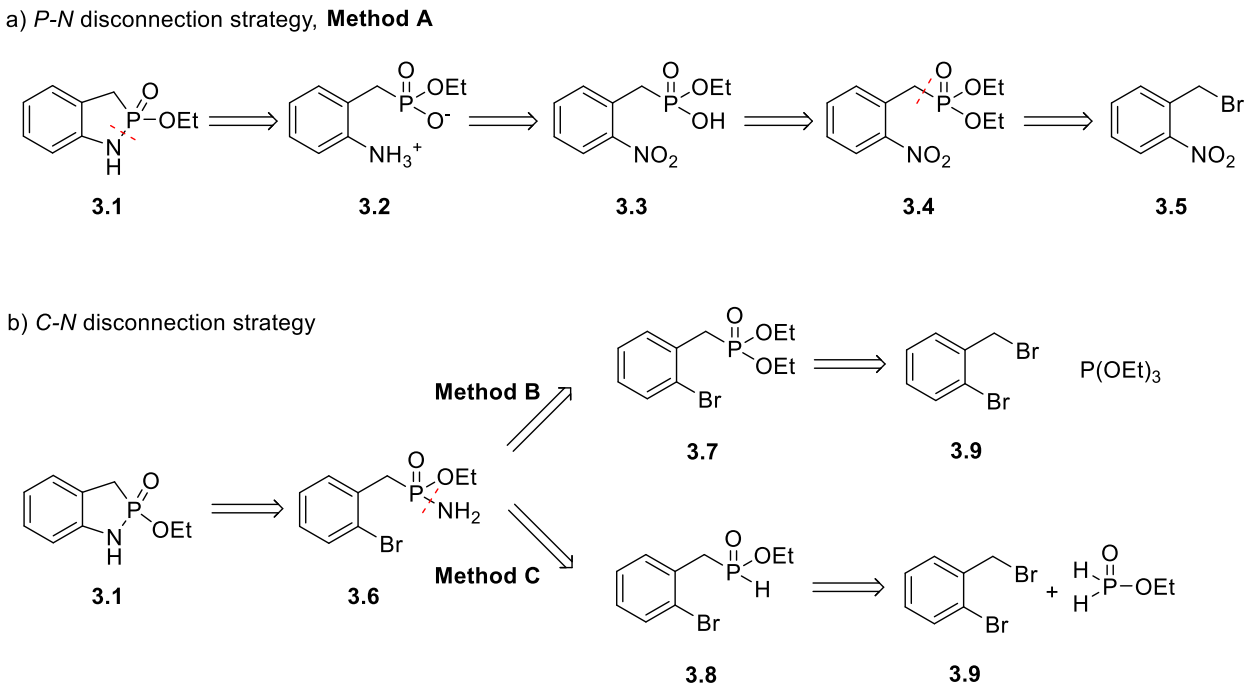
3.1

Figure 3.3 Chosen model benzophostam **3.1**

III.1.1 Retrosynthetic strategies

The retrosynthetic analysis of phostam **3.1** led to two main strategies based on two different strategic disconnection. The first approach, very similar to Collins et al. (see Scheme 3.1),[24] relies on a *P-N* disconnection. Cyclization of **3.2** was anticipated to be performed either via phosphopeptidic-type coupling or via mixed anhydride cyclization based on literature precedents (Scheme 3.1, a).[24] Zwitterion **3.2** would simply be obtained from the reduction of 2-nitrobenzylphosphonate monoester **3.3**, itself prepared from the known diethyl phosphonate **3.4**. Phosphonate **3.4** would be derived from commercially available 2-nitrobenzyl bromide **3.5** by a *P-C* bond formation.

The second strategy is based on a *C-N* disconnection (Scheme 3.1, b). Phostam **3.1** would be obtained via a metal-catalyzed heterocyclization of phosphonamide **3.6**. Preparation of phosphonamide **3.6** could be performed either by a chlorination/amination sequence of diethyl 2-bromobenzylphosphonate **3.7** (method B) or by an Atherton-Todd reaction of *H*-phosphinate **3.8** (method C). Interestingly, both phosphonate **3.7** and *H*-phosphinate **3.8** could be obtained from 2-bromobenzyl bromide **3.9**, respectively by an Arbuzov reaction or by alkylation with an alkyl phosphinate.



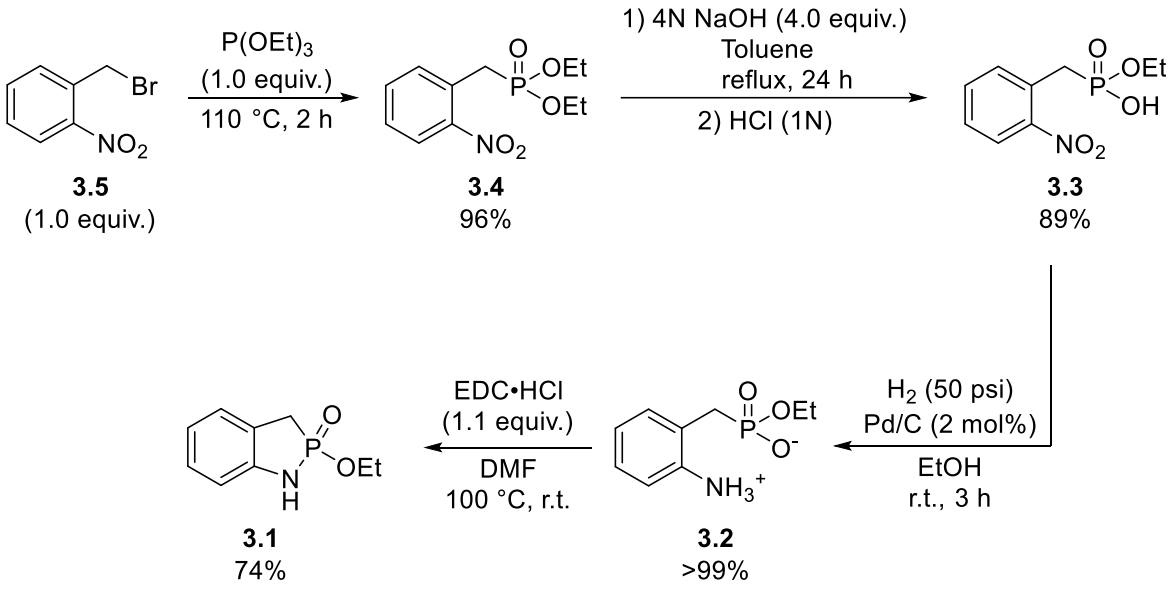
Scheme 3.1 Retrosynthetic strategies for target phostam **3.1**

Thus, a total of three methods were envisioned to access model compound **3.1**. All that was left was to perform the different synthetic routes to evaluate them and, then, use them to synthesize other phostams.

III.1.2. Syntheses of target phostam **3.1**

III.1.2.1. P-N disconnection strategy

The first step is a Michaelis-Arbuzov reaction occurring under equimolar conditions between triethyl phosphite and 2-nitrobenzyl bromide **3.5** at 110 °C to afford phosphonate **3.4** in an excellent yield (Scheme 3.2). The next step consists of the selective cleavage of one ethyl group under standard basic conditions to access acid **3.3** in 89% yield, after treatment with aqueous HCl. Palladium-catalyzed hydrogenation of acid **3.3** delivered zwitterion **3.2** in an essentially quantitative yield. Finally, EDC-promoted cyclization afforded the target phostam **3.1** in a 74% yield in good purity after a simple work-up.



Scheme 3.2 Synthesis of phostam **3.1** through a *P-N* disconnection strategy

Various cyclization conditions to obtain target phostam **3.1** were attempted (Table 3.1). Mixed anhydride formation with PivCl only led to the *N*-acylated product (Table 3.1, entry 1). We, then, turned towards peptidic coupling reagents, which proved a lot more efficient (Table 3.1, entry 2 5). DCC, as in Collins' work, resulted in the formation of the desired phostam (Table 3.1, entry 2). However, other carbodiimides reagents like DIC and EDC afforded the desired product in a better yield (Table 3.1, entries 3 and 4). Finally, EDC**.**HCl in DMF (at 0.1 M) emerged as the ideal coupling agent and delivered pure phostam **3.1** in 74% isolated yield with a simple aqueous work-up (Table 3.1, entry 4). Unsurprisingly, running the reaction at a higher concentration (0.33 M) led to a lower yield, due to competing intermolecular reactions (Table 3.1, entry 5).

Table 3.1 Cyclization attempts of zwitterion **3.2** into phostam **3.1**

Entry	Conditions	Yield of phostam 3.1[a]
1	PivCl, Et_3N, DMF (0.1 M), r.t., 16 h	n.d. [b]
2	DCC, DMF (0.1 M), 100 °C, 10 h	75%
3	DIC, DMF (0.1 M), 100 °C, 8 h	97% (32%) [c]
4	EDC.HCl, DMF (0.1 M), 100 °C, 3 h	97% (74%)
5	EDC.HCl, DMF (0.33M), 100 °C, 3 h	52%

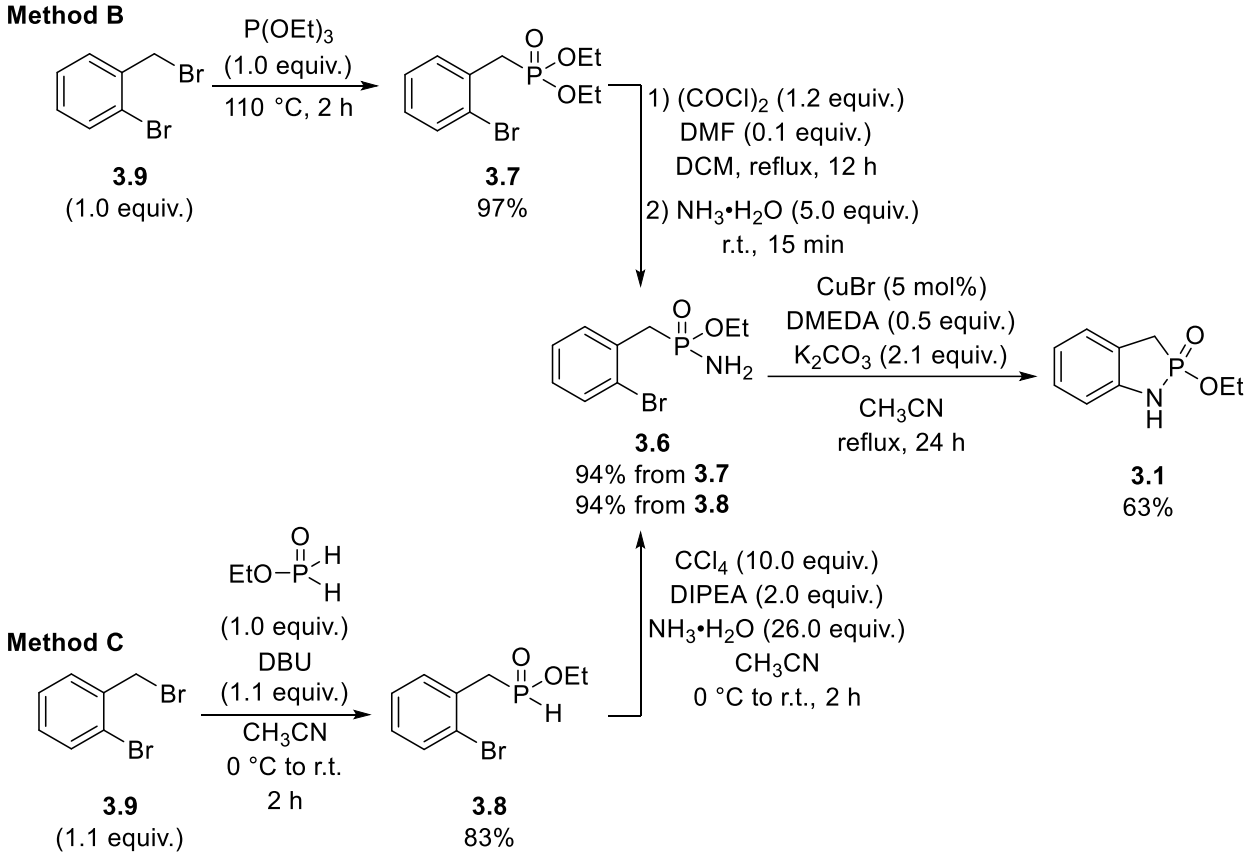
a: Determined by ^{31}P-NMR. The yield of isolated pure product is shown in parentheses. b: Only *N*-pivaloylation was observed. c: Isolated by crystallization.

This synthesis presents several advantages. First, the overall yield is high (63% for 4 steps) and the synthesis does not require any chromatographic purification. Moreover, the synthetic sequence is very robust as we were able to perform the synthesis on a 20-gram scale. Some drawbacks of this approach are: 1) the cost of palladium on carbon, which is high (9,044 $/mol) and 2) the large quantity of DMF (0.1 M) used for the cyclization to prevent any intermolecular reactions. However, the loading of palladium is only 2 mol% and could potentially be decreased further, especially on large scales.

III.1.2.2. C-N disconnection strategy

The *C-N* disconnection strategy relies on the synthesis of the key intermediate phosphonamide **3.6** (Scheme 3.3). The latter could be synthesized in two manners from 2-bromobenzyl bromide **3.9**. The first approach (method B, presented in scheme 3.1) starts with a Michaelis-Arbuzov reaction between 2-bromobenzyl bromide **3.9** and triethyl phosphite to yield phosphonate **3.7** in 97% yield

(Scheme 3.3, a). Then, a one-pot chlorination/amination sequence using oxalyl chloride converted phosphonate **3.7** into key phosphonamide **3.6**.



Scheme 3.3: Syntheses of phostam **3.1** through C-N disconnection strategies. Method B (from scheme 3.1) : "oxalyl chloride pathway". Method C (from scheme 3.1): "Atherton-Todd" pathway

The other synthetic route (method C, presented in scheme 3.1) uses a nucleophilic substitution of 2-bromobenzyl bromide **3.9** with phosphinic ester, based on Montchamp's DBU-promoted alkylation of alkyl phosphinates,[49] to yield *H*-phosphinate **3.8** (Scheme 3.3, b). An Atherton-Todd reaction allowed to convert H-phosphinate **3.8** into compound **3.6**, which was then cyclized under our own copper-catalyzed conditions (See section IV.2.1. for details on how the conditions were developed) to afford the desired target benzophostam **3.1** in a good 63% yield.

Method B and method C were also performed on "large" scales (15 grams for method B and 10 grams for method C) with overall yields of 57% for method B and 49% for method C. Some drawbacks can be outlined: 1) method C can pose safety and/or cost issues associated with the large excess of carbon tetrachloride required for the Atherton-Todd reaction, 2) chromatographic purification is required for each step for method C.

III.1.2.3. Evaluations of the different syntheses

Three different syntheses of model phostam **3.1** were developed using two main strategies: an EDC-promoted coupling for the *P-N* bond formation (method A) and a copper-catalyzed heterocyclization to generate the *C-N* bond (methods B and C). We decided to compare these syntheses in Table 3.2 through various parameters, including CAM* which was presented in Chapter 2.

Table 3.2 Comparison of the methods for the synthesis of phostam **3.1**

Entry	Method	Scale [a]	Number of Steps	Overall Yield of **3.1** [b]	CAM* [c] ($/mol)
1	Method A *P-N* disconnection	25 g (115 mmol)	4	63%	517
2	Method B C-*N* disconnection	15 g (60 mmol)	4	57%	217
3	Method C C-*N* disconnection	10 g (40 mmol)	3	49%	573

a: Amount of starting material. b: isolated yields. c: see Chapter 2 for details on CAM calculations.

All methods could be completed on relatively large multi-gram scales, proving their robustness, and have CAM* values of the same order of magnitude, although method B is about half the cost

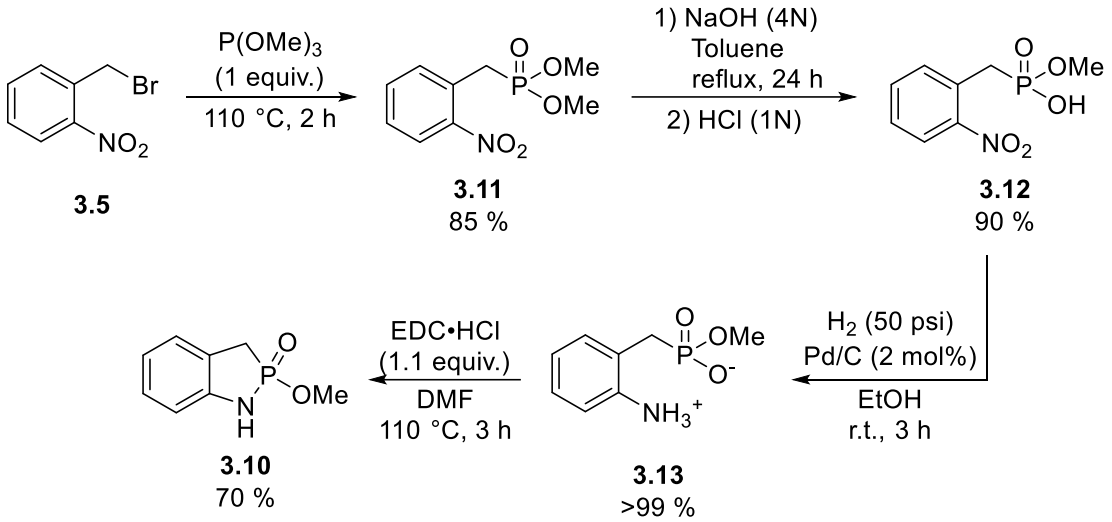
of the other two methods (Table 3.2, entry 2). In method A, the main cost comes from the starting material **3.5** and the palladium catalyst for the hydrogenation, while in method C, most of the cost is associated with the excess carbon tetrachloride. It is worth noting that alternatives to carbon tetrachloride such as *N*-chlorosuccinimide-promoted or catalytic halogenation of *H*-phosphinate **3.8** could be investigated.[50] In terms of overall yield, method A has the highest one, with 63%, closely followed by method B with 57%, both being 4-step long. Method C, despite being the shortest sequence with 3 steps, has a lower overall yield of 49%.

A major advantage of method A (*P*-*N* disconnection) is the fact that the entire sequence does not require any chromatographic purification. Method B ("Oxalyl chloride" pathway) requires only one chromatography for the final product, whereas Method C, although the shortest one, requires chromatographic purification at every step. An advantage of the *C*-*N* disconnection strategies (methods B and C) is that by using primary amines in lieu of ammonium hydroxide would allow for a potentially easy diversification of phostams in terms of nitrogen substitution. Three different strategies were successfully developed, to access model compound **3.1**. To our delight, the synthesis proved to be robust and straightforward. The next step of the project was to implement said syntheses for the obtention other phostams, with as little modification as possible.

III.2. Synthesis of other *P*-substituted phostams

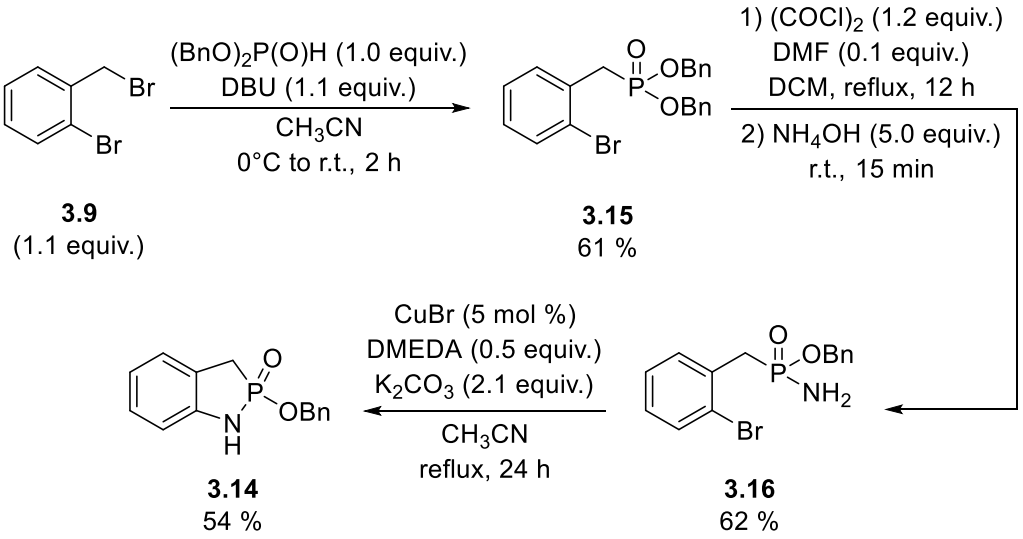
III.2.1. Other 5-membered phostams

P-methoxy phostam **3.10** was smoothly synthesized using method A (Scheme 3.4). To our delight the yields are comparable to the case of phostam **3.1**, with an overall yield of 54% for 4 steps. The main contributor to the lower yield comes from the first step, the Arbuzov-Michaelis reaction, since the by-product, *i.e.*, bromomethane, competes with the benzyl bromide substrate for the substitution step.



Scheme 3.4 Synthesis of phostam **3.10** using method A (*P-N* disconnection, see scheme 3.1)

Next, our effort turned towards benzyl ester **3.14** which was synthesized according to method B (*C-N* disconnection strategy) with a small modification: instead of generating the desired phosphonate **3.15** through a Michaelis-Arbuzov reaction with tribenzylphosphite, Montchamp's DBU-methodology was used with dibenzylphosphite (Scheme 3.5).

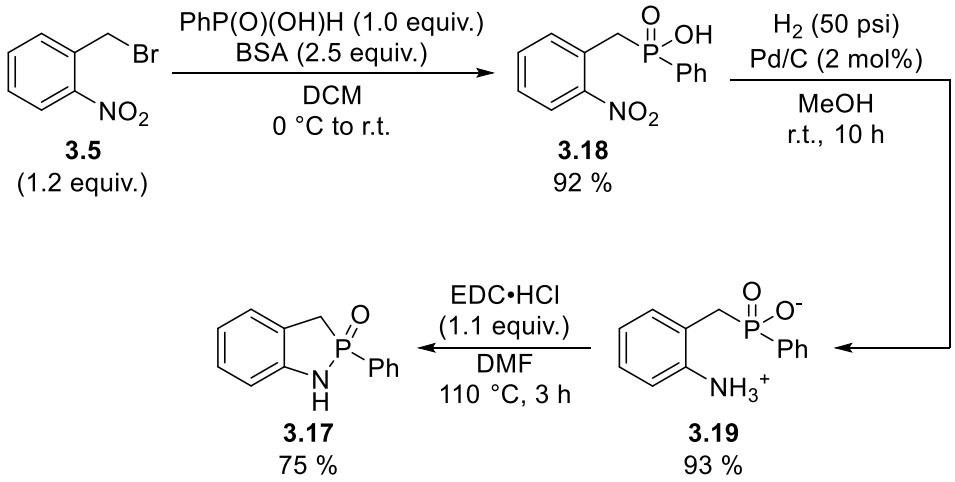


Scheme 3.5 Synthesis of phostam **3.14** via method B (*C-N* disconnection, see Scheme 3.1)

Chlorination/amination of phosphonate **3.15** produced phosphonamide **3.16** in good yield. Interestingly, the yield of this step is lower than in the case of phostam **3.1** due to the exalted

reactivity of the benzylic carbon. Indeed, ^{31}P-NMR monitoring of the reaction showed formation of the phosphonodichloride intermediate (about 21%) which was not observed in the diethyl case. Then, the copper-catalyzed conditions previously developed produced phostam **3.14** in moderate yield, similarly to phostam **3.1**.

Then our attention turned towards *P*-alkyl and *P*-aryl substituted phostams to test the "scope" of our methods. The synthesis of the phenyl-substituted heterocycle **3.17** proceeded uneventfully via a slightly modified method A (*C*-*N* disconnection) using commercially available phenylphosphinic acid (Scheme 3.6). Subjecting phenylphosphinic acid to treatment with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) led to the *in situ* formation of bis(trimethylsilyl)phenylphosphonite $PhP(OTMS)_2$, which reacted with 2-nitrobenzyl bromide **3.5** via a Michaelis-Arbuzov reaction to afford phosphinic acid **3.18** in excellent yield, after subsequent methanolysis. Hydrogenation of acid **3.18** led to zwitterion **3.19** in excellent yield, Then, the EDC-promoted coupling produced the desired *P*-phenyl phostam **3.17** in good yield.

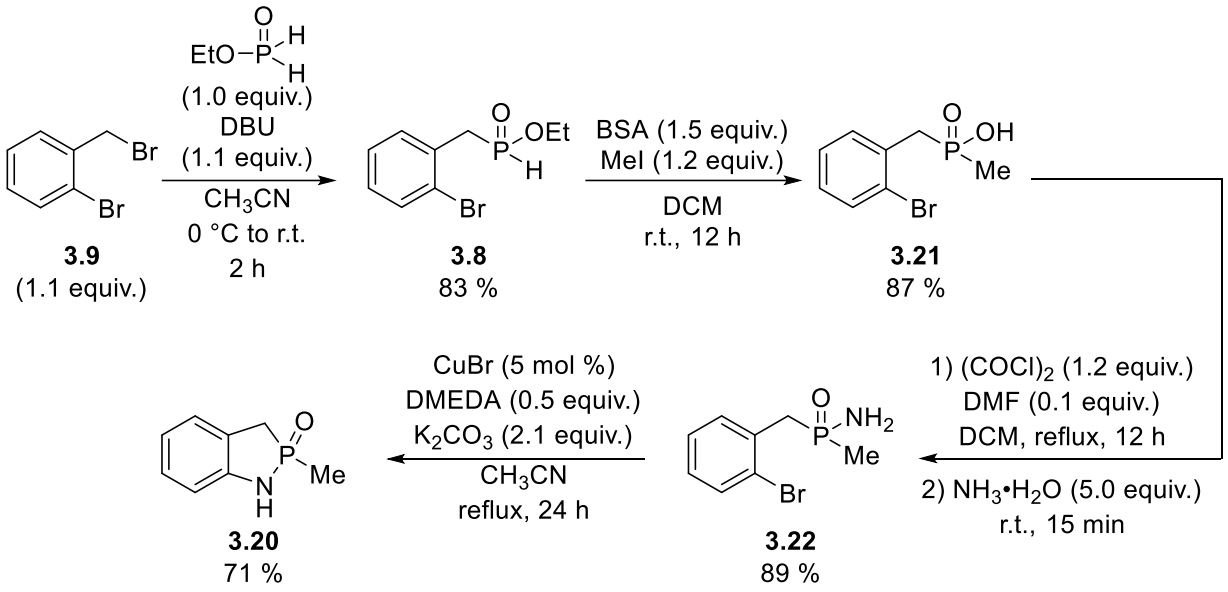


Scheme 3.6 Synthesis of phostam **3.17** via method A (*P*-*N* disconnection, see Scheme 3.1)

Phostam **3.14** was already known and synthesized by Collins *et al.* from a phthalimide derivative and dimethyl phenylphosphonite (see Scheme 1.2, Chapter I) via a similar disconnection. The

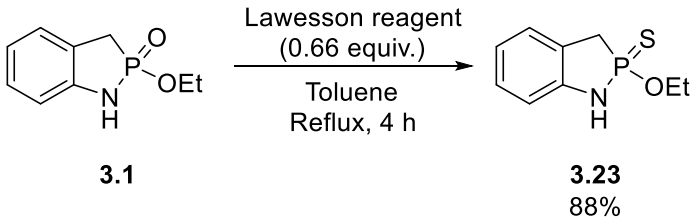
overall reported yield is 56% which is comparable to our synthesis with an overall yield of 64%, but Collins and coworkers used more expensive reagents and high temperatures (> 200 °C).

Finally, *P*-methyl phostam **3.20** was synthesized using a modified version of method B (*C*-*N* disconnection, "oxalyl chloride" pathway). DBU-promoted alkylation of benzylbromide **3.9** gave *H*-phosphinate **3.8** in good yield, which was then reacted via Arbuzov reaction with iodomethane to yield acid **3.21** in excellent yield (Scheme 3.7). The chlorination/amination sequence followed by the copper-catalyzed cross-coupling led to heterocycle **3.20** in good yields.



Scheme 3.7 Synthesis of phostam **3.20** using method B (*C*-*N* disconnection, see Scheme 3.1)

Out of curiosity and since thiophosphorus moieties have a significant place among insecticides,[51] we also decided to attempt the thionation of phostam **3.1**. To our delight, thionation using Lawesson's reagent afforded thiophostam **3.23** in very good yield (Scheme 3.7).[52]

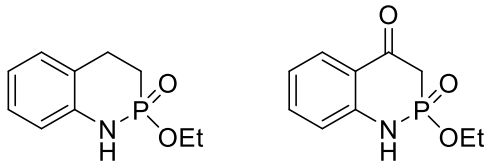


Scheme 3.8 Thionation of phostam **3.1**

After having synthesized several 5-membered *P*-substituted phostams, our focus shifted towards 6-membered phostams (Figure 3.2).

III.2.2. Synthesis of 6-membered phostams

Even though the focus of the phostam project was mainly on 5-membered heterocycles, it was interesting to expand the scope of the study to 6-membered heterocycles, especially since this type of structures is, surprisingly, not described in the literature. Phostam **3.24** and **3.25** were chosen as our 6-membered targets (Figure 3.4).



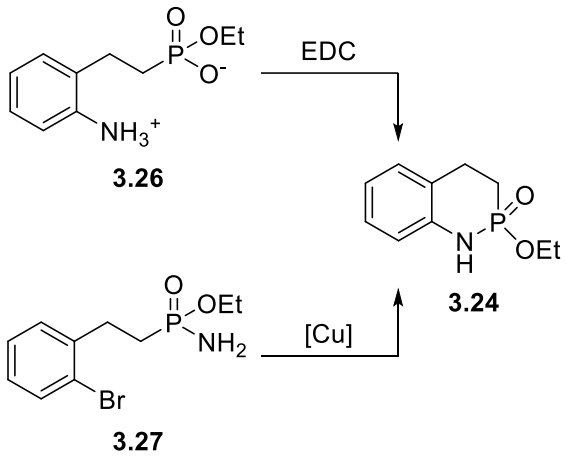
3.24 **3.25**

Figure 3.4 Structure of target phostams **3.24** and **3.25**

Due to similarity between 6-membered phostam **3.24** with 5-membered phostam **3.1**, we decided to focus on its synthesis first.

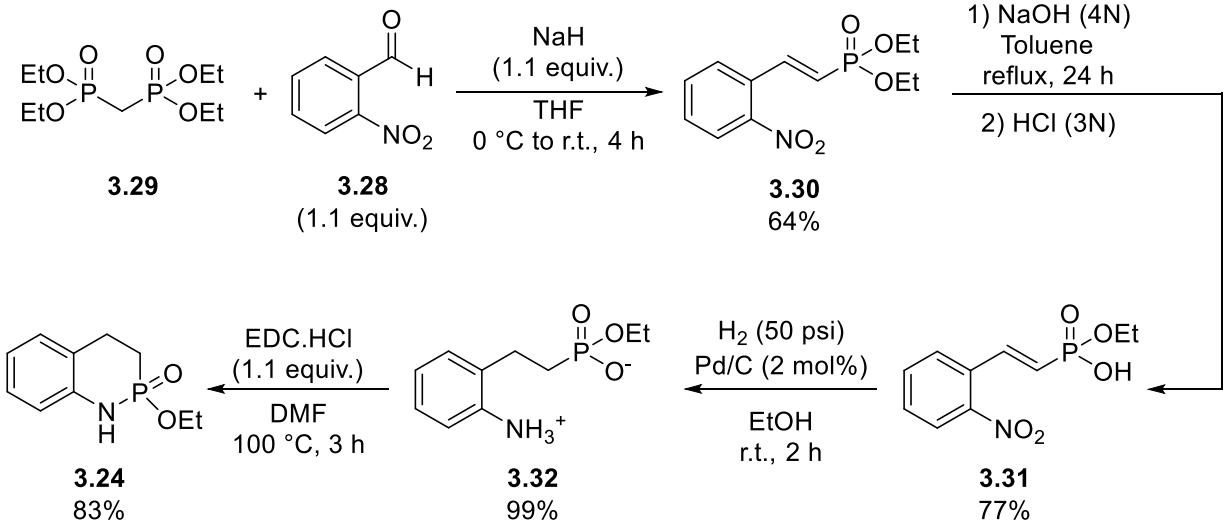
III.2.2.1. Synthesis of phostam **3.24**

Based on our experience from the 5-membered phostam case, two strategies to access heterocycle **3.24** were envisioned: 1) a *P*-*N* bond formation strategy via an EDC-promoted cyclization of zwitterion **3.26** and 2) a *C*-*N* bond formation strategy via our copper-catalyzed cross-coupling of phosphonamide **3.27** (Scheme 3.9).



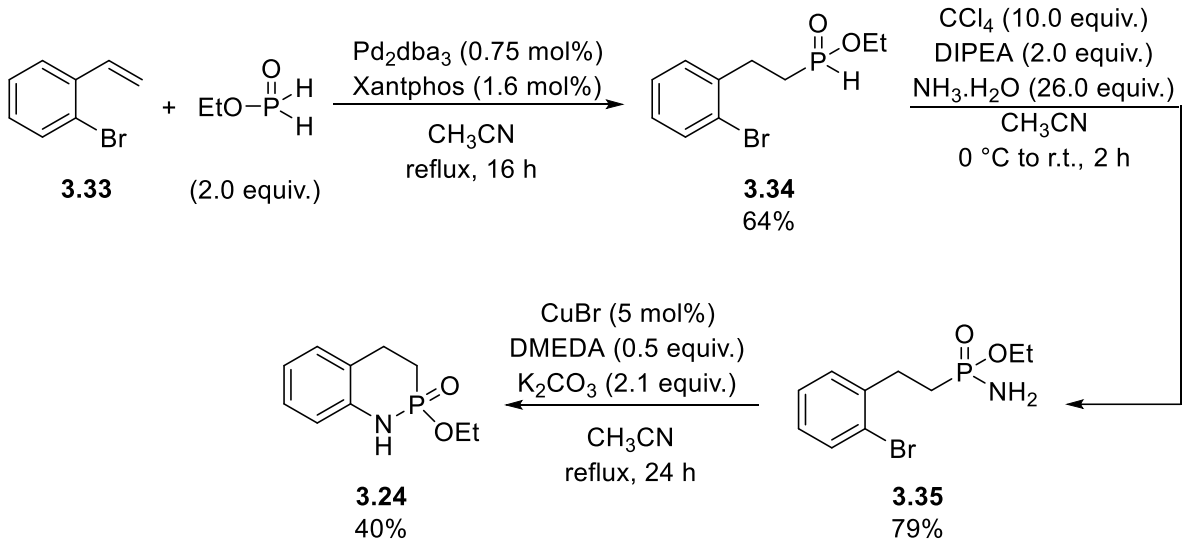
Scheme 3.9 Synthetic strategies towards phostam **3.24**

The first synthesis of phostam **3.24** (via a *P*-*N* disconnection strategy) started via a Wadsworth-Horner-Emmons olefination of 2-nitrobenzaldehyde **3.28** with tetraethyl methylenebisphosphonate **3.29** to give trans-alkenylphosphonate **3.30** uneventfully (Scheme 3.10).[53] The standard monodealkylation conditions used previously then gave phosphonic acid **3.31**. Dual-reduction of the alkene and the nitro group was performed via hydrogenation over palladium on carbon to yield zwitterion **3.32** in quantitative yield. Finally, cyclization promoted by EDC gave phostam **3.24** in excellent yield. The entire 4-step sequence proceeded in 40% overall yield.



Scheme 3.10 Synthesis of phostam **3.24** through *P*-*N* disconnection strategy

The second approach based on the *C-N* disconnection strategy is presented in Scheme 3.11. Montchamp's palladium-catalyzed hydrophosphinylation of 2-bromostyrene **3.33** gave known *H*-phosphinate **3.34**.[54] Then, identical Atherton-Todd conditions as in section III.1.2.2. (Scheme 3.3) gave phosphonamide **3.35**,[50] and finally copper-catalyzed cross-coupling produced **3.24** successfully although in lower yield than in the case of 5-membered phostam **3.1**. Despite being only 3-step long, this synthesis has an overall yield of only 20%. Efforts to improve the overall yield of this strategy could be made by re-optimizing the copper-catalyzed heterocyclization step. However, since the *P-N* strategy presented previously also led to the desired target and since the focus of this project was primarily on 5-membered phostams, this was not investigated further.



Scheme 3.11 Synthesis of phostam **3.24** via a *C-N* disconnection strategy

Table 3.3 allows for a comparison of the two syntheses of phostam **3.24**. Interestingly, even though the overall yield of the *P-N* disconnection strategy is twice higher than the *C-N* disconnection (respectively 40% and 20%), its CAM* value is almost twice higher (respectively 3,707 $/mol and 2,140 $/mol). Most of the cost in the *P-N* disconnection strategy actually comes from with tetraethyl methylenebisphosphonate **3.29** (2,310 $/mol). Moreover, the *C-N* disconnection

presents the advantage that *H*-phosphinate intermediate **3.34** could be converted into other *P*-substitution patterns and the use of primary amine in the Atherton-Todd reaction could give access to *N*-susbtituted 6-membered phostams.

Table 3.3 Comparison of the two synthetic routes towards phostam **3.24**

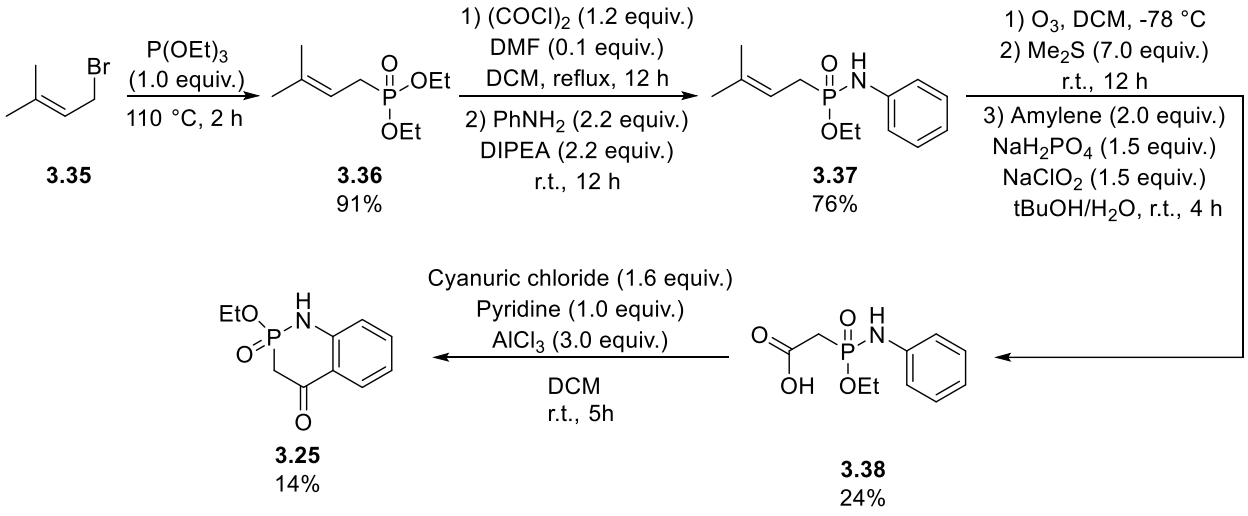
Entry	Method	Number of Steps	Overall Yield of **3.24** [b]	CAM* [c] ($/mol)
1	*P*-*N* disconnection	4	40%	3,707
2	C-*N* disconnection	3	20%	2,540

To our delight, strategies developed in the case of 5-membered phostams were successfully applicable to the synthesis of 6-membered phostam **3.24**.

III.2.2.2. Synthesis of phostam **3.25**

Phostam **3.25** has a slightly different structure from all other phostams presented so far with its extra carbonyl group. It piqued our curiosity as it is a phosphorus analog of quinolinedione. Indeed, quinolinedione-containing structures present interesting pharmacological activities and have been used in the preparation of natural products and related compounds.[55]

Phostam **3.25** was synthesized through a 4-step sequence starting by an Arbuzov reaction between triethyl phosphite and prenyl bromide **3.35** (Scheme 3.12). Phosphonate **3.36** was converted in phosphonamide **3.37** in good yield using a chlorination/amination sequence. Subsequent ozonolysis followed by Pinnick oxidation yielded acid **3.38**,[56] which then underwent a Friedel-Crafts-type cyclization to afford the desired phostam **3.25**.[57] Unfortunately, the last two steps of the sequence gave the desired products in very low yield, which made that strategy unsuitable for the large scale synthesis of **3.25**.



3.35

3.36
91%

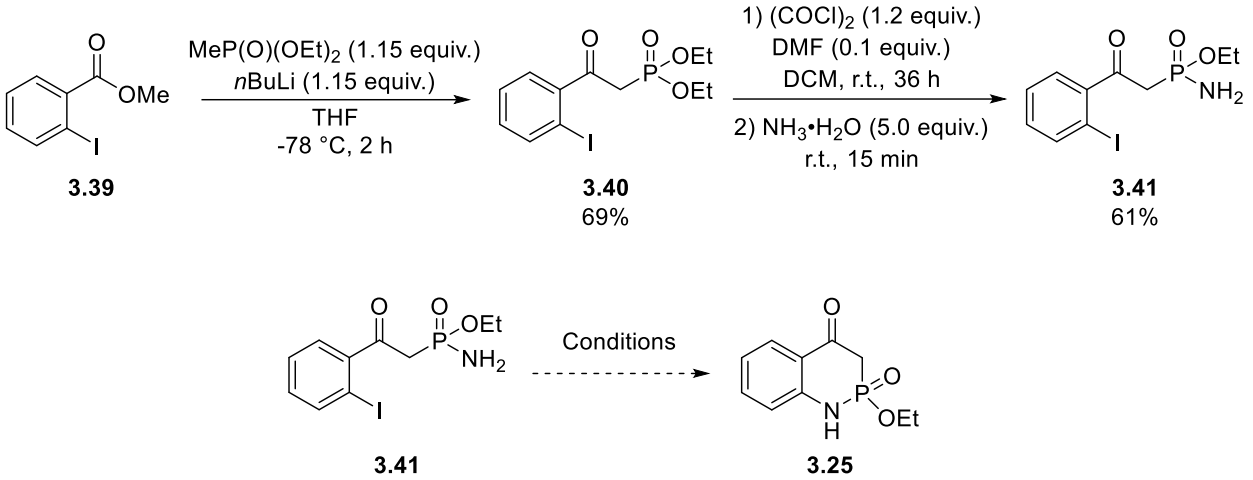
3.37
76%

3.38
24%

3.25
14%

Scheme 3.12 Synthesis of ketophostam **3.25** using a Friedel-Crafts approach (*C*-*C* disconnection)

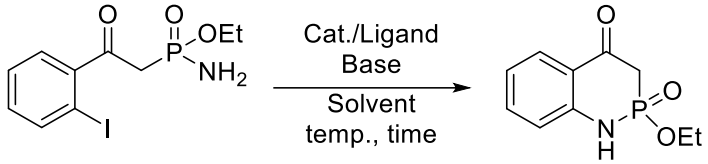
We then turned our effort towards a second approach based on a *C*-*N* disconnection (Scheme 3.13). Starting with the nucleophilic addition of diethyl methylphosphonate to methyl 2-iodobenzoate **3.39**, β-ketophosphonate **3.40** was obtained in a 69% yield.[58] Compound **3.40** was then converted to β-ketophosphonamide **3.41** in a moderate yield via the standard chlorination/amination sequence. At this point all that was left to do was the key cyclization step.



Scheme 3.13 Tentative to synthesize ketophostam **3.25** through a *C-N* disconnection strategy

Unfortunately, the cyclization of **3.24** into phostam **3.25** appeared to be very challenging, but this is not surprising. The acidic methylene protons are likely to be responsible for this failure. Table 3.4 summarizes the different cyclization conditions unsuccessfully performed. Several metal sources were screened as well as different ligands, different bases, etc. Unfortunately, none of these conditions gave a satisfactory result.

Table 3.4 Metal-catalyzed cyclization attempts of compound **3.41** into ketophostam **3.25**



3.41 **3.25**

Entry	Catalyst (equiv.)	Ligand (equiv.)	Base (equiv.)	Solvent	Temp.	Time	Yield (^{31}P NMR)
1	CuBr (10 mol%)	DMEDA (0.5)	K_2CO_3 (2.1)	CH_3CN	reflux	20 h	6% **3.25**
2	CuI (10 mol%)	DMEDA (0.20)	K_3PO_4 (2.0)	CH_3CN	reflux	20 h	n.d.
3	CuI (10 mol%)	DMEDA (0.20)	K_3PO_4 (2.0)	Toluene	reflux	20 h	n.d.
4	CuI (10 mol%)	L1 (0.20)	K_3PO_4 (2.0)	Toluene	reflux	20 h	16% **3.25**
5	CuI (2.0)	-	Cs_2CO_3 (3.0)	Dioxane	reflux	20 h	n.d.
6	CuI (10 mol%)	TMHD (0.20)	K_3PO_4 (2.0)	Dioxane	reflux	20 h	Complex mixture
7	CuI (10 mol%)	TMHD (0.20)	K_3PO_4 (2.0)	CH3CN	reflux	20 h	Complex mixture
8	CuI (10 mol%)	TMHD (0.20)	K_3PO_4 (2.0)	DMSO	reflux	20 h	n.d.
9	$Pd(OAc)_2$ (5 mol%)	Xantphos (10 mol%)	Cs_2CO_3 (1.5)	Dioxane	reflux	20 h	15% **3.25**
10	Pd_2dba_3 (2.5 mol%)	Xantphos (10 mol%)	Cs_2CO_3 (1.5)	Dioxane	reflux	20 h	Complex mixture

a: TMHD: 2,2,6,6-tetramethyl-3,5-heptadione

The effort towards the synthesis of ketophostam **3.25** were stopped at this stage as other parts of the project were deemed to be more relevant and interesting, such as the reactivity of the nitrogen

center and of the benzylic position of already synthesized phostams. For the sake of the discussion, one could imagine circumventing the issues of cyclization of phosphonamide **3.41** either by dialkylating the methylene carbon (which would lead to a dialkylated derivative of ketophostam **3.25**) or by generating the corresponding (E)-enol ether (Figure 3.5).

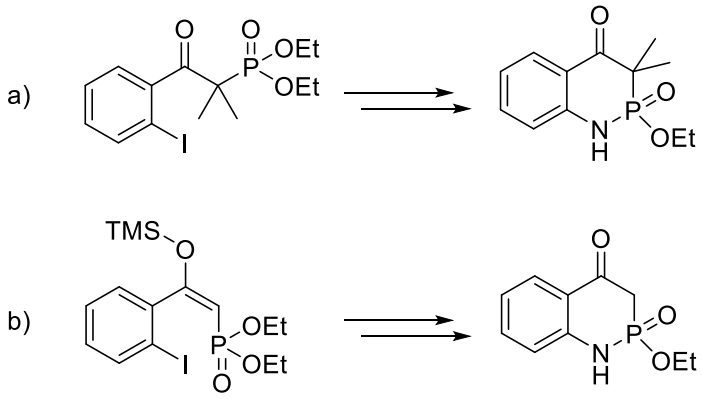
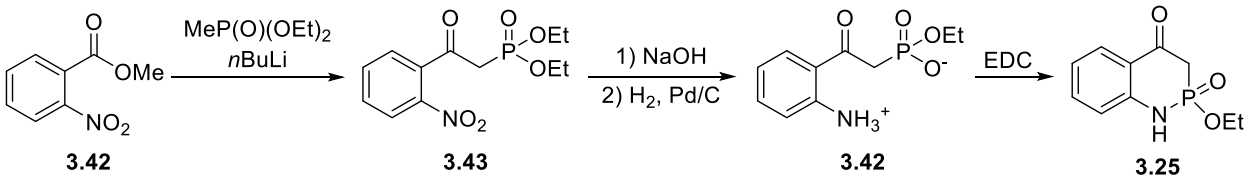


Figure 3.5 Potential derivatization to allow the *C-N* cyclization step. a) Dimethylation of methylene position b) Silyl enol ether formation

In addition to these potential derivatizations, one could envision a synthesis of phostam **3.25** based on a *P-N* disconnection strategy that would rely on the key EDC-promoted cyclization developed in this project (Scheme 3.14). Indeed, nucleophilic addition of diethyl methylphosphonate to 2-nitrobenzaldehyde **3.42** would afford β-ketophosphonate **3.43**, which would afford key zwitterion **3.44** after the hydrolysis-reduction sequence presented previously in this chapter. Finally, EDC-promoted cyclization of compound **3.44** would give the desired β-ketophostam **3.25**. The acidic protons in α of the carbonyl and of the phosphorus would likely not interfere in this strategy.



Scheme 3.14 *P-N* disconnection strategy toward β-ketophostam **3.25**

The syntheses of variously *P*-substituted benzophostams have been presented. In the case of heterocycle **3.1**, three different approaches were compared and contrasted. These approaches could be directly applied to other substitution patterns at the phosphorus atom, allowing for the synthesis of four other 5-membered phostams. Two different syntheses were also developed for the preparation of benzophostam **3.24** as the representative example of a new class of phosphorus heterocycles: 6-membered phostams. The next step of this work is the study of the reactivity of the synthesized benzophostams for the preparation of *N*- and *C*-substituted phostams.

Chapter IV: Preparation of *N*- and *C*-substituted benzophostams

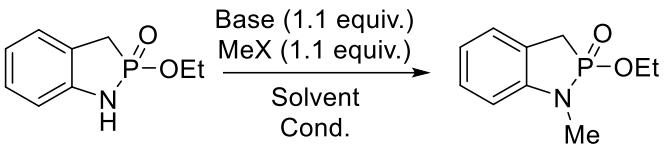
In order to explore potential biological activities of phostams, the logical next step was to expand the chemical space by studying substitution at the nitrogen and benzylic carbon of these compounds. Several methods were evaluated to accomplish these transformations and the results are presented in this chapter.

IV.1. *N*-alkylated phostams

IV.1.1. Direct *N*-alkylation of phostams

First, we decided to start with the *N*-methylation of phostam **3.1**, as we hoped the optimal conditions to methylate the nitrogen would allow for other electrophiles to be reacted with the library of phostams. Table 4.1 summarizes the various conditions tested for the *N*-methylation of phostam **3.1**. LiHMDS (Table 4.1, entry 4) happened to be the perfect middle ground between the very strong bases and the weak bases. The use of strong bases led only to ring-opened products (Table 4.1, entries 1-3 and 5) and the weak bases lead to low conversion and required longer reaction times and/or higher temperature for lower conversions (Table 4.1, entries 6-9). Other methylating agents, such as dimethylsulfate and methyl *p*-toluenesulfonate, were tested but gave significantly lower conversion than iodomethane (Table 4.1, entries 10-11).

Table 4.1 *N*-methylation of phostam **3.1** optimization conditions

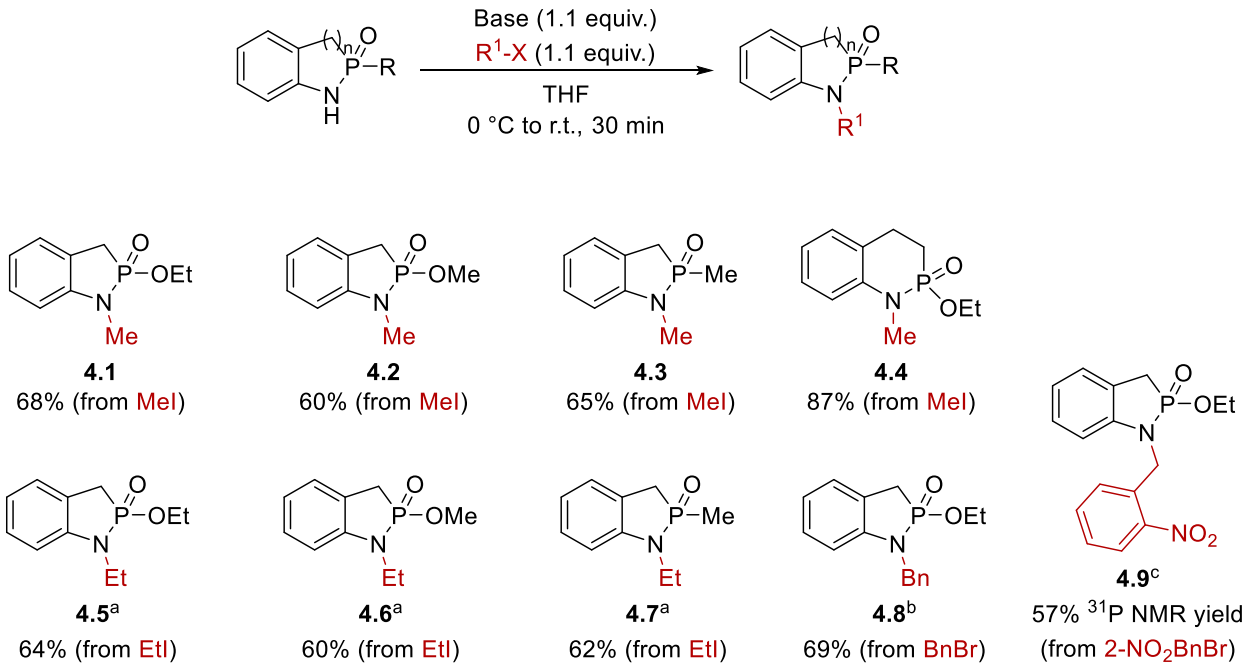


3.1 **4.1**

Entry	MeX	Base	Conditions	Yield of **4.1** [a]
1	MeI	NaH	THF, -78 °C to r.t., 10 min	n.d. [b]
2	MeI	NaH (2.0 equiv.)	THF, 0 °C, 10 min	n.d. [b]
3	MeI	*n*-BuLi	THF, -78 °C, 10 min	n.d. [b]
4	**MeI**	**LiHMDS**	**THF, 0 °C to r.t., 30 min**	**90% (68%)**
5	MeI	*t*-BuOK	THF, 0 °C to r.t., 3 h	n.d. [b]
6	MeI	Pyridine	DMF, r.t., 3 h 120 °C, 3 h	at r.t.: n.d. at 120 °C: n.d.
7	MeI	DBU	DMF, r.t., 3 h 120 °C, 3 h	at r.t.: 9% at 120 °C: 13%
8	MeI	K_2CO_3	DMF, r.t., 3 h 120 °C, 3 h	at r.t.: 14% at 120 °C: 55%
9	MeI	K_2CO_3	DMF, sealed tube 120 °C, 3 h	66%
10	$(MeO)_2SO_2$	K_2CO_3	DMF, sealed tube 120 °C, 3 h	30%
11	*p*-TsOMe	K_2CO_3	DMF, 120 °C, 3 h	17%

a: Determined by ^{31}P-NMR. The yield of isolated pure product is shown in parentheses. b: Only *P-N* bond hydrolysis compounds detected

Once the optimized conditions for *N*-methylation were found, we set out to test them with other synthesized phostams as well as with other electrophiles. Results are presented in Scheme 4.1. *N*-methylation of 5-membered phostams and of 6-membered phostam **3.24** proceeded respectively in good and excellent yields. *N*-ethylation using iodoethane gave yields in the same range for 5-membered rings but required a longer reaction time (6 hours instead of 30 minutes) due to the decrease in reactivity of iodoethane for S_N2 reactions. Finally, we turned our effort towards potentially removable groups. A benzyl and a 2-nitrobenzyl groups were successfully introduced on phostam **3.1** in good yield. Interestingly and to our surprise, other potential protecting groups (PMBCl, AllylBr, BOMCl, Boc_2O, AcCl, $MeSO_2Cl$) were tested but none gave satisfactory results. Unsurprisingly, 2-iodopropane failed to react with phostam **3.1**.



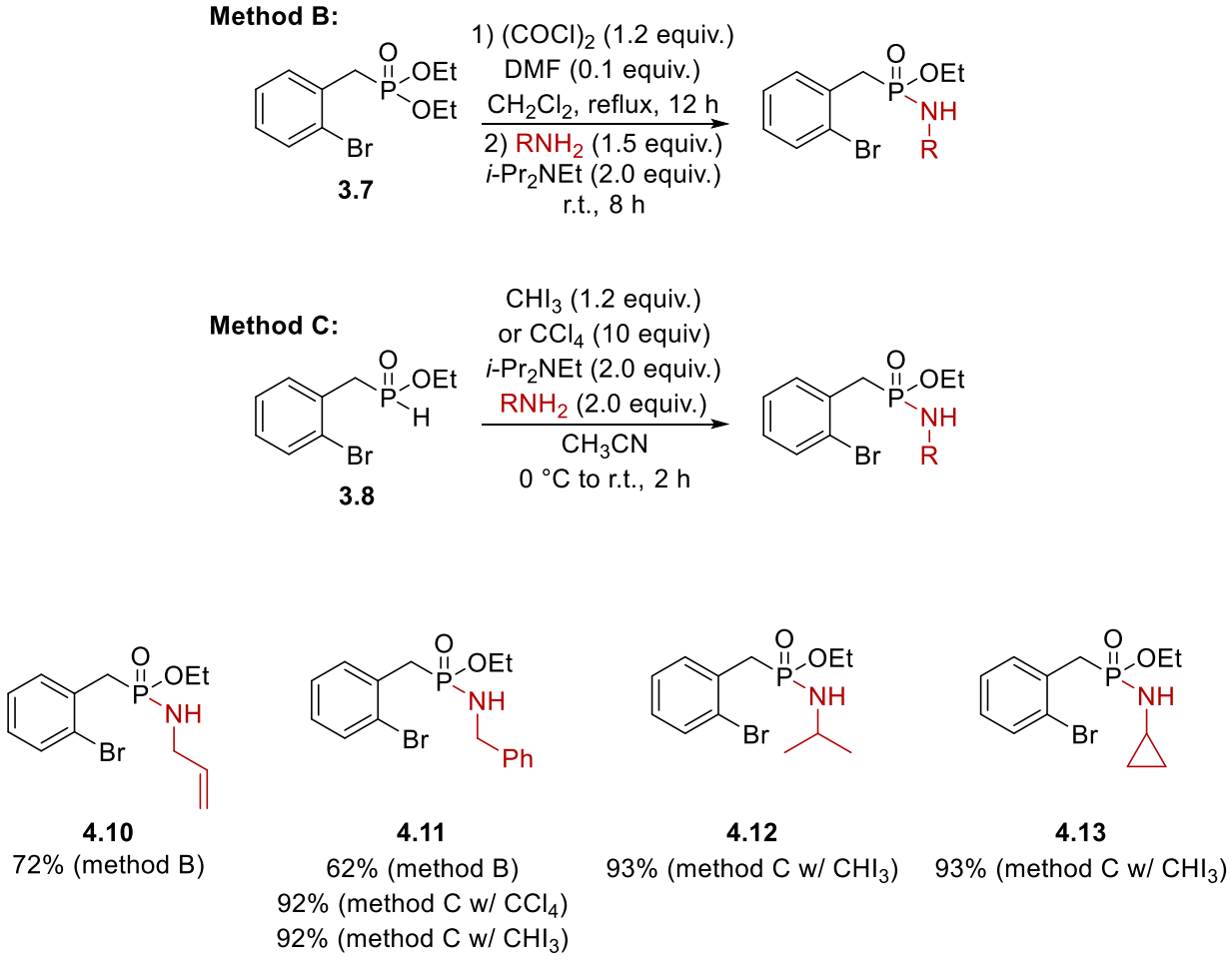
Scheme 4.1 Scope of *N*-alkylation of phostams. Yields are yields of isolated pure product unless otherwise noted. a: reaction time was increased to 6 h. b: reaction was refluxed for 1 h

LiHMDS-promoted direct *N*-alkylation of phostams gave access to several new *N*-substituted phostam in good yields. However, due to the S_N2 reactivity and the propensity of 5-membered

phostams to undergo a *P*-*N* bond lysis, only a handful of primary electrophiles gave good results. We decided to use the strategy previously developed for the synthesis of phostams to gain access to other *N*-substituted phostams.

IV.1.2. Alternative synthesis of *N*-substituted 5-membered phostams

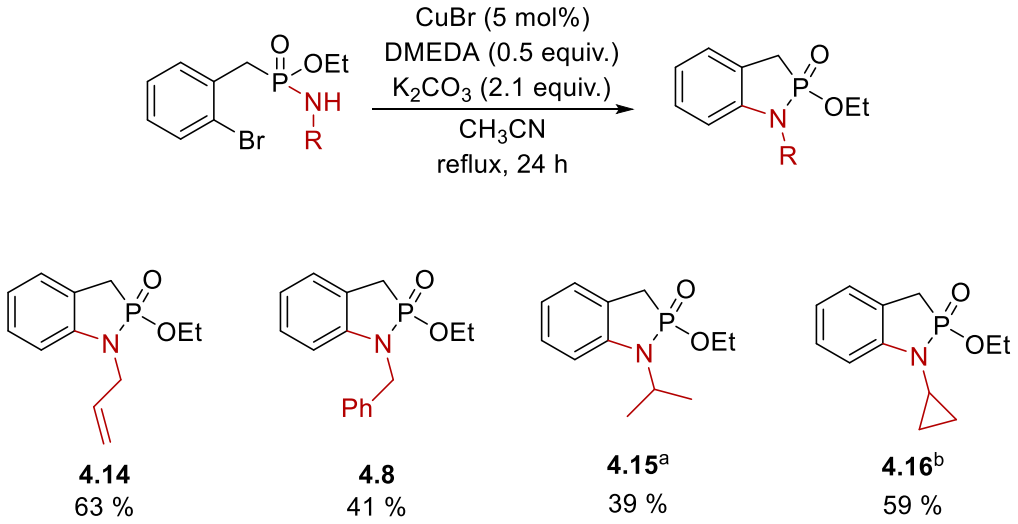
As mentioned in chapter III, a prior to heterocyclization *N*-substitution strategy, by replacing ammonium hydroxide with primary amines in synthetic methods B and C (see scheme 3.1, sections III.1.2.2 and III.1.2.3.), could lead to various *N*-substituted phostams. The required acyclic materials were prepared using method B (phosphonate **3.7** → phosphochloridate → acyclic phosphonamide) or method C (*H*-phosphonate **3.8** → acyclic phosphonamide). Results are summarized in Scheme 4.2.



Scheme 4.2 Syntheses of *N*-substituted phosphonamides prior to heterocyclization

Four acyclic phosphonamides were synthesized in good to excellent yields using either of the two methods. Method C appears to be superior in terms of yield as shown by the example of *N*-benzyl phosphonamide which was synthesized using both methods, as well as the two excellent yields corresponding to *N*-isopropyl and *N*-cyclopropyl phosphonamides **4.12** and **4.13**. To our delight, the introduction of a cyclopropylamine moiety, whose prevalence in pharmaceuticals and agrochemicals has been increasing over the past two decades,[59] worked extremely well. Concerning method C, using carbon tetrachloride or iodoform does not seem to modify the yield of the reaction. Thus, for toxicity and safety reasons, the iodoform alternative is probably the better choice.

The acyclic phosphonamides were then subjected to the copper-catalyzed cross-coupling conditions previously developed to afford the desired *N*-substituted phostams in moderate to good yields (Scheme 4.3). Yields seem to indicate that the transformation is rather sensitive to steric hindrance. Indeed, *N*-allyl phostam **4.14** was obtained with the highest yield of 63% while *N*-benzyl phostam **4.8** was obtained only with a modest 41%. Moreover, *N*-cyclopropyl phostam **4.15** and *N*-cyclopropyl phostam **4.16** required prolonged heating compared to the other two with, respectively, 96 h and 48 h of reflux.



4.14 63 %

4.8 41 %

4.15[a] 39 %

4.16[b] 59 %

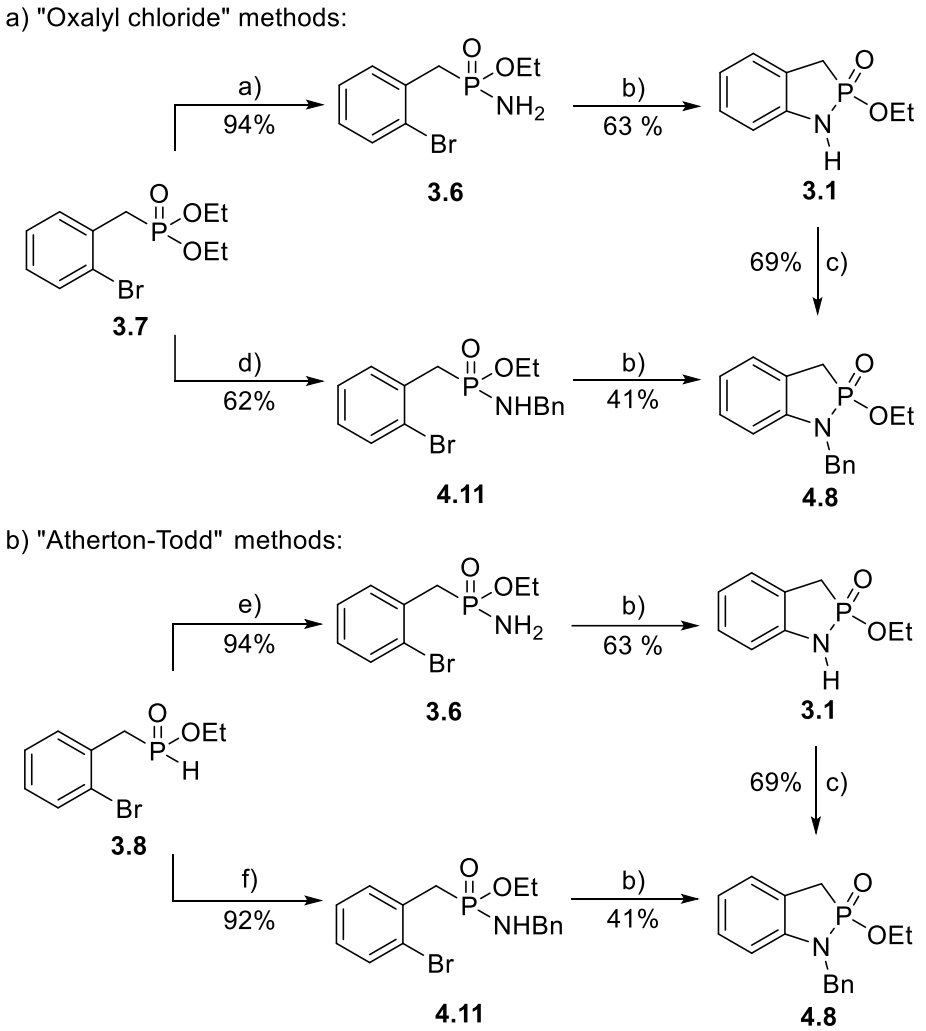
Scheme 4.3 Copper-catalyzed heterocyclization of *N*-substituted phosphonamides. a: 96 h at reflux. b: 48 h at reflux

We were able to synthesize phostams that were otherwise not accessible via direct alkylation, such as *N*-allyl phostam **4.14**, *N*-isopropylphostam **4.15** and biologically relevant *N*-cyclopropyl phostam **4.16**. The case of *N*-benzyl phostam **4.8** allow for a comparison of the different strategies (*i.e.* cyclization first then *N*-alkylation or *N*-derivatization then cyclization).

IV.1.3. Comparison of the different methods to access phostam **4.8**

A total of four different methods have been developed to access *N*-benzyl phostam **4.8** (Scheme 4.4). Both the "oxalyl chloride" strategy (Scheme 4.4, a) the "Atherton-Todd" strategy

(Scheme 4.4, b) can lead to target phostam **4.8** using either the copper-catalyzed cyclization first then *N*-benzylation method or the N-benzylation followed by cyclization.



Scheme 4.4 Various synthesis of phostam **4.8**. a) $(COCl)_2$ (1.2 equiv.), DMF (0.1 equiv.), DCM, reflux, 12 h then NH_4OH (5.0 equiv.), r.t., 15 min. b) CuBr (5 mol %), DMEDA (0.5 equiv.), K_2CO_3 (2.1 equiv.), CH_3CN, reflux, 24 h. c) LiHMDS (1.1 equiv.), BnBr (1.1 equiv.), THF, reflux, 1 h. d) $(COCl)_2$ (1.2 equiv.), DMF (0.1 equiv.), DCM, reflux, 12 h then i-Pr_2NEt (2 equiv.), $BnNH_2$ (2 equiv.), r.t., 15 min. e) CCl_4 (10 equiv.), i-Pr_2NEt (2 equiv.), NH_4OH (26 equiv.) CH_3CN, 0 °C to rt, 2 h. f) CCl_4 (10 equiv.) or CHI_3 (2.0 equiv.), i-Pr_2NEt (2 equiv.), BnNH2 (2 equiv.), CH_3CN, 0 °C to rt, 2 h.

Table 4.2 Comparison of the synthetic routes towards phostam **4.8**

Entry	Method	Number of Steps [a]	Overall Yield of **4.8** [b]	CAM* [c] ($/mol)
1	Oxalyl chloride Cyclization first	4	41%	894
2	Oxalyl chloride Cyclization last	3	25%	312
3	Atherton-Todd Cyclization first	3	41%	1,250
4	Atherton-Todd Cyclization last	2	38%	417 (with CHI_3) 557 (with CCl_4)

a: From phosphonate **3.7** for the oxalyl chloride methods and from *H*-phosphonate **3.8** for the Atherton-Todd methods. b: isolated yields starting from phosphonate **3.7** or *H*-phosphonate **3.8**. c: see Chapter II for details on calculations.

Table 4.2 summarizes the comparison of all four methods. In each case, cyclization-first strategies require one more step than the cyclization-last strategy and "Atherton-Todd" methods are one step shorter than the corresponding "oxalyl chloride" strategies. The overall yields are relatively close in the case of the "oxalyl chloride – cyclization first" (Table 4.2, entry 1) and both "Atherton-Todd" strategies (Table 4.2, entry 3 vs. entry 4), while the "oxalyl chloride – cyclization last" method gave an overall yield of only 25%. Interestingly, when looking at the CAM* values for all strategies, both "cyclization last" methods appear to be the better alternatives (Table 4.2, entries 2 and 4), even the one with only a 25% overall yield. The main reason for the higher cost of "cyclization first" methods come from LiHMDS. Indeed, it was found during this project that the best commercial source was a 1.0 M solution of LiHMDS in toluene, which has a high molar cost of 209 $/mol, in comparison to other classic strong bases. If, "cyclization first" methods allow for

a more divergent synthesis of other phostams, CAM* calculations might indicate that "cyclization last" methods might be more interesting in an economy approach. Moreover, the diversity of commercially available amines makes the "cyclization last" methods even more attractive.

IV.2. *N*-(hetero)arylated phostams

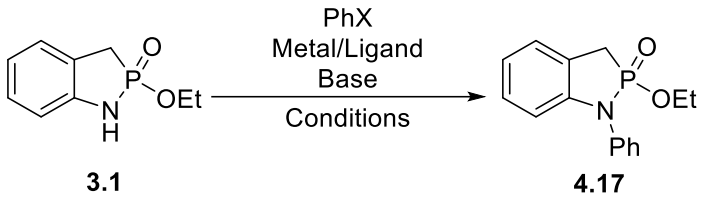
Once accesses to *N*-alkylated phostams had been successfully developed, the next logical step was to study *N*-arylated phostams. Aryl and heteroaryl moieties are of significant importance in pharmaceuticals and agrochemicals.[59] Thus, being able to diversify phostams with (hetero)aryl structures, especially in a "late-stage" fashion would be extra added value to the project.

IV.2.1. Direct *N*-(hetero)arylation of phostams

We decided to focus on the *N*-phenylation of phostam **3.1** as our model reaction. Unlike the *N*-alkylation of phostams, this transformation appeared to be very challenging and required extensive experimentation. Some of the conditions tested are summarized in Table 4.4. First, different Buchwald-Hartwig type conditions were tested without success (Table 4.4, entries 1-5).[60] Different palladium catalysts and ligand systems were tested as well as various halobenzenes. Then, efforts were moved to focus on copper-catalyzed reactions. The *N*-phenylation of compound **3.1** was tried under Chan-Lam conditions using phenylboronic acid but only ring opened byproducts were detected (Table 4.4, entry 6).[61a] Then, we decided to move to Ullmann (or Goldberg) coupling conditions screening various copper(I) sources, ligands, bases and solvents (Table 4.4, entries 7-18),[61b-f] which led ultimately to our own optimal conditions presented in Table 4.4, entry 15, where phostam **4.17** was obtained in a 78% isolated yield using a CuBr/DMEDA catalytic system and iodobenzene as the phenyl source. We noted that increasing the loading of copper catalysts (Table 4.4, entry 18) did not modify the result and that, unfortunately, using less

reactive bromobenzene as the aryl source led to an important decrease in yield (Table 4.4, entry 17).

Table 4.4 *N*-phenylation of phostam **3.1** optimization conditions



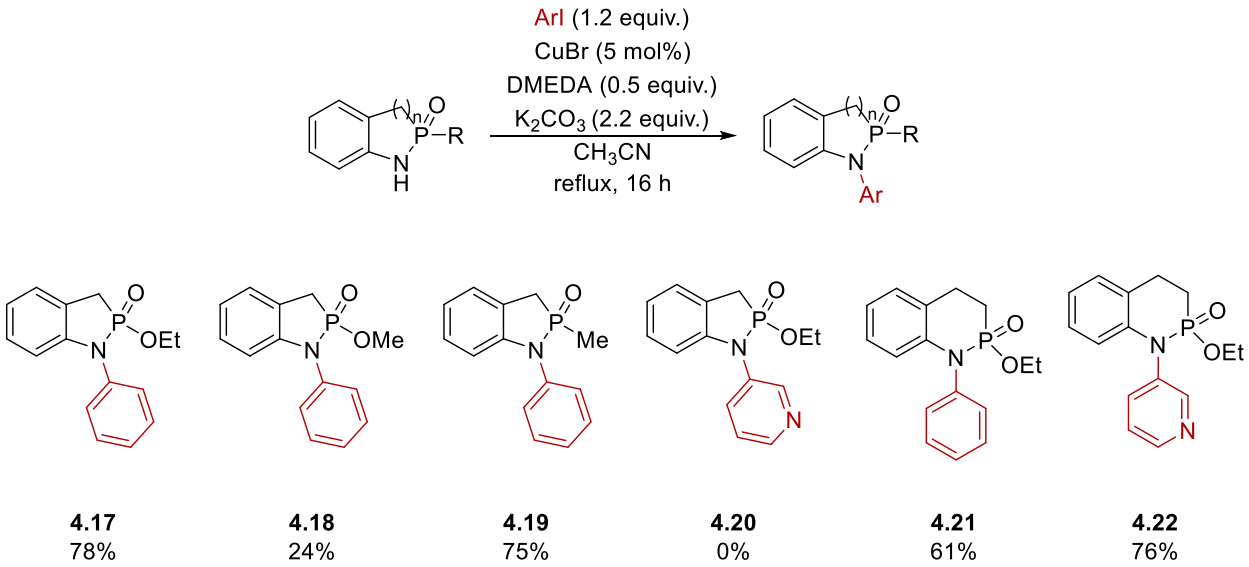
3.1 **4.17**

Entry	PhX (equiv.)	Metal (equiv.)	Ligand (equiv.)	Base (equiv.)	Conditions	Yield [a]
1	PhI (1.0)	$Pd(OAc)_2$ (5 mol%)	dppf (5.5 mol%)	LiHMDS (1.2)	Toluene Reflux, 15h	n.d.[b]
2	PhI (1.0)	$Pd(OAc)_2$ (5 mol%)	dppf (5.5 mol%)	LiHMDS (1.2)	THF Reflux, 15h	n.d.[b]
3	PhI (1.0)	Pd_2dba_3 (2.0 mol%)	DavePhos (4.8 mol%)	LiHMDS (1.1)	THF Reflux, 13h	n.d.[b]
4	PhBr (1.0)	$[Pd(allyl)Cl]_2$ (2 mol%)	tBuXPhos (8 mol%)	K_2CO_3 (2.0)	THF Reflux, 10h	8%
5	PhBr (1.0)	$[Pd(allyl)Cl]_2$ (2 mol%)	tBuXPhos (8 mol%)	LiHMDS (2.0)	THF Reflux, 10h	n.d.[a]
6	$PhB(OH)_2$ (1.2)	$Cu(OAc)_2$ (2.0)	-	Cs_2CO_3 (2.0)	Toluene Reflux, 10 h	n.d. [a]
7	PhI (1.2)	CuI (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (3.0)	CH_3CN Reflux, 16h	40% (26%)
8	PhBr (1.2)	CuI (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (3.0)	CH_3CN Reflux, 16h	28%
9	PhI (1.2)	CuI (5 mol%)	DMCDA (0.5) [c]	K_2CO_3 (3.0)	CH_3CN Reflux, 16h	22%
10	PhI (1.2)	CuI (5 mol%)	Proline (0.5)	K_2CO_3 (3.0)	CH_3CN	4%

					Reflux, 16h	
11	PhI (1.2)	CuI (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (2.2)	CH_3CN Reflux, 16h	40%
12	PhI (1.2)	CuI (5 mol%)	DMEDA (0.5) [d]	Cs_2CO_3 (3.0)	CH_3CN Reflux, 16h	n.d.[b]
13	PhI (1.2)	CuBr (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (3.0)	CH_3CN Reflux, 16h	50% (45%)
14	PhI (1.2)	CuCl (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (3.0)	CH_3CN Reflux, 16h	41%
15	**PhI (1.2)**	**CuBr (5 mol%)**	**DMEDA (0.2)** [d]	**K_2CO_3 (2.2)**	**CH_3CN Reflux, 16h**	**81% (78%)**
16	PhI (1.2)	CuBr (5 mol%)	DMEDA (0.5) [d]	K_3PO_4 (3.0)	CH_3CN Reflux, 16h	74% (70%)
17	PhBr (1.2)	CuBr (5 mol%)	DMEDA (0.5) [d]	K_2CO_3 (2.2)	CH_3CN Reflux, 16h	34%
18	PhI(1.2)	CuBr (10 mol%)	DMEDA (0.5) [d]	K_2CO_3 (2.2)	CH_3CN Reflux, 16h	75% (63%)

a: Yield of phostam **4.17** determined by ^{31}P-NMR. The yield of isolated pure product is shown in parentheses. b: Only *P-N* bond hydrolysis compounds detected. c: DMCDA: *N,N'*-dimethylcyclohexyldiamine. d: DMEDA: *N,N'*-dimethylethylenediamine

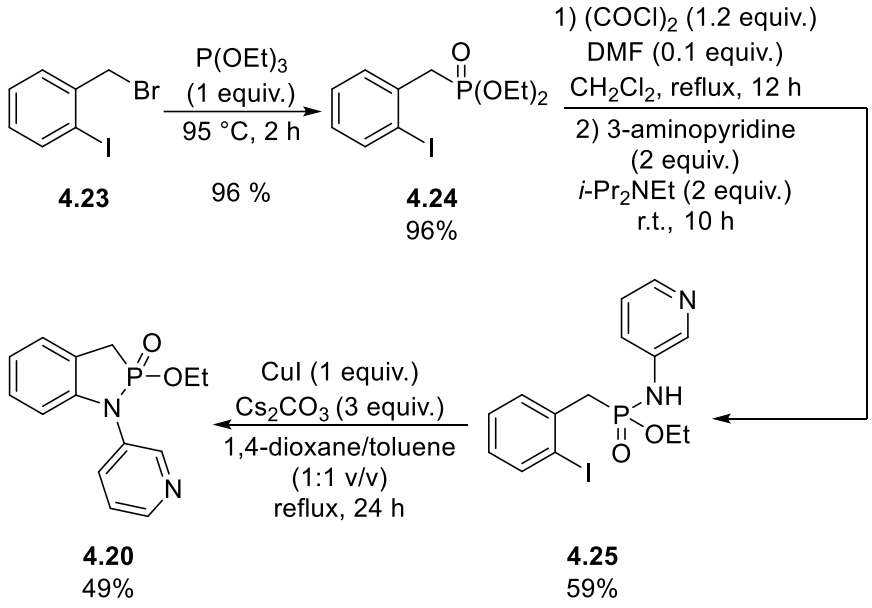
These conditions were subsequently tested with other phostams and other electrophiles (Scheme 4.5). The *N*-phenylation reaction proceeded well (in the 60-80% range) for 5- and 6-membered phostams. The only exception is phostam **4.18** which was obtained with a low yield of 24%. The ease of hydrolysis and dealkylation of the methoxy group compared to the ethoxy group might be one of the reasons for this low yield. We decided to see if these conditions could be extended to *N*-heteroarylation, and especially to *N*-3-pyridyl phostams. If the reaction, worked in good yield in the case of the 6-membered phostam **4.22**, it was not the case of phostam **4.20**. At this point, more experimentation for the *N*-pyridylation of phostam **3.1** was performed in order to solve this issue, but to no avail. Thus, another strategy was explored in which the pyridine moiety would be installed pre-cyclization.



Scheme 4.5 Copper-catalyzed *N*-arylation of various phostams

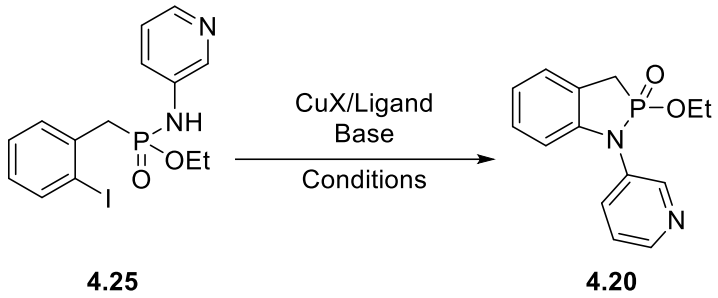
IV.2.2. Alternative synthesis of *N*-pyridyl phostam **4.20**

The alternative synthesis started with an Arbuzov reaction between triethyl phosphite and 2-iodobenzyl bromide **4.23**. Conversion of the resulting phosphonate **4.24** into the phosphonochloridate and amidation in one-pot produced phosphonamide **4.25** in moderate yield. After some experimentation (Table 4.5), **4.25** could finally be cyclized into the desired *N*-aryl-substituted phostam **4.20**, using a stoichiometric amount of copper(I) (Table 4.5, entry 5). Here too, the conditions that were previously used for cyclization (Table 4.5, entry 1) failed completely. It is unclear why this might be the case when 6-membered heterocycle **4.22** was obtained in good yield (Scheme 4.5).



Scheme 4.6 Synthesis of *N*-pyridyl phostam **4.20**

Table 4.5 Cyclization optimization of compound **4.25** to phostam **4.20**



4.25 **4.20**

Entry	CuX (equiv.)	Ligand (equiv.)	Base (equiv.)	Conditions	Yield
1	CuBr (5 mol%)	DMEDA (0.5)	K_2CO_3 (2.2)	CH_3CN Reflux, 34 h	n.d.
2	CuI (1.0)	-	Cs_2CO_3 (3.0)	Dioxane Reflux, 36 h	n.d.
3	CuI (1.0)	-	$NaHCO_3$ (2.0)	Dioxane Reflux, 36 h	n.d.
4	CuI (1.0)	-	$NaHCO_3$ (2.0)	Dioxane/Toluene Reflux, 24 h	n.d.
5	**CuI (1.0)**	**-**	**Cs_2CO_3 (3.0)**	**Dioxane/Toluene Reflux, 24 h**	**55% (49%)**

The "free" benzylic position on the 5-membered ring benzophostams may play a role in the failure of our pyridylation attempts due to its acidic protons. We then turned our attention towards *C*-derivatization of phostams in order to further explore the reactivity of such structures and in the hope that *C*-disubstituted 5-membered phostams could undergo the heteroarylation reaction.

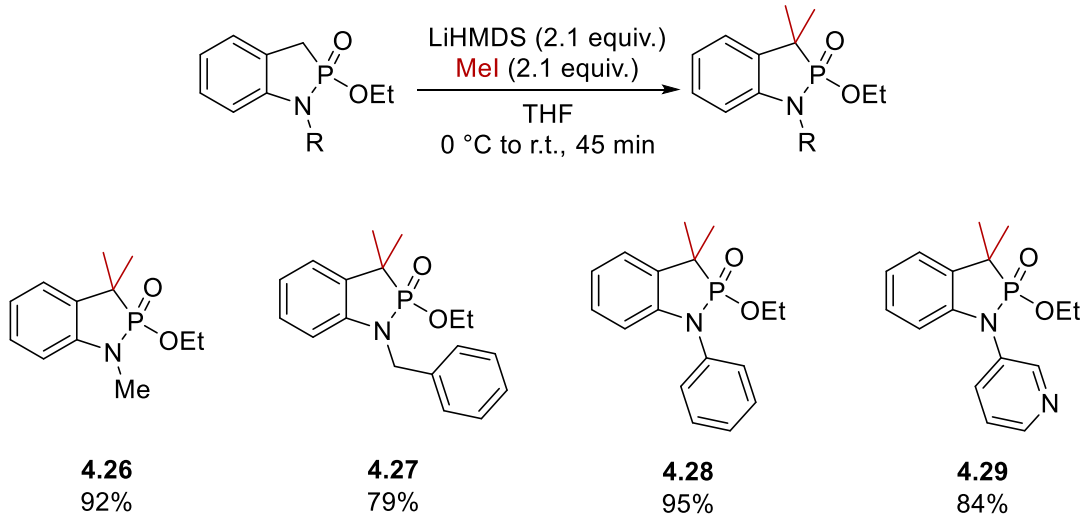
IV.3. Derivatization of the carbon backbone of phostams

Being able to derivatize the benzylic position of phostams would allow for a better evaluation of phostams' biological, chemical and physical properties and would provide, if needed, another

handle for the diversification of their structures. The first type of *C*-derivatization envisioned was the dialkylation of the benzylic position.

IV.3.1. Dialkylation of the benzylic position of *N*-substituted phostams

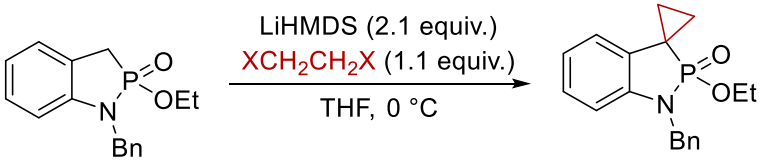
Dimethylation in basic conditions appeared as a good transformation to test out benzylic reactivity of phostams. The dimethylation of *N*-substituted phostams using LiHMDS, conditions derived from the N-alkylation methods developed in Chapter III, led to a series of *gem*-dimethyl phostams in good to excellent yields (Scheme 4.7). Both *N*-alkyl and *N*-(hetero)aryl reacted well under these conditions. It is interesting to note that phostam **4.26** could probably be synthesized directly from phostam **3.1** in a one pot fashion using three equivalents of LiHMDS and three equivalents of iodomethane.



Scheme 4.7 *Gem*-dimethylation of *N*-substituted phostams

Next, we decided to focus on the possibility of accessing spirocyclic structures, which are of great interest in biologically active compounds,[59] through similar conditions. Cyclopropyl phostam **4.30** was chosen as the first spirocyclic target. Unfortunately, dialkylation attempts of phostam **4.8** using various bis-electrophiles all resulted in unsatisfactory outcomes (Table 4.6).

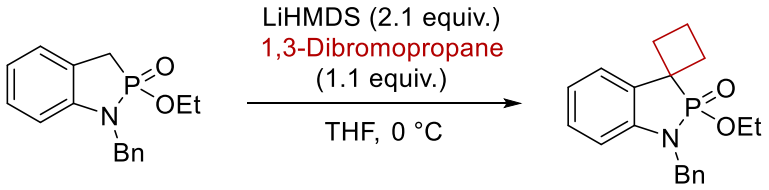
Table 4.6 Cyclopropanation attempts of phostam **4.8** via dialkylation



4.8 **4.30**

Entry	XCH_2CH_2X	Time	Results (^{31}P NMR)
1	ICH_2CH_2I	30 min	Byproducts only
2	$BrCH_2CH_2Br$	30 min	22% **4.30** 13% **4.8** 41% deprotonated **4.8**
3	$ClCH_2CH_2Cl$	1 h	24% **4.30** 65% **4.8**

We believe that elimination reactions of the dihalogenoethane reagents were competing and preventing the dialkylayion of the phostam to properly proceed. Not discouraged by these results, we attempted to install a cyclobutane moiety with the hopes that the elimination byproduct reaction would not happen as fast as in the case of dihalogenopropanes. To our delight, phostam **4.31** was obtained in a 49% yield (Scheme 4.8).

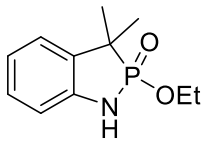


4.8 **4.31**
49 %

Scheme 4.8 Cyclobutanation of phostam **4.8**

Dialkylation of the benzylic position of *N*-substituted 5-membered phostams was successfully developed. The nitrogen being already substituted, what could be done with these compounds was relatively limited. Thus, we wondered if the potentially labile benzyl group on phostam **4.27** could

be cleaved to give access to the parent non-*N*-substituted gem-dimethylphostam **4.32** (Figure 4.1). Upon obtention of phostam **4.32** we could also test our hypothesis about the *N*-heteroarylation of 5-membered phostams being feasible on disubstituted in benzylic position phostams.



4.32

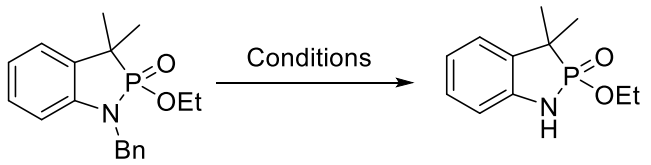
Figure 4.1 Structure of phostam **4.32**

IV.3.2. Strategies towards the synthesis of *gem*-dimethyl phostam **4.32**

IV.3.2.1. Deprotection of *N*-benzyl phostam **4.27**

Our effort towards the synthesis of phostam **4.32** started logically with the study of the benzyl group removal in phostam **4.27**. Table 4.7 summarizes various attempts to cleave the benzyl group. Hydrogenation over palladium on carbon conditions were first tested but no reaction was observed, even when acid was added to the reaction (Table 4.7, entries 1-3). We, then, turned our attention towards halogenative and radical debenzylation (Table 4.7, entries 4-8).[62] Pleasantly, radical bromination followed by hydrolysis (Table 4.7, entry 4)[62e] and lithium naphthalenide (Table 4.7, entry 7)[62d] lead to the desired phostam **4.32** in a 48% and 52% yield respectively. An ionic bromination of phostam **4.27** using NBS was tried but no reaction was observed (Table 4.7, entry 5)[62a]. However, ionic iodination with a large excess of NIS afforded the desired product in 58% but could not entirely convert the starting material even when heated and left to react longer (Table 4.7, entry 6).[62b]

Table 4.7 Debenzylation attempts conditions of phostam **4.27**



4.27 **4.32**

Entry	Reaction conditions	Result
1	H_2 (50 psi), Pd/C (5 mol %) EtOH, rt, 10 h	N.R.
2	H_2 (50 psi), Pd/C (5 mol %), AcOH (2.0 equiv.), EtOH, rt, 10h	N.R.
3	H_2 (50 psi), Pd/C (5 mol %), HCl (2.0 equiv.) EtOH, rt, 10h	N.R.
4	1) NBS (2 equiv.), AIBN (0.2 equiv.), PhCl, reflux, 20 h; 2) H_2O, rt, 4 h	62 % (48% isolated) **4.32** 38 % **4.27**
5	1) NBS (2.5 equiv.), $CHCl_3$, rt, 20 h; 2) NaOH (10 equiv.), rt, 10 min	N.R.
6	NIS (10 equiv.) CH_2Cl_2, rt, 24 h	58 % **4.32** 42% **4.27**
7	BBr_3 (10 equiv.) CH_2Cl_2, rt, 24 h	N.R.
8	Li (10 equiv.) naphthalene (1 equiv.) THF, rt, 2 h	67 % (52% isolated) **4.32** + byproducts

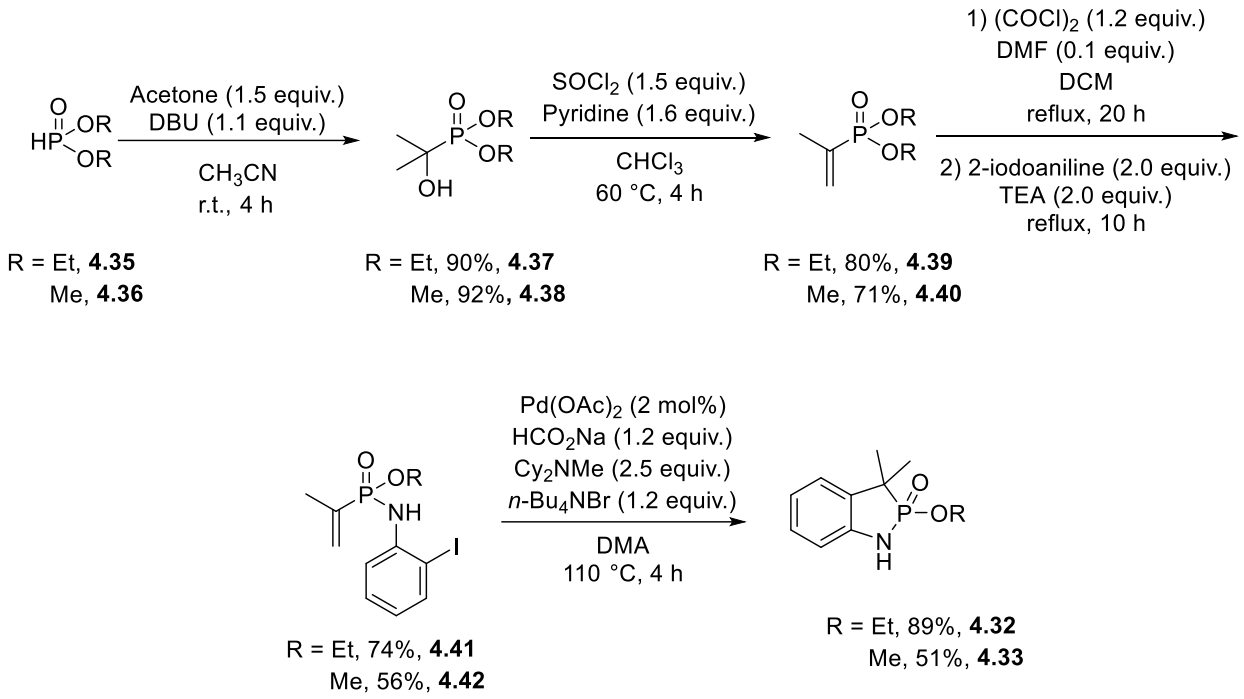
a: Based on ^{31}P NMR yields of crude reaction. Yields in parentheses are isolated yields. b: N.R.: no reaction observed, phostam **4.27** was recovered.

Thus, gem-dimethyl phostam **4.32** could be synthesized, not without difficulties, through a protection-deprotection strategy. Although a better protecting group could be chosen that would

improve the overall sequence, we thought that perhaps the best strategy would be to develop an entire new approach towards phostam **4.32** that would avoid completely the use of a protecting group.

IV.3.2.2. Synthesis of phostam **4.32** via a reductive Heck strategy.

A reductive Heck strategy which would give the dimethyl moiety directly as the cyclization occurs was devised for the synthesis of non-*N*-substituted *gem*-dimethyl phostams.[63] This strategy was applied to the synthesis of phostams **4.32** and **4.33** (Scheme 4.9). Subjecting dialkyl phosphites **4.35** and **4.36** to nucleophilic addition to acetone yielded hydroxyisopropylphosphonates **4.37** and **4.38** in 90% and 92% yield respectively**.** They were then dehydrated using thionyl chloride to afford vinylphosphonates **4.39** and **4.40** in 80% and 71% yield respectively. This strategy to access vinyl phosphonates avoids the use of expensive precursors and transition metal catalysts. A chlorination/amination with 2-iodoaniline lead to the formation of key intermediates **4.41** and **4.42** in 74% and 56% yields respectively. Finally, compounds **4.41** and **4.42** were successfully cyclized under Liu's reductive Heck conditions to afford the desired gem-dimethyl phostams **4.32** and **4.33** in 89% and 51% yields respectively.[63c] In the case of phostam **4.32**, the key reductive Heck step was performed on a 5-gram scale without affecting the yield.

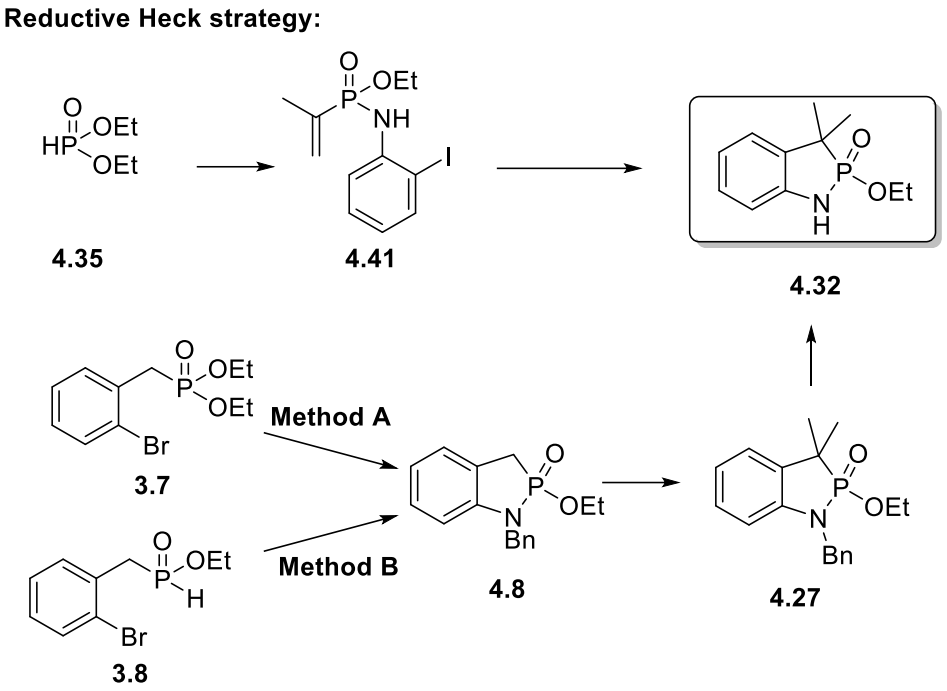


Scheme 4.9 Synthesis of gem-dimethyl phostams **4.32** and **4.33** via a reductive Heck strategy

Thus, a more straightforward synthesis of gem-dimethyl phostams was developed that did not require a protection/demethylation/deprotection sequence. The different syntheses of phostam **4.32** could be compared.

IV.3.2.3. Comparison of the different syntheses of phostam **4.32**

Since several synthetic pathways towards phostam **4.32** are available, it may be interesting to compare them. Phostam **4.32** can be produced through three strategies presented in Scheme 4.10: 1) a reductive Heck strategy, 2) a protection-deprotection strategy via the oxalyl chloride method presented in section IV.1.3 (Method A in Scheme 4.10) and 3) a protection-deprotection strategy via the Atherton-Todd method presented in section IV.1.3 (Method B in Scheme 4.10).



Scheme 4.10 Summary of the different strategies developed to access phostam **4.32**

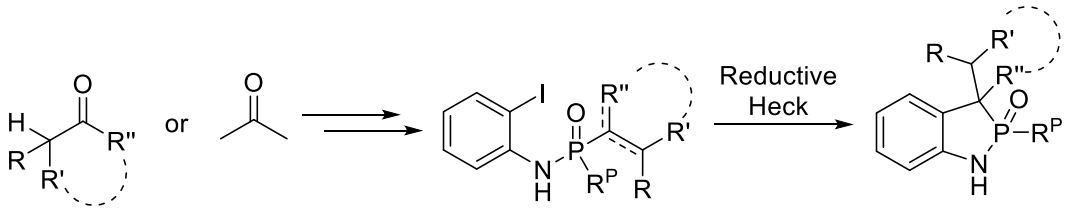
Both methods using the protection-deprotection sequences (Methods A and B) have low overall yields of 10% and 16% respectively (Table 4.8, entries 2-3), while the reductive Heck strategy is only 4-step long and has an overall yield of 47% (Table 4.8, entry 1). Moreover, looking at the CAM* metric (Chapter II), the reductive Heck clearly comes out as the best alternative with a cost evaluated at 718 $/mol, almost half the price of the other two methods (1,140 $/mol for method A and 1,298 $/mol for method B). In the case of methods A and B, the 41% yield copper-catalyzed heterocyclization and the LiHMDS-promoted dialkylation are responsible for most of the costs. Although the reductive Heck strategy uses a palladium catalyst which is very expensive (5,735 $/mol), it avoids the whole protection-dimethylation-deprotection sequence which happens to be a major contributor to the CAM* values of methods A and B. Indeed, the sequence **4.8** → **4.27** → **4.32** was calculated to cost 827 $/mol.

Table 4.8 Comparison of the synthetic routes towards phostam **4.32**

Entry	Method	Number of Steps [a]	Overall Yield of **4.32** [b]	CAM* [c] ($/mol)
1	Reductive Heck	4	47%	718
2	Method A	7	10%	1,140
3	Method B	6	16%	1,298

a: From diethyl phosphite **4.35** for the reductive Heck strategy, from triethyl phosphite for method A and from ethyl phosphinate for method B. b: isolated yields starting from diethyl phosphite **4.35**, triethyl phosphite or ethyl phosphinate. c: see Chapter II for details on calculations.

Thus, the reductive Heck strategy to access phostam **4.32** is superior to the other previously developed methods on all the comparison points: synthetic sequence length, overall yield, and cost. Another additional argument in favor of this strategy is that it would potentially allow for easy substitution of the benzylic position by simply modifying the ketone used in the first step to lead to various *C*-disubstituted phostams (Scheme 4.11).

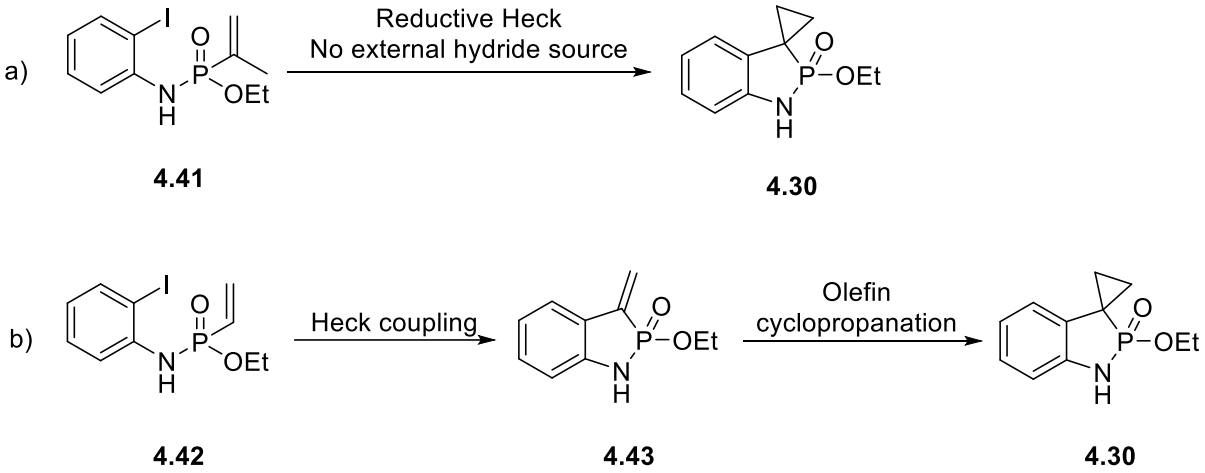


Scheme 4.11 Potential of reductive Heck strategy in terms of benzylic substituent diversification

Before investigating the *N*-derivatization of phostam **4.32** and supported by the success of the reductive Heck strategy, we decided to work on the development of new strategies to access cyclopropyl phostam **4.30** which had eluded us so far (see Table 4.6).

IV.3.3. Strategies towards cyclopropyl phostam **4.30**

From the success encountered with the *gem*-dimethyl moiety, two approaches based on palladium catalysis were envisioned to access cyclopropyl phostam **4.30**: 1) a reductive Heck strategy (Scheme 4.12, a) which relies on key intermediate **4.41** and is based on literature precedent of the carbon equivalent of phostams, oxindoles.[63a] 2) a classic Heck approach followed by a cyclopropanation of an olefin (Scheme 4.12, b). This would require the preparation of intermediate **4.42** which would cyclize to yield phostam **4.43** and would then be cyclopropanated to afford phostam **4.30**.[64]



Scheme 4.12 Palladium-catalyzed approaches towards phostam **4.30**. a) Reductive Heck strategy b) "Classic" Heck/Cyclopropanation strategie

IV.3.3.1. Reductive Heck approach towards phostam **4.30**

The idea behind this strategy was to perform a similar palladium-catalyzed cyclization on compound **4.41** that was performed in section IV.3.2.2 but without an external hydride source. The methyl group of compound **4.41** could become the internal hydride source and thus lead to the cyclopropyl phostam **4.30**. Based on a literature precedent (Figure 4.2)[63a] and our own experience

on reductive Heck, we carried out several experiments to convert compound **4.41** into phostam **4.30**.

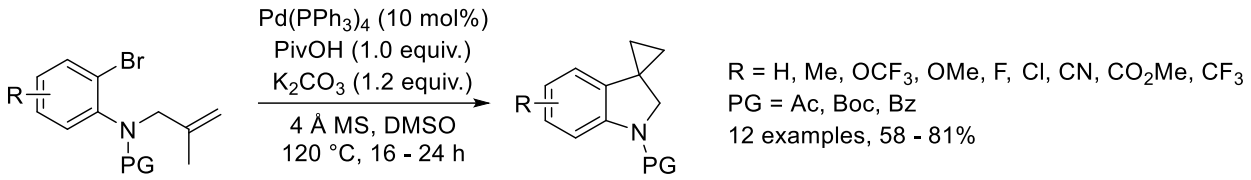
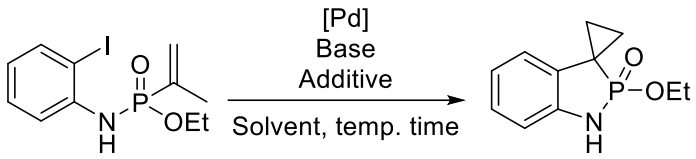


Figure 4.2 Literature precedent for the reductive Heck cyclopropanation

The results are presented in Table 4.9. All conditions tested led to disappointing results. It seems that the catalytic system always finds another hydride source and does not use the desired methyl group of **4.41** as the hydride source. Indeed, when the conditions which worked for the gem-dimethyl phostam **4.32** were tested for this reaction without sodium formate (hydride source), the main product was still phostam **4.32** (Table 4.9, entry 4). We believe the *N,N'*-dicyclohexylmethylamine is involved in this hydride transfer.[60a,b] However, even by switching the base and the palladium source, no satisfactory result was obtained. The "best" result was obtained using Pd_2dba_3 (Table 4.9, entry 14) and even then, only 7% of the desired product **4.30** was detected along with a higher amount of gem-dimethyl phostam **4.32**. Thus, it was decided to pull the plug on this strategy and move on to the more conventional Heck approach.

Table 4.9 Attempts at cyclopropanation/cyclization of compound **4.41** into phostam **4.32**



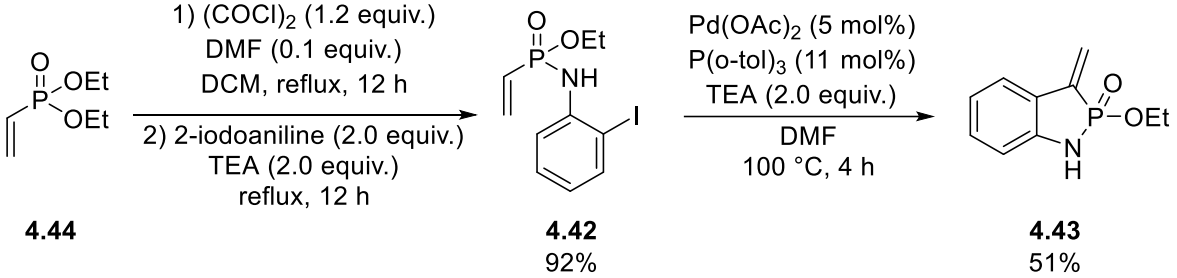
4.41 **4.30**

Entry	Pd (equiv.)	Ligand (equiv.)	Base (equiv.)	Additive (equiv.)	Solvent	Temp.	Time	Result (^{31}P NMR)
1	$Pd(PPh_3)_4$ (10 mol%)	-	K_2CO_3 (1.2)	PivOCs (1.0)	DMSO	100 °C	4 h	Byproducts
2	$Pd(PPh_3)_4$ (10 mol%)	-	-	PivOCs (1.0)	DMSO	100 °C	4 h	Byproducts
3	$Pd(PPh_3)_4$ (10 mol%)	-	K_2CO_3 (1.2)	PivOH (1.0)	DMSO	100 °C	4 h	Byproducts
4	$Pd(OAc)_2$ (5 mol%)	-	Cy_2NMe (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	78% **4.32**
5	$Pd(OAc)_2$ (5 mol%)	PPh_3 (11 mol%)	Ag_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMF	100 °C	16 h	Byproducts
6	$Pd(OAc)_2$ (5 mol%)	PPh_3 (11 mol%)	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMF	100 °C	16 h	Byproducts
7	$Pd(OAc)_2$ (5 mol%)	PPh_3 (11 mol%)	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMF	100 °C	16 h	Byproducts 23% **4.41**
8	$Pd(OAc)_2$ (5 mol%)	PPh_3 (11 mol%)	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2) AcOH (3.0)	DMF	100 °C	16 h	Byproducts 35% **4.41**
9	$Pd(OAc)_2$ (5 mol%)	-	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	Byproducts
10	$Pd(OAc)_2$ (5 mol%)	-	Cs_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	Byproducts
11	$Pd(OAc)_2$ (5 mol%)	-	PivOCs (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	Byproducts

12	$Pd(OAc)_2$ (5 mol%)	-	AcOCs (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	Byproducts
13	$Pd(PPh_3)_4$ (2 mol%)	-	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	16 h	Byproducts
14	Pd_2dba_3 (2 mol%)	-	K_2CO_3 (2.5)	*n*-Bu_4NBr (1.2)	DMA	100 °C	26 h	11% **4.32** 7% **4.30** 32% **4.41**

IV.3.3.2. "Conventionnal" Heck approach

Phostam **4.43** was obtained through a straightforward synthesis (Scheme 4.13). Commercially available diethyl vinylphosphonate **4.44** was chlorinated then aminated with 2-iodoaniline to yield compound **4.42**. A Heck reaction was then performed to afford the key phostam **4.43** in a moderate yield.[65]

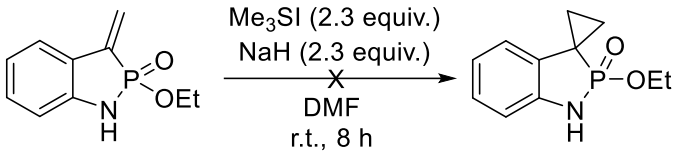


Scheme 4.13 Synthesis of key phostam **4.43**

With phostam **4.43** in hand, we could proceed to the cyclopropanation of the double bond. Several cyclopropanation reactions were considered at this point: 1) a Corey-Chaykovsky cyclopropanation,[12] 2) a Simmons-Smith cyclopropanation,[25] and 3) a [3+2] dipolar cycloaddition with a diazomethane-type reagent.[26]

Standard Corey-Chaykovsky cyclopropanation conditions were applied to compound **4.43** but the reaction failed (Scheme 4.14). Indeed, 75% of phostam **4.43** was recovered, the rest being hydrolyzed *P-N* bond products. One possible explanation lies in the pKa difference of the N-H of

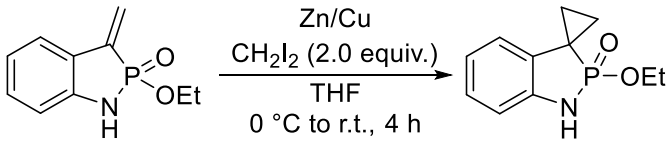
phostam **4.43** (pKa ~19) and trimethylsulfonium (pKa ~25).[66] To alleviate this, an excess of NaH was used. Unfortunately, it appears that once compound **4.43** is deprotonated, the negative charge donates too much electron density and prevents conjugate nucleophilic addition to the *C-C* double bond. The trimethylsulfoxonium pKa is estimated at ~18, which is not a significant enough difference with the N-H to circumvent the issue.[66] An obvious, but inelegant solution would be to protect the nitrogen and then perform the cyclopropanation reaction, but it was not pursued.



4.43 **4.30**

Scheme 4.14 Cyclopropanation attempt on **4.43** using a Corey-Chaykovsky reaction

The Simmons-Smith reaction was performed on phostam **4.43** using the standard conditions (Scheme 4.15).[64a] However, only 16% of expected product **4.30** was detected by ^{31}P NMR. Other side products are hydrolyzed *P-N* bond compounds, which are believed to be formed through nucleophilic attack of the electrophilic phosphorus. A possible modification would perhaps be to use diethylzinc to generate the useful Simmons-Smith reagent but we decided to pursue other strategies as this one was not deemed very likely to work.

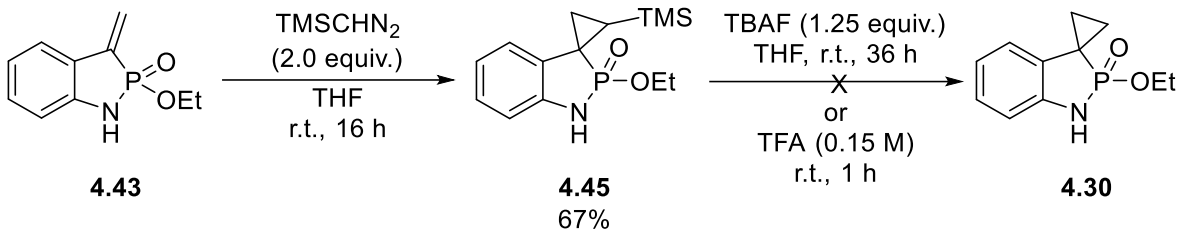


4.43 **4.30**
16% (^{31}P NMR)

Scheme 4.15 Cyclopropanation of compound **4.43** using Simmons-Smith reaction

The last option was the cycloaddition of $TMSCHN_2$ followed by nitrogen elimination to generate TMS-cyclopropyl phostam **4.45** (Scheme 4.16).[64b] The reaction proceeded smoothly at r.t. to

afford a mixture of stereoisomers of phostam **4.45**. However, the carbon-silicon bond cleavage to yield phostam **4.30** appeared to be more difficult than expected due to the absence of activating groups close enough to the carbon center.[67] Neither TBAF nor TFA were able to cleave the TMS group. In the case of TBAF, no reaction occurred even after 24 h at r.t., afterwards the phostam ring started to hydrolyze, whereas in the case of TFA, the phostam ring was hydrolyzed right away.



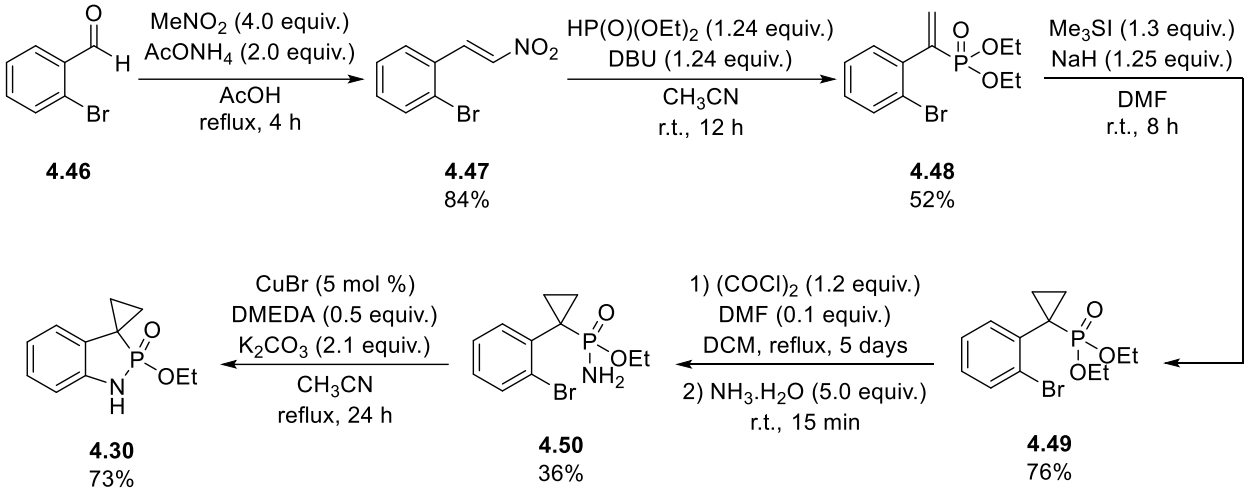
Scheme 4.16 Cyclopropanation of **4.43** through addition of $TMSCHN_2$ to the C=C double bond

Unfortunately, neither the dialkylation strategy (See section IV.3.1), nor the reductive Heck strategy gave any satisfactory results. The conventional Heck approach, as presented above, did not lead to better results. One could argue that performing the Corey-Chaykovsky on a *N*-protected phostam would very likely deliver the desired phostam **4.30**, pending deprotection, as would the use of diazomethane instead of its trimethylsilyl derivative, but dealing with such dangerous compound is far from being ideal. However, a totally different approach based on the *C*-*N* disconnection strategy presented in Chapter III was successfully developed.

IV.3.3.3. Alternative synthesis of cyclopropyl phostam **4.30**

As before, switching the sequence (early installation of the cyclopropyl moiety followed by the key copper-catalyzed heterocyclization) offered a solution to the synthesis of phostam **4.30** (Scheme 4.17). First, a nitro-aldol reaction between 2-bromobenzaldehyde **4.46** and nitromethane gave nitrostyrene derivative **4.47** in good yield.[68] Then a tandem phospha-Michael/elimination reaction delivered vinyl phosphonate **4.48** in moderate yield.[69] Next a Corey-Chaykovsky

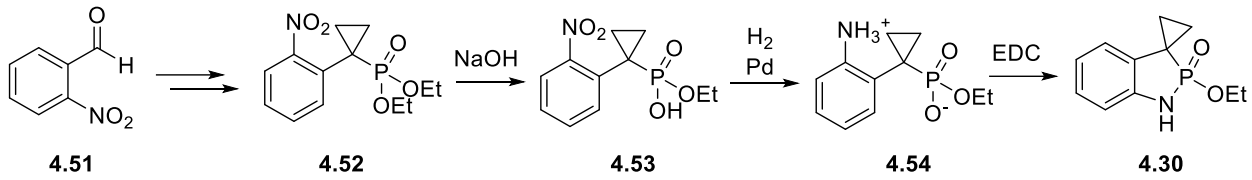
cyclopropanation proceeded uneventfully to cyclopropane **4.49**.[70] One-pot chlorination/amidation gave amide **4.50** albeit in low yield, likely due to steric hindrance interference during the chlorination step. Cyclization via our copper-catalyzed cross-coupling conditions finally delivered the desired cyclopropane phostam **4.30** in good yield.



Scheme 4.17 Synthesis of phostam **4.30** via a *C-N* disconnection strategy

Finally, a viable synthesis of phostam **4.30** had been performed in a 6-step sequence and with an overall yield of 9%, mainly due to the one-pot chlorination/amination step. A possible alternative to solve this issue would be to use the *P-N* strategy developed on phostam **3.1** (Scheme 4.18). Indeed, starting from 2-nitrobenzaldehyde **4.51**, the corresponding nitrated cyclopropylphosphonate **4.52** could likely be obtained following the same synthetic sequenceas presented in Scheme 4.17, Then, instead of the chlorination/amination sequence, a dealkylation reaction, which should not be impacted by the steric hindrance could be envisioned to deliver the corresponding acid **4.53**. Then, reduction of the nitro group by hydrogenation would deliver

zwitterion **4.54** which could eventually afford cyclopropyl phostam **4.30** using the EDC-promoted cyclization conditions.



4.51 **4.52** **4.53** **4.54** **4.30**

Scheme 4.18 Potential alternative synthesis of phostam **4.30** via *P*-*N* disconnection strategy

X-Ray diffraction (XRD) experiments were performed to compare the structures of cyclopropyl phostam **4.30** and phostam **3.1** (Figure 4.3). Unsurprisingly, the two structures are very similar both in terms of bond lengths as in bond angles. Indeed, all the angles of the 5-membered ring are identical within one degree. As expected, the nitrogen is not conjugated with the P(O) bond.

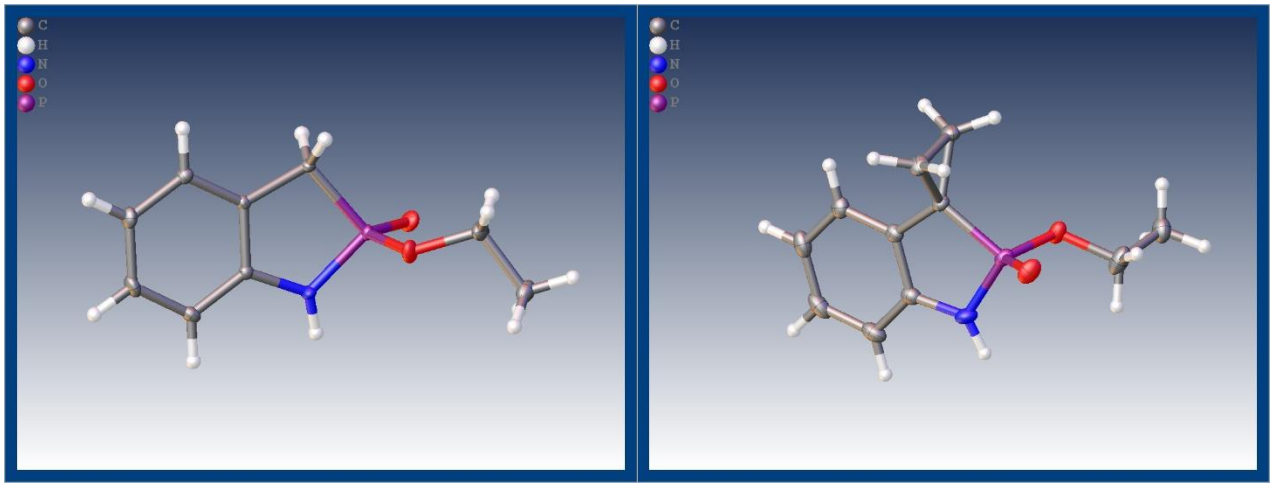


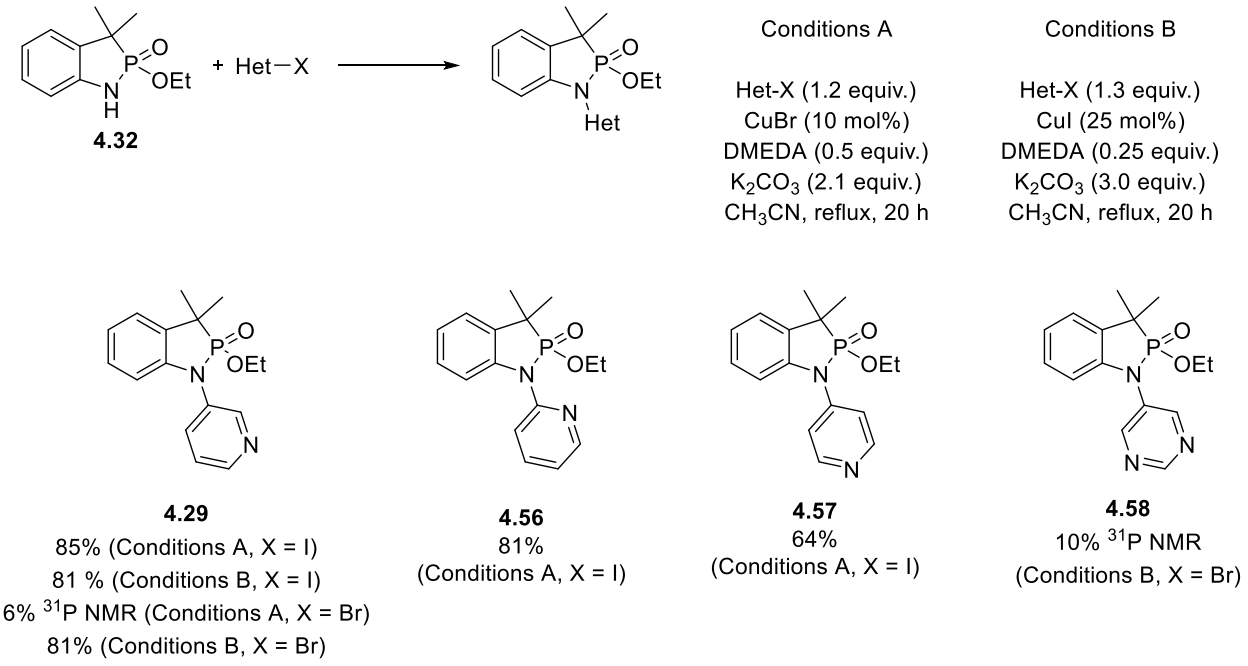
Figure 4.3: XRD structures of phostam **3.1** (left) and cyclopropyl phostam **4.32** (right)

Several *C*-disubstituted phostams were obtained using various strategies, from a simple dialkylation under basic conditions to a reductive Heck approach. *Gem*-dimethyl phostam **4.30**, piqued our interest as we could study its *N*-derivatization, in particular the *N*-pyridylation that kept eluding us.

IV.4. *N*-derivatization of *gem*-dimethyl phostam **4.32**

IV.4.1. *N*-pyridylation of phostam **4.32**

With phostam **4.32** in hand, we could finally attempt the *N*-pyridylation reaction in order to confirm or deny our hypothesis about the benzylic methylene interfering with the heteroarylation of phostam **3.1**. Two sets of copper-catalyzed conditions were tried (Scheme 4.19): 1) the conditions previously developed in the Montchamp laboratory on this project to *N*-phenylate phostams (Method A) and 2) conditions reported on an amide equivalent of phostams (Method B).[71] To our delight, pyridylation of phostam **4.32** with the three isomers of iodopyridine gave the desired products in good yields using conditions A. Using 3-bromopyridine with conditions B, phostam **4.29** was obtained with in virtually identical yield. Unfortunately, when 5-bromopyrimidine was used, for unclear reasons, only 10% of the product was detected by ^{31}P NMR.

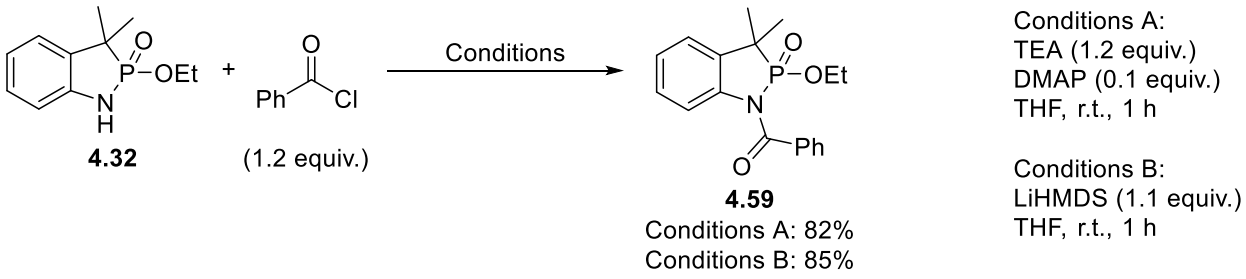


Scheme 4.19 *N*-pyridylation of phostam **4.32**

One can note that phostam **4.29** was also obtained from the LiHMDS-promoted demethylation of *N*-pyridyl phostam **4.20** (See sections IV.2.2. and IV.3.1). The synthesis based on the reductive Heck strategy appears as superior as it allows for a more divergent synthesis of *N*-substituted phostams.

IV.4.2. *N*-acylation and *N*-sulfonylation of phostam **4.32**

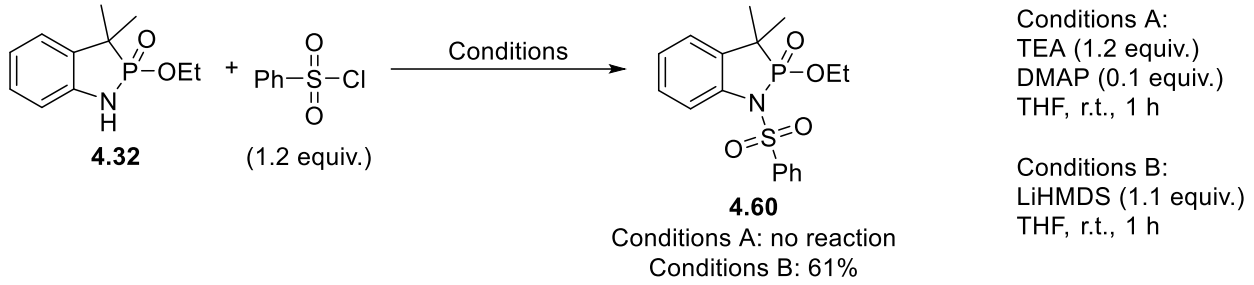
Since *N*-pyridylation of phostam **4.32** led to good results, we decided to see if *N*-acylation and *N*-sulfonylation, reactions that were unsuccessful when attempted with phostam **3.1** (See section IV.1.1), would also give access to the desired mixed anhydride type phostams. Indeed, amides and sulfonamides are prevalent functional groups in pharmaceuticals and agrochemicals. *N*-acylation of phostam **4.32** using benzoyl chloride delivered benzoyl phostam **4.59** using two sets of conditions in good yields (Scheme 4.20). It is interesting to note that the high reactivity of the acyl chloride allows for both the use of a weak base (Scheme 4.20, method A) or of a strong base (Scheme 4.20, method B).



Scheme 4.20 *N*-benzoylation of phostam **4.32**

To explore this type of reactivity further, phostam **4.32** was subjected benzenesulfonyl chloride using the two sets of conditions previously presented (Scheme 4.21). If LiHMDS-promoted conditions delivered *N*-sulfonylated phostam **4.60** in good yield, the TEA-promoted conditions failed to afford the desired compound. Indeed, no reaction was observed and phostam **4.32** was

recovered. We believe that the relative stability of sulfonyl chlorides is responsible for the lack of reactivity under "mild" conditions.

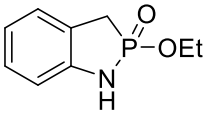
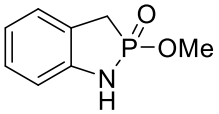
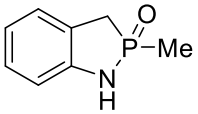
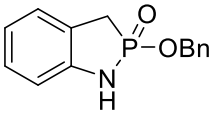
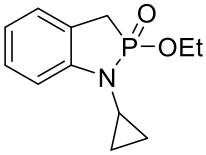
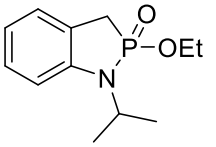
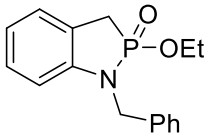
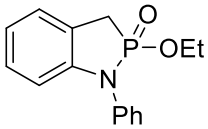
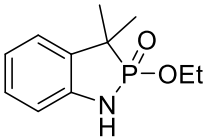
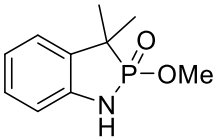
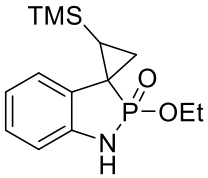
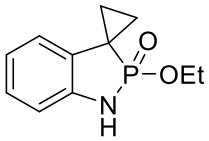
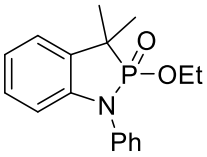
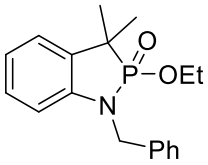
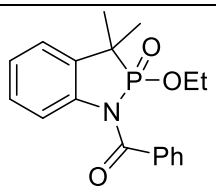
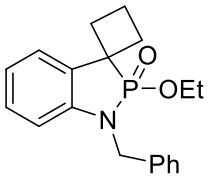
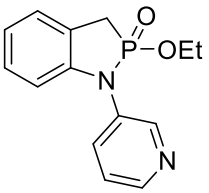
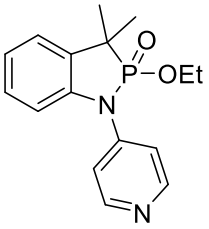
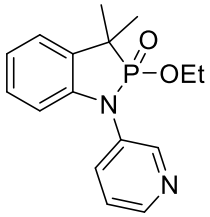
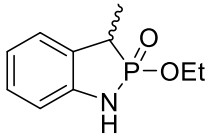
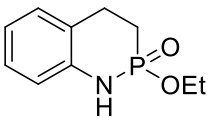
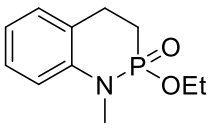
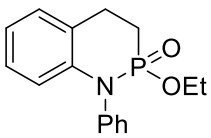
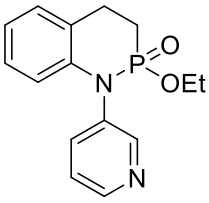


Scheme 4.21 *N*-sulfonylation of phostam **4.30**

N-derivatization of gem-dimethyl phostam **4.32** seem to point towards the fact that the disubstituted benzylic position really increases the stability of 5-membered phostams structure towards various reactions conditions compared to the "naked" benzylic position. A Thorpe-Ingold effect might be at play which would explain the relative stability of *gem*-dimethyl phostam **4.32** compared to phostam **3.1**.

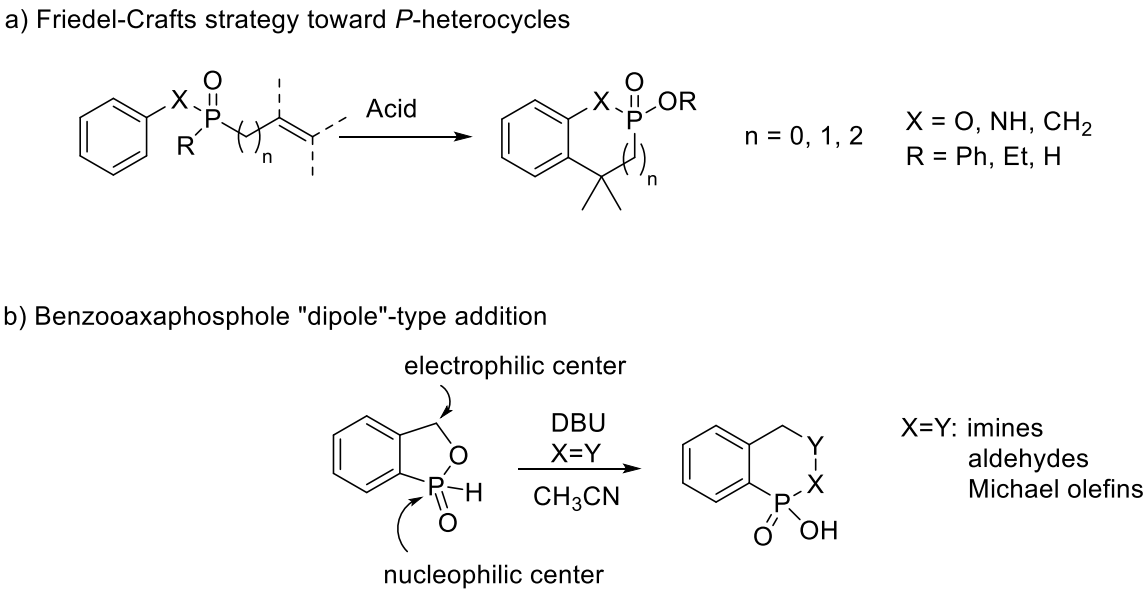
This collaboration between TCU and Bayer S.A.S. focused on the synthetic study of various 5- and 6-membered phostam compounds and their reactivity. We reported several synthetic routes to key phostam building-blocks; for both 5-membered and 6-membered families of phostams, along with the development of several types of methodologies to functionalize these compounds (*i.e.* *N*-alkylation, *N*-(hetero)arylation, benzylic dialkylation, etc.). This work also elaborated on the difficulties that were encountered as well as certain types of reactions that could not be performed successfully. A total of 37 5-membered phostams and five 6-membered phostams were isolated. Selected phostams were sent to Bayer S.A.S for physical properties measurement (Table 4.10).

Table 4.10 Structures and quantities of phostams sent to Bayer S.A.S for biological and physico-chemical testings

 90 mg	 115 mg	 68 mg	 541 mg
 100 mg	 68 mg	 644 mg	 132 mg
 1.83 g	 344 mg	 102 mg	 226 mg
 174 mg	 82 mg	 35 mg	 50 mg
 55 mg	 57 mg	 134 mg	 133 mg
 614 mg	 100 mg	 32 mg	 99 mg

Chapter V: Access to other benzo-fused *P*-heterocycles

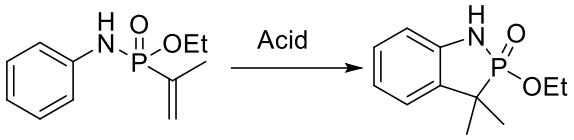
Our pursuit of methods to synthesize more *P*-heterocycles prompted us to explore the underrepresented synthesis of 5-, 6- and 7-membered benzofused *P*-heterocycles via other strategies. We decided to pursue two strategies that would potentially expand access to phostams as well as access to other type of *P*-heterocycles: 1) a C-C bond formation Friedel-Crafts reaction of unsaturated organophosphorus compounds (Scheme 5.1, a) and 2) a "dipole"-like addition of benzooxaphosphole to polarized molecules such as imines or ketones (Scheme 5.1, b).



Scheme 5.1 Other strategies towards *P*-heterocycles

V.1. Friedel-Crafts-type cyclization of unsaturated organophosphorus compounds

The original reason that led us to work on that Friedel-Crafts strategy was that it could be one more approach towards phostams, and especially towards gem-dimethyl phostam **4.30** (Scheme 5.2). Additionally, it could also give access to a variety of underrepresented *P*-heterocycles other than the benzophostams presented in chapters III and IV.



4.30

Scheme 5.2 Potential access to benzophostam **4.30** via a Friedel-Crafts strategy

Using Friedel-Crafts conditions to access benzofused *P*-heterocycles is not new. Stankevic worked on the cyclization of various β-hydroxyalkylphosphine oxides to access 5- and 6-membered *P*-heterocycles under acidic conditions (Figure 5.1).[72] The 6-membered *P*-heterocycles were obtained if the substitution pattern allowed for the formation of a more stable carbocation intermediate via 1,2-hydride shift.

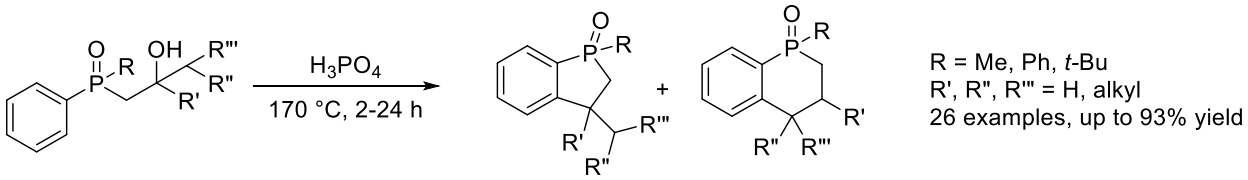
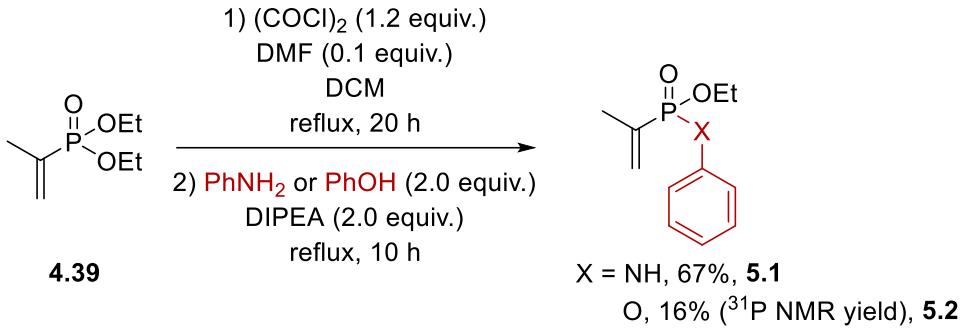


Figure 5.1 Stankevic's work on cyclization of β-hydroxyalkylphosphine oxides under Friedel-Crafts conditions [72]

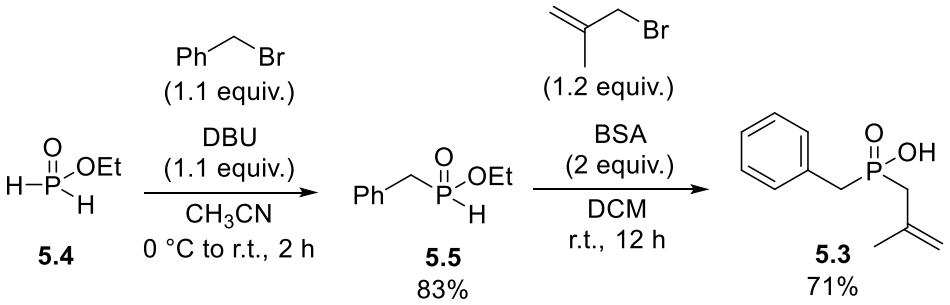
V.1.1 Synthesis of the different synthons before cyclization

The first step of the project was the synthesis of the various synthons that could then lead to the 5-, 6- and 7-membered *P*-heterocycles. According to the envisioned strategy, synthons that would lead to 5-membered heterocycles would have to be some type of vinylphosphorus compounds. Thus, we used the approach developed in section IV.3.2.2. (See scheme 4.9 for more details) to synthesize vinyl phosphonate **4.39**, which was then submitted to chlorination with oxalyl chloride and then treated either with aniline or phenol in the presence of DIPEA (Scheme 5.3). Only the aniline derivative **5.1** was obtained in acceptable yield while phenol derivative **5.2** was only detected at 16% by ^{31}P NMR.



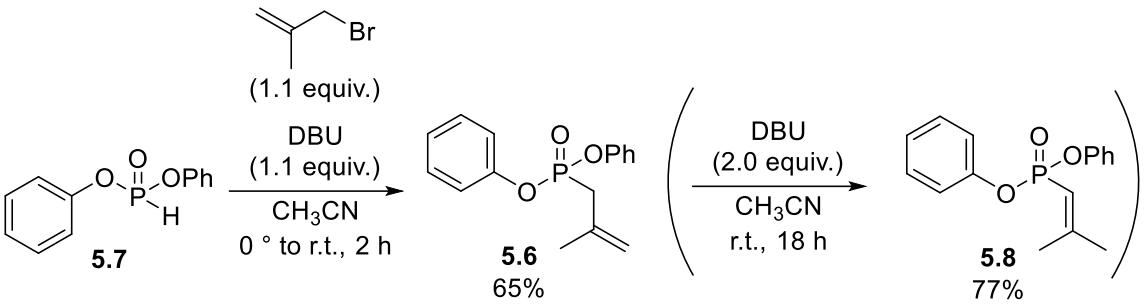
Scheme 5.3 Synthesis of synthons **5.1** and **5.2** for the Friedel-Crafts strategy

Next, we turned towards the synthesis of the synthons that could lead to 6-membered phostams starting with the phosphinate **5.3**. Its synthesis started from Montchamp's DBU-promoted alkylation of ethyl phosphinate **5.4** with benzyl bromide to yield known *H*-phosphinate **5.5** in good yield (Scheme 5.4). Then, compound **5.5** was reacted with methallyl bromide in presence of BSA via an Arbuzov reaction to yield the desired phosphinic acid **5.3** in good yield.



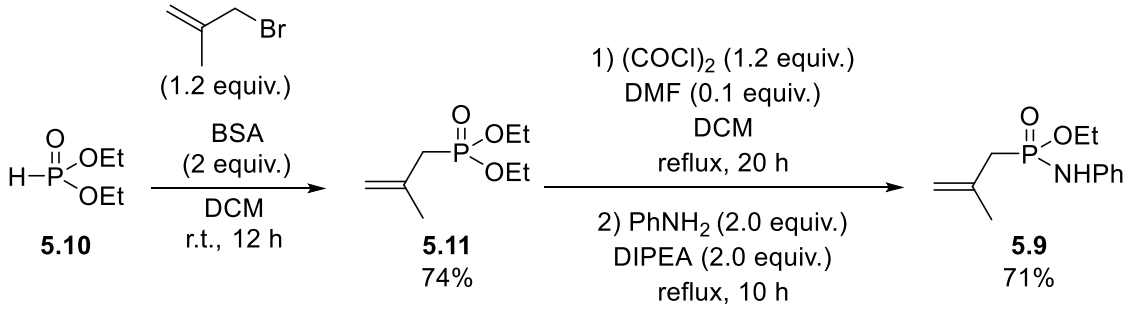
Scheme 5.4 Synthesis of phosphinate **5.3** from ethyl phosphinate **5.4**

The next target on our list was phenol derivative **5.6**, which was synthesized in good yield in one step from diphenyl phosphite **5.7** and methallylbromide in the presence of DBU (Scheme 5.5). A small amount (around 15% by ^{31}P NMR) of phosphinate **5.6** isomerized into vinyl phosphinate **5.8** during the reaction. The isomerization of the carbon-carbon double bond of phosphinate **5.6** could be pushed under basic conditions to afford the pure isomer **5.8** in good yield too. Interestingly, both compounds could potentially lead to the same *P*-heterocycles upon cyclization under acidic conditions.



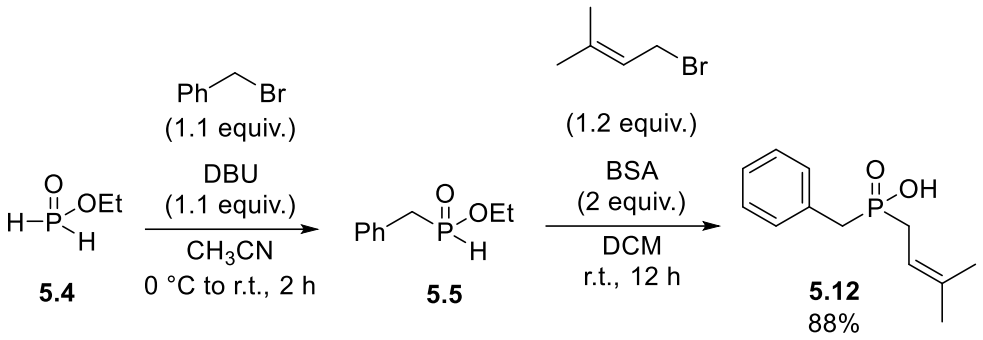
Scheme 5.5 Synthesis of phosphinates **5.6** and **5.8** from diphenyl phosphite

Finally, the last synthon needed for the 6-membered family of *P*-heterocycles was the aniline derivative **5.9**. Its synthesis started from diethylphosphite **5.10** which was alkylated with methallyl bromide in presence of BSA to yield phosphonate **5.11** in good yield (Scheme 5.6). Compound **5.11** was then converted into target phosphonamide **5.9** in good yield via a chlorination/amination sequence



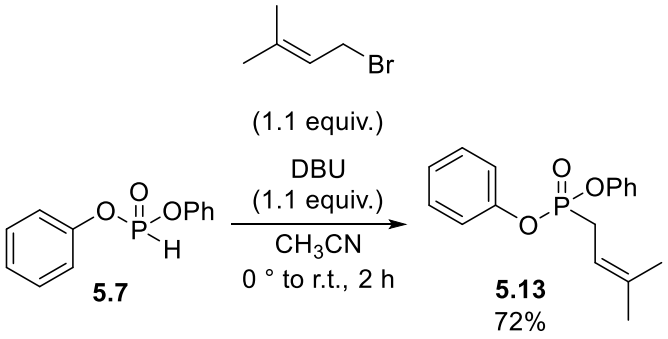
Scheme 5.6 Synthesis of phosphonamide **5.9** from diethyl phosphite **5.10**

All desired precursors to 6-membered *P*-heterocycles in hand, we turned our attention to precursors to 7-membered *P*-heterocycles. Accessing the desired targets was achieved by simply replacing methallyl bromide with prenyl bromide in the three previous syntheses of compounds **5.3** and **5.5.** Thus, reaction between *H*-phosphinate **5.5** and prenyl bromide afforded phosphinic acid **5.12** in excellent yield (Scheme 5.7).



Scheme 5.7 Synthesis of phosphinic acid **5.12**

The synthesis of phosphonate **5.13** proceeded similarly to the synthesis of phosphonate **5.6** (Scheme 5.8). Diphenyl phosphite **5.7** was reacted with prenyl bromide in the presence of DBU to uneventfully afford compound **5.13**. Unlike phosphonate **5.6**, no isomerization of the carbon-carbon double bond was observed, as it is stable enough due to its trisubstitution.



Scheme 5.8 Synthesis of phosphonate **5.13** from diphenyl phosphite **5.7**

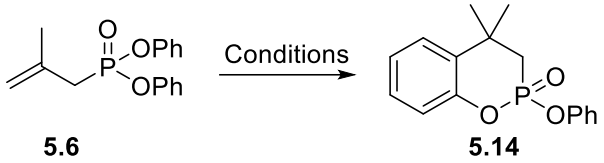
The precursors to *P*-heterocycles were synthesized with good yields using classic alkylation methods. With all the compounds prepared, all that was left to do was to attempt the cyclization under Friedel-Crafts conditions.

V.1.2. Friedel-Crafts cyclization of unsaturated organophosphorus compounds

Phosphonate **5.6** was chosen as the model for the development of the cyclization conditions. The first acidic conditions tested involved polyphosphoric acid (PPA) (Table 5.1, entries 1 and 2). Unfortunately, no product was detected in the reaction mixture or after aqueous work-up.

Moreover, PPA is relatively impractical to work with on small scales due to its viscosity and the lack of solubility of compounds in it. Then, the intramolecular Friedel-Crafts was attempted in trifluoroacetic acid (TFA) without any reaction observed both at room temperature or at reflux (Table 5.1, entries 3 and 4). Fortunately, using a much stronger acid as the solvent (*i.e.*, sulfuric acid) led to the formation of the desired cyclic compound **5.14** which was obtained pure and in good yields after a simple aqueous extraction (Table 5.1, entrie 5 and 6).

Table 5.1 Optimization of cyclization conditions of phosphonate **5.6** into heterocycle **5.14**

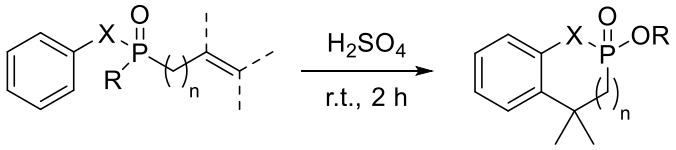


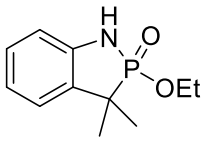
5.6 **5.14**

Entry	Conditions	Yield [a]
1	PPA, 80 °C, 1 h	n.d. [b]
2	PPA, r.t., 2 h	n.d. [b]
3	TFA (0.35 M), r.t., 16 h	n.d. [c]
4	TFA (0.35 M), reflux, 12 h	n.d. [c]
5	H_2SO_4 (0.10 M), r.t., 2 h	83% (60%)
6	H_2SO_4 (0.20 M), r.t., 2 h	78% (61%)

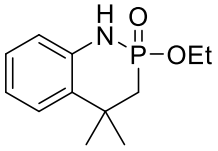
a: Yield were determined by ^{31}P NMR. Isolated yields are given in parenthesis. b: no product detected in reaction mixture or after work-up. c: only unreacted **5.6**

Once sulfuric acid was found to be the ideal media for the intramolecular Friedel-Crafts reaction, we set out to test these conditions on the other synthesized compounds. Results are summarized in Scheme 5.9. Unfortunately, only the phenol derivatives afforded the desired heterocyclic compounds **5.14** and **5.17** after a simple work-up while the aniline derivatives lead to hydrolyzed starting materials or to reaction mixtures with a lot of unidentified side products. Benzylic phosphinic acids **5.3** and **5.12** were left unreacted under these conditions.

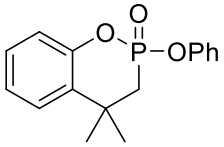




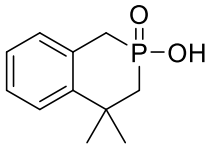
4.30
(0% from **5.1**)[a]



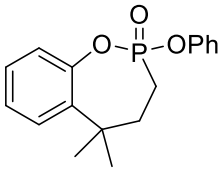
5.15
(0% from **5.9**)[b]



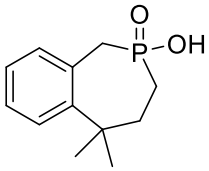
5.14
(61% from **5.6**)
(66% from **5.8**)



5.16
(0% from **5.3**)[c]



5.17
(55% from **5.13**)



5.18
(0% from **5.12**)[c]

Scheme 5.9 Scope of the intramolecular Friedel-Crafts to access various *P*-heterocycles. Yields are isolated yields. a: Only hydrolysis of the aniline substituent was formed. b: no product detected by ^{31}P NMR. c: Unreacted starting material

The project was stopped at this stage as it seems only very electron-rich phenol derivatives were able to undergo the cyclization while others were either too sensitive to the conditions (aniline derivatives) or were simply not electron rich enough to allow for the formation of the Wheland's intermediates (benzylic phosphinic acids). At the same time, we were working on the development

of a benzooxaphosphole building block (Scheme 5.1, b) which could potentially give access to multiple *P*-heterocycles.

V.2. Benzooxaphosphole oxide as a precursor to various *P*-heterocycles

In an effort to access more *P*-heterocycles, compounds of interest in drugs and agrochemistry,[12] we focused on the development of a key building block containing both an electrophilic carbon center and a nucleophilic phosphorus center for [4+2] additions to dipoles to yield 6-membered *P*-heterocycles (Figure 5.2).

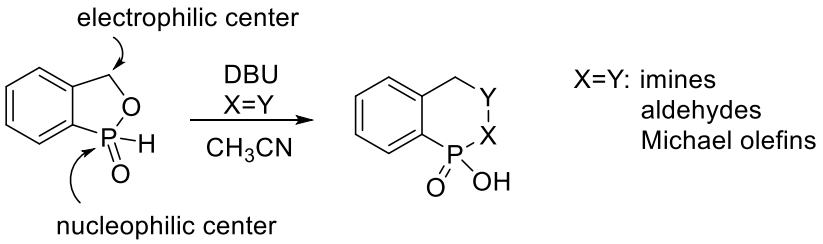
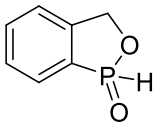


Figure 5.2 Dipole-type synthon able to undergo tandem addition to afford 6-membered *P*-heterocycles

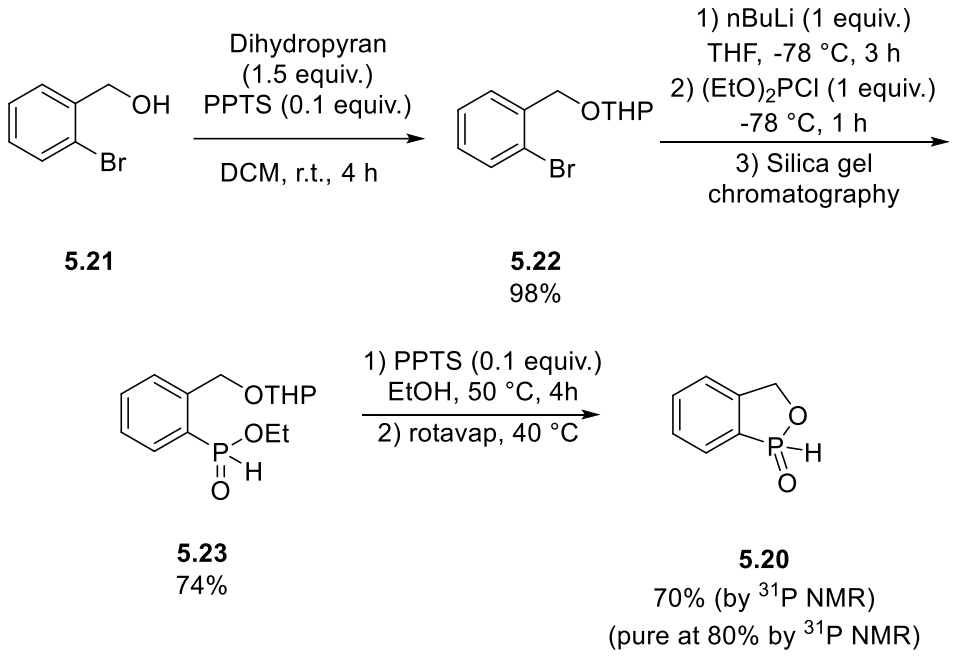
The trivial approach to get the desired reactivity on the dipole represented in figure 5.2 would be to add an electron rich leaving group on the carbon, making it electrophilic, and to use a phosphinylidene moiety ($R_1R_2P(O)H$), which would allow to react the phosphorus center as a nucleophile. However, instead of devising a compound bearing a leaving group distinct from the phosphinyledene moiety, we decided to combine both. Thus, benzooxaphosphole **5.20** bears a phosphinyledene moiety acting as the nucleophilic center and as the leaving group, by linking it to the benzylic carbon via a *C-O* bond (Figure 5.3).



5.20

Figure 5.3 Structure of benzooxaphosphole **5.20**

The synthesis of compound **5.20** started with the protection of 2-bromobenzyl alcohol **5.21** with a tetrahydropyranyl group in excellent yield to afford compound **5.22** (Scheme 5.10). Then, lithium-halogen exchange using butyllithium was performed. Nucleophilic addition of the obtained organolithium reagent onto chlorodiethylphosphine at cryogenic temperatures followed by acidic hydrolysis yielded *H*-phosphinate **5.23** in a good yield. The deprotection of the THP in presence of PPTS followed by condensation under vacuum gave the desired benzooxaphosphole oxide **5.20** in a 70% NMR yield. Unfortunately, we were not able to purify key compound **5.20** as it readily gets hydrolyzed on silica or in aqueous work-ups. We were able to get a maximum purity of 80% by phosphorus NMR using two successive triturations in hexanes.



5.21

5.22
98%

5.23
74%

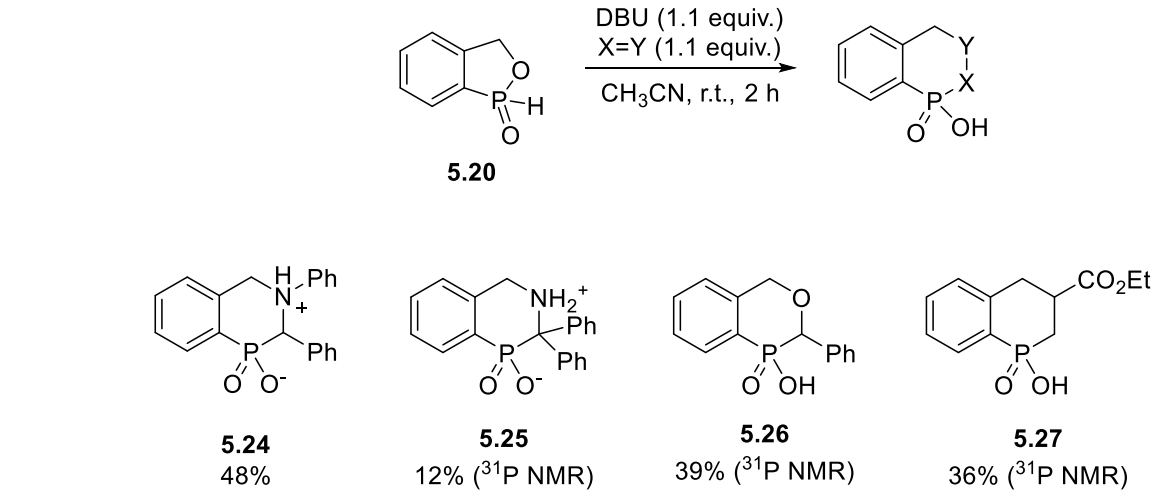
5.20
70% (by ^{31}P NMR)
(pure at 80% by ^{31}P NMR)

Scheme 5.10 Synthesis of compound **5.20** from 2-bromobenzyl alcohol **5.21**

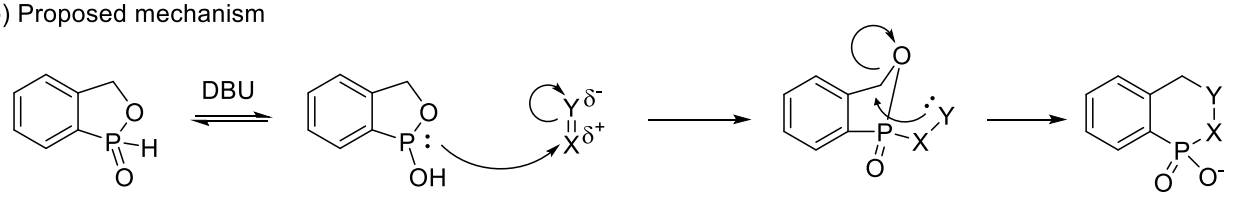
Even if compound **5.20** could not be obtained pure, formation of *P*-heterocycles using various dipoles was attempted (Scheme 5.11). Unfortunately, zwitterion **5.24**, obtained by reacting heterocycle **5.20** with n-benzylideneaniline, was the only *P*-heterocycles that was isolated as it crystalized out of the reaction mixture. Product **5.25** was only detected at 12% and did not

precipitate out of the solution. The low yield and the zwitterionic character of compound **5.25** prevented isolation by an aqueous work-up. Steric hindrance with due to the two phenyl groups might be partly responsible for the lack of reactivity. Phosphinic acids **5.26** and **5.27** were obtained in somewhat higher yields (respectively, 39% and 36% by ^{31}P NMR) but, once again, were not obtained pure even after an aqueous work-up and the fact that they are acids prevented purification by column chromatography.

a) Reaction scope



b) Proposed mechanism



Scheme 5.11 a) Reaction of benzooxaphosphole **5.20** with different dipoles b) Proposed reaction mechanism

Overall, this method appeared to be very impractical. Indeed, even if it would have been an elegant process to access very different *P*-heterocycles from a single building block, we were unable to obtain pure compound **5.20** and the actual addition step to a dipole only worked on one substrate.

The two strategies presented in this chapter were not deemed worth pursuing due to their impracticality and narrow scope of substrates.

EXPERIMENTAL SECTION

Materials and methods:

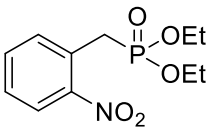
^{1}H NMR spectra were recorded on a 400-MHz Bruker Avance spectrometer. Chemical shifts for

^{1}H NMR spectra (in parts per million) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with deuterated chloroform. $^{13}C\{^{1}H\}$ NMR spectra were recorded at 101 MHz. Chemical shifts for $^{13}C\{^{1}H\}$ NMR spectra are reported (in parts per million) relative to $CDCl_3$ ($\delta = 77.0$ ppm) or DMSO-*d6* ($\delta = 39.5$ ppm). $^{31}P\{^{1}H\}$ and ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid ($\delta = 0.0$ ppm). Flash chromatography experiments were carried out on Silica Gel premium Rf grade (40−75 μm). Ethyl acetate/hexane or ethyl acetate/methanol mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by UV or immersion in permanganate potassium (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aq. NaOH and 300 mL of water) followed by heating. High resolution mass spectra (HRMS) were obtained by electrospray ionization using a TOF analyzer.

Reagent and solvents:

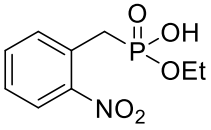
All starting materials were purchased from commercial sources and used as received, unless otherwise noted. Anhydrous THF and DMF were purchased and used as received. The solvents were distilled under N_2 and dried according to standard procedures (CH_3CN, toluene and dichloromethane from CaH_2).

Diethyl (2-nitrobenzyl)phosphonate 3.4 [75]



To a round-bottom flask was added triethyl phosphite (19.23 g, 115.7 mmol, 1.0 equiv.) and 2-nitrobenzyl bromide **3.2** (25.00 g, 115.7 mmol, 1.0 equiv.) under N_2. A short-path distillation apparatus was mounted on the flask to trap bromoethane generated during the reaction. The reaction mixture was stirred at 110 °C for 2 h. The reaction yielded diethyl (2-nitrobenzyl)phosphonate **3.4** (30.35 g, 96%) as a dark oil. Product was used without further purification (NMR purity: 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.59-7.56 (m, 1H), 7.50-7.47 (m, 1H), 7.46-7.41 (m, 1H), 4.04 (dq, J = 8.1, 7.1 Hz, 4H), 3.73 (d, J = 22.7 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.2 (d, J = 6.6 Hz), 133.1 (d, J = 5.9 Hz), 132.9 (d, J = 3.1 Hz), 127.9 (d, J = 3.5 Hz), 127.1 (d, J = 10.0 Hz), 125.0 (d, J = 2.9 Hz), 62.2 (d, J = 6.7 Hz), 30.3 (d, J = 137 Hz), 16.1 (d, J = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.0 (s).

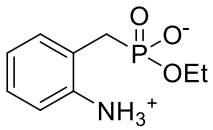
Synthesis of ethyl (2-nitrobenzyl)phosphonic acid 3.3



To a round-bottom flask was added diethyl (2-nitrobenzyl)phosphonate **3.4** (30.35 g, 111.0 mmol, 1.0 equiv.) in toluene (100 mL). An aqueous solution of 4N NaOH (110 mL, 440 mmol, 4.0 equiv.) was added to the flask. The reaction mixture was then heated at reflux for 24h. The organic layer and aqueous layer were separated. The aqueous layer was then acidified to pH 1 with aqueous 1N HCl and extracted with DCM (2x). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford ethyl (2- nitrobenzyl)phosphonic acid **3.3** (24.20 g, 89%) as a brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.60-7.55 (m, 1H), 7.48-7.40 (m, 2H), 3.97 (dq, J = 7.9 and 7.1 Hz, 2H), 3.70 (d, J

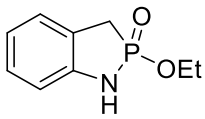
= 23.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.4 (d, *J* = 7.0 Hz), 133.3 (d, *J* = 6.2 Hz), 133.0 (d, *J* = 3.4 Hz), 128.0 (d, *J* = 3.5 Hz), 127.1 (d, *J* = 10 Hz), 125.2 (d, *J* = 2.9 Hz), 62.0 (d, J = 7.0 Hz), 30.8 (d, *J* = 140 Hz), 16.1 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 27.0 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{12}NO_5P$ 246.0526, found 246.0514.

Synthesis of ethyl (2-ammoniumbenzyl)phosphonate 3.2



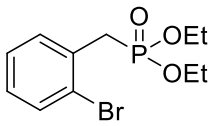
To a Parr hydrogenation reactor containing palladium on carbon (10% w/w, 2.10 g, 2.0 mmol, 0.02 equiv.) under nitrogen, was added a solution of ethyl (2-nitrobenzyl)phosphonic acid **3.3** (24.2 g, 98.8 mmol, 1.0 equiv.) in EtOH (300 mL). The reactor was mounted on a Parr hydrogenation apparatus. The reactor was placed under vacuum and refilled with hydrogen (50 psi). The reaction mixture was agitated at r.t. for 3 h. The hydrogen atmosphere was then slowly evacuated with a water aspirator and replaced with nitrogen. The reaction mixture was then filtered over celite. The filtrate was concentrated under vacuum to yield ethyl (2-aminobenzyl)phosphonic acid **3.2** as a beige solid (21.25 g, >99 %): ^{1}H NMR (400 MHz, DMSO) δ 8.20 (s, 3H), 7.13-7.05 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 7.4 and 7.1 Hz, 1H), 3.81 (m, 2H), 3.01 (d, *J* = 20.4 Hz, 2H), 1.10 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO) δ 141.1 (d, *J* = 4.5 Hz), 131.9 (d, *J* = 6.4 Hz), 127.5 (d, *J* = 3.3 Hz), 123.8 (d, *J* = 8.7 Hz), 122.0 (s), 119.5 (s), 60.8 (d, *J* = 5.9 Hz), 31.4 (d, *J* = 129.3 Hz), 16.9 (d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, DMSO) δ 21.8 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{14}NO_3P$ 216.0784, found 216.0770.

Synthesis of 2-ethoxy-2,3-dihydro-1H-1,2-benzaphosphole 2-oxide 3.1 from 3.2



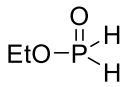
To a round-bottom flask was added ethyl (2-aminobenzyl)phosphonic acid **3.2** (20.0 g, 92.9 mmol, 1.0 equiv.) in anhydrous DMF (900 mL). The solution was heated at 60 °C until everything is solubilized then EDC.HCl (19.59 g, 102.2 mmol, 1.1 equiv.) was added to the solution. The reaction mixture was then heated at 110 °C for 3h. DMF was removed under vacuum and the residue was taken up in CH_2Cl_2 and washed with brine. The organic layer was then dried over $MgSO_4$ and concentrated under vacuum to yield compound **3.1** as a beige solid (13.55 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.05 (m, 2H), 6.86 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.01 (d, *J* = 8.1 Hz, 1H), 4.31-4.04 (m, 2H), 3.23-2.89 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.3 (d, *J* = 22.1 Hz), 128.26 (s), 126.9 (d, *J* = 17.5 Hz), 121.2 (d, *J* = 5.2 Hz), 120.2 (d, *J* = 1.1 Hz), 111.8 (d, *J* = 13.4 Hz), 62.1 (d, *J* = 6.4 Hz), 26.5 (d, *J* = 119.9 Hz), 16.4 (d, *J* = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.1 (s). HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{12}NO_2P$ 198.0678, found 198.0670.

Synthesis of diethyl (2-bromobenzyl)phosphonate 3.7 [73]



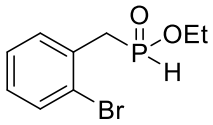
To a round-bottom flask was added triethyl phosphite (16.6 g, 100 mmol, 1.0 equiv.) and 2-bromobenzyl bromide **3.9** (25.0 g, 100 mmol, 1.0 equiv.) under N_2. A short-path distillation apparatus was mounted on the flask to trap the bromoethane generated during the reaction. The reaction mixture was heated for 2 h at 110 °C. The reaction yielded diethyl (2-bromobenzyl)phosphonate **3.7** as a colorless oil (29.8 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.46 (m,1H), 7.27 (m, 1H), 7. 11 (m, 1H), 4.05 (m, 4H), 3.41 (d, *J* = 21.9Hz, 2H), 1.26 (t, *J* = 7.1Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.6 (s).

Synthesis of ethyl phosphinate solution



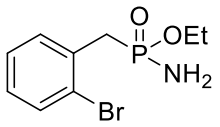
Aqueous hypophosphorous acid H_3PO_2 (50% w/w in water, mmol, mL, 1.0 equiv.) was concentrated *in vacuo* (30 min, 30 °C). It was then dissolved in CH_3CN (mL) and diethoxydimethylsilicate (mmol, g, 2.0 equiv.) was added. Reaction mixture was then heated at reflux for 2h. After cooling to r.t., the stock solution was stored at r.t. under nitrogen and used as such. NMR yield: >99%: ^{31}P NMR (162 MHz, CH_3CN solvent) δ 15.36 (tt, J = 564 and 9.7 Hz).

Synthesis of ethyl (2-bromobenzyl)-H-phosphinate 3.8 [49]



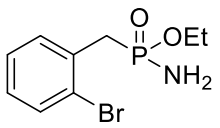
To a solution of ethyl phosphinate (0.5M in CH_3CN, 125 mmol, 250 mL, 1.0 equiv.) was added 2-bromobenzyl bromide **3.9** (34.4 g, 137.5 mmol, 1.1 equiv.). The solution was then cooled down to 0 °C and DBU (20.6 mL, 137.5 mmol, 1.1 equiv.) was added dropwise via an addition funnel. Reaction mixture was allowed to warm up to r.t. and was stirred for 2 h. Reaction mixture was concentrated *in vacuo* to remove CH_3CN. Residue was taken up in AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by silica gel column chromatography (Hexanes/AcOEt 6:4 to 0:10) to yield the desired product **3.8** as a colorless oil (27.3 g, 83%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 553 Hz, 1H), 7.47-7.44 (m, 2H), 7.24-7.16 (m, 2H), 7.05-7.01 (m, 1H), 4.09-3.90 (m, 2H), 3.39-3.24 (m, 2H), 1.20 (t, J = 7.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 132.92 (d, J = 3.3 Hz), 131.87 (d, J = 5.8 Hz), 130.42 (d, J = 7.5 Hz), 128.94 (d, J = 4.0 Hz), 127.86 (d, J = 3.4 Hz), 124.57 (d, J = 7.4 Hz), 62.76 (d, J = 6.9 Hz), 37.08 (d, J = 88.9 Hz), 16.20 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 33.0 ppm (d, J = 550 Hz).

Synthesis of ethyl (2-bromobenzyl)phosphonamidate 3.6 from 3.7



To a solution of compound **3.7** (29.8g, 97 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL) under N_2 was added oxalyl chloride (10.0 mL, 116 mmol, 1.2 equiv.) carefully. DMF (0.75 mL, 9.7 mmol, 0.1 equiv.) was added dropwise and the reaction mixture was stirred at reflux for 12 h. This mixture was then added dropwise to a flask containing ammonium hydroxide (28% NH_3 in H_2O, 9.2 mL, 485 mmol, 5.0 equiv.) and stirred at r.t. for 15 min. Sat. aq. NH_4Cl was added to the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield ethyl (2-bromobenzyl)phosphonamidite **3.6** as an off-white solid (25.3 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9, 1H), 7.46 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 4.15-4.00 (m, 2H), 3.40 (dd, *J* = 21.3 and 2.3 Hz, 2H), 2.89 (br. s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.0 (d, *J* = 3.1 Hz), 132.9 (d, *J* = 8.3 Hz), 131.8 (d, *J* = 4.8 Hz), 128.5 (d, *J* = 3.7 Hz), 127.7 (d, *J* = 3.3 Hz), 124.9, 60.4 (d, *J* = 7.0 Hz), 36.5 (d, *J* = 124.3 Hz), 16.4 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{13}BrNO_2P$ 277.9940, found 277.9934.

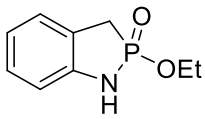
Synthesis of ethyl (2-bromobenzyl)phosphonamidate 3.6 from 3.8 by an Atherton-Todd reaction



To a round-bottom flask was added *H*-phosphonate **3.8** (10.0 g, 38.0 mmol, 1.0 equiv.) in CCl_4 (37 mL, 10 equiv.) and CH_3CN (75 mL) under N_2. The solution was cooled down to 0 °C and Et_3N (10.6 mL, 76.0 mmol, 2.0 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then ammonium hydroxide (28% NH_3 in H_2O, 3.8 mL, 26 equiv.) was added dropwise. The reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. It was then concentrated under vacuum to remove the solvents. The residue

was diluted with EtOAc, washed with NH_4Cl, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield ethyl (2-bromobenzyl)phosphonamidate **3.6** as an off-white solid (9.89 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9, 1H), 7.46 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 4.15-4.00 (m, 2H), 3.40 (dd, *J* = 21.3 and 2.3 Hz, 2H), 2.89 (br. s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.0 (d, *J* = 3.1 Hz), 132.9 (d, *J* = 8.3 Hz), 131.8 (d, *J* = 4.8 Hz), 128.5 (d, *J* = 3.7 Hz), 127.7 (d, *J* = 3.3 Hz), 124.9, 60.4 (d, *J* = 7.0 Hz), 36.5 (d, *J* = 124.3 Hz), 16.4 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{13}BrNO_2P$ 277.9940, found 277.9934.

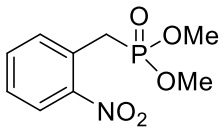
Synthesis of 2-ethoxy-2,3-dihydro-1H-1,2-benzaphosphole 2-oxide 3.1 from 3.6



To a round-bottom flask was added phosphonamide **3.6** (10.1 g, 36.4 mmol, 1.0 equiv.), copper(I) bromide (262 mg, 1.82 mmol, 0.05 equiv.), K_2CO_3 (10.6 g, 76.4 mmol, 2.1 equiv.) in CH_3CN (365 mL) under N_2. DMEDA (1.96 mL, 18.2 mmol, 0.5 equiv.) was added to the mixture. The reaction mixture was refluxed for 24 h. Then, it was concentrated under vacuum to remove the solvent. The residue was taken up in EtOAc, washed with sat. aq. NH_4Cl. The organic layer was separated. The aqueous layer was extracted with EtOAc (2x). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (Hex/EtOAc 3:7 to 1:9) to afford 2-ethoxy-2,3-dihydro-1*H*-1,2-benzaphosphole 2-oxide **3.1** as a white solid (4.52 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.05 (m, 2H), 6.86 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.01 (d, *J* = 8.1 Hz, 1H), 4.31-4.04 (m, 2H), 3.23-2.89 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.3 (d, *J* = 22.1 Hz), 128.26 (s), 126.9 (d, *J* = 17.5 Hz), 121.2 (d, *J*

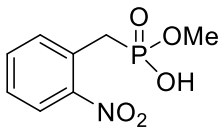
= 5.2 Hz), 120.2 (d, *J* = 1.1 Hz), 111.8 (d, *J* = 13.4 Hz), 62.1 (d, *J* = 6.4 Hz), 26.5 (d, *J* = 119.9 Hz), 16.4 (d, *J* = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.1 (s). HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{12}NO_2P$ 198.0678, found 198.0670.

Synthesis of dimethyl (2-nitrobenzyl)phosphonate 3.11 [24b]



To a round-bottom flask was added trimethyl phosphite (20.7 mL, 175.9 mmol, 1.9 equiv.) and 2-nitrobenzyl bromide **3.5** (20.0 g, 92.6 mmol, 1.0 equiv.) under N_2. A short-path distillation apparatus was mounted on the flask to trap bromomethane generated during the reaction. Reaction mixture is heated at 90 °C for 2 h. Crude was then purified by Silica gel column chromatography (Hexanes/EtOAc 5:5 to 0:10) to afford pure dimethyl (2-nitrobenzyl)phosphonate **3.11** as a yellow oil (19.2 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.58-7.54 (m, 1H), 7.47-7.40 (m, 2H), 3.72 (d, *J* = 22.6 Hz, 2H), 3.67 (d, *J* = 10. 9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.3 (d, J = 6.5 Hz), 133.2 (d, *J* = 3.6 Hz), 133.1 (s), 128.2 (d, *J* = 3.5 Hz), 126.9 (d, *J* = 9.8 Hz), 125.3 (d, *J* = 2.9 Hz), 52.9 (d, *J* = 6.7 Hz), 29.8 (d, *J* = 139 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.6 (s).

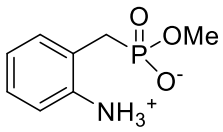
Synthesis of methyl (2-nitrobenzyl)phosphonic acid 3.12



To a round-bottom flask was added, dimethyl (2-nitrobenzyl)phosphonate **3.11** (12.5 g, 51.1 mmol, 1.0 equiv.) in toluene (30 mL). An aqueous solution of 4N NaOH (51 mL, 204.6 mmol, 4.0 equiv.) was added to the flask. The reaction mixture was then heated at reflux for 24h. The organic layer and aqueous layer were separated. The aqueous layer was then acidified to pH 1 with aqueous 1N HCl and extracted with DCM (2x). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford methyl (2-

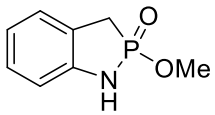
nitrobenzyl)phosphonic acid **3.12** as a brown solid (10.6 g, 90 %): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.24 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.59-7.55 (m, 1H), 7.48-7.40 (m, 2H), 3.70 (d, *J* = 23.2 Hz, 2H), 3.61 (d, *J* = 11.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.3 (s), 133.3 (s), 133.1 (s), 128.1 (s), 127.0 (d, *J* = 9.7 Hz), 125.3 (s), 52.3 (d, *J* = 7.6 Hz), 30.3 (d, *J* = 140.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.9 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_8H_{10}NO_5P$ 232.0369, found 232.0363.

Synthesis of methyl (2-ammoniumbenzyl)phosphonate 3.13



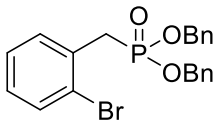
To a Parr hydrogenation reactor containing Palladium on carbon (10% w/w, 842 mg, 0.8 mmol, 0.02 equiv.) under nitrogen, was added a solution of methyl (2-nitrobenzyl)phosphonic acid **3.12** (9.14 g, 39.5 mmol, 1.00 equiv.) in MeOH (200 mL). The reactor was mounted on a Parr hydrogenation apparatus. The reactor was placed under vacuum and refilled with hydrogen (50 psi). The reaction mixture was agitated at r.t. for 3 h. The hydrogen atmosphere was then slowly evacuated with a water aspirator and replaced with nitrogen. The reaction mixture was then filtered over celite. The filtrate was concentrated under vacuum to yield methyl (2-aminobenzyl)phosphonic acid **3.13** as a beige solid (7.92 g, >99 %): ^{1}H NMR (400 MHz, DMSO) δ 8.51 (s, 3H), 7.15-7.07 (m, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.91-6.87 (m, 1H), 3.44 (d, *J* = 11.3 Hz, 3H), 3.02 (d, *J* = 20.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 140.4 (d, *J* = 4.2 Hz), 131.9 (d, *J* = 6.4 Hz), 127.6 (d, *J* = 2.5 Hz), 124.3 (d, *J* = 8.3 Hz), 122.5 (s), 119.8 (s), 52.0 (d, *J* = 6.1 Hz), 30.8 (d, *J* = 128.9 Hz); ^{31}P NMR (162 MHz, DMSO) δ 22.5 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_8H_{12}NO_3P$ 202.0628, found 202.0618.

Synthesis of 2-ethoxy-2,3-dihydro-1H-1,2-benzaphosphole 2-oxide 3.10



To a round-bottom flask was added methyl (2-aminobenzyl)phosphonic acid **3.13** (7.48 g, 37.2 mmol, 1.0 equiv.) in anhydrous DMF (375 mL). The solution was heated at 60 °C until everything is solubilized then EDC.HCl (7.84 g, 40.9 mmol, 1.1 equiv.) was added to the solution. The reaction mixture was then heated at 110 °C for 3h. DMF was removed under vacuum and the residue was taken up in CH_2Cl_2 and washed with brine. The organic layer was then dried over $MgSO_4$ and concentrated under vacuum to yield **3.10** as an off-white solid (4.76 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.11 (m, 2H), 6.87-6.83 (m, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 3.76 (d, *J* = 11.8 Hz, 3H), 3.18-2.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.9 (d, *J* = 21.5 Hz), 128.4 (d, *J* = 1.2 Hz), 127.0 (d, *J* = 17.5 Hz), 121.1 (d, *J* = 5.0 Hz), 120.5 (d, *J* = 1.5 Hz), 111.8 (d, *J* = 13.5 Hz), 52.5 (d, *J* = 6.7 Hz), 25.8 (d, *J* = 120.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.6 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_8H_{10}NO_2P$ 184.0522, found 184.0511.

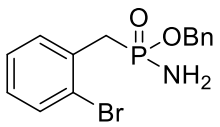
Synthesis of dibenzyl (2-bromobenzyl)phosphonate 3.15



To a round-bottom flask was added dibenzyl phosphite (10.00 g, 38.1 mmol, 1.0 equiv.) and 2-bromobenzyl bromide **3.9** (10.48 g, 41.9 mmol, 1.1 equiv.) in acetonitrile (80 mL) under nitrogen. The mixture was cooled down to 0 °C and DBU (6.3 mL, 41.9 mmol, 1.1 equiv.) was added dropwise via an addition funnel. The reaction mixture was allowed to warm up to r.t and was stirred 2 h. After 2 h, the reaction mixture was concentrated under vacuum to remove the solvent. The residue was taken up in EtOAc, washed with brine (sat.), dried over MgSO4 and concentrated under vacuum. The crude oil was purified by silica gel

chromatography (Hex/EtOAc, 5:5 to 1:9) to afford dibenzyl (2-bromobenzyl)phosphonate **3.15** (10.02 g, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.44 (ddd, *J* = 7.7, 2.9, 1.7 Hz, 1H), 7.39-7.28 (m, 10 H), 7.28-7.20 (m, 1H), 7.15-7.06 (m, 1H), 5.09-4.86 (m, 4H), 3.49 (d, *J* = 22.1 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.24 (d, *J* = 6.1 Hz), 133.07 (d, *J* = 3.0 Hz), 131.79 (d, *J* = 5.2 Hz), 131.52 (d, *J* = 9.1 Hz), 128.70 (d, *J* = 3.7 Hz), 128.58, 128.42, 128.01, 127.57 (d, *J* = 3.6 Hz), 125.04 (d, *J* = 9.0 Hz), 67.77 (d, *J* = 6.6 Hz), 33.79 (d, *J* = 138.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}BrO_3P$ 431.0406, found 431.0398.

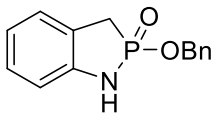
Synthesis of benzyl (2-bromobenzyl)phosphonamide 3.16



Dibenzyl (2-bromobenzyl)phosphonate **3.15** (4.31 g, 10.0 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (30 mL) in a flask under N_2. Oxalyl chloride (1.1 mL, 12.0 mmol, 1.2 equiv.) was added cautiously to the solution (bubbles a lot). DMF (77 μL, 1.0 mmol, 10 mol%) was added dropwise to the mixture. The reaction mixture was stirred under N_2 at r.t. for 24 h. The solution was then added dropwise into a flask containing $NH_3.H_2O$ (28% in weight NH_3 in H_2O, 3.4 mL, 5.00 equiv.) and the resulting mixture was stirred at r.t. for 10 min and, then, $NaHSO_4$ (0.5 M) was added until the pH was acidic. The organic layer was washed with $NaHCO_3$ (sat.), brine (sat.), dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by silica gel chromatography (Hex/EtOAc, 5/5 to 2/8) to afford benzyl (2-bromobenzyl)phosphonamide **3.16** as a white solid (2.11 g, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 7.7, 2.8, 1.8 Hz, 1H), 7.41-7.32 (m, 5H), 7.31-7.24 (m, 1H), 7.17-7.06 (m, 1H), 5.19-4.94 (m, 2H), 3.63-3.27 (m, 2H), 2.82 (d, *J* = 5.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)

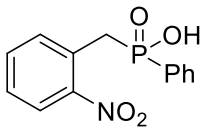
δ 136.68 (d, *J* = 6.9 Hz), 133.06 (d, *J* = 3.4 Hz), 132.57 (d, *J* = 8.6 Hz), 131.89 (d, *J* = 5.3 Hz), 128.60, 128.57, 128.21, 127.72 (d, *J* = 3.8 Hz), 127.63, 124.81 (d, *J* = 8.2 Hz), 65.67 (d, *J* = 6.8 Hz), 36.53 (d, *J* = 124.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.7 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}BrNO_2P$ 340.0097, found 340.0092.

Synthesis of 2-(benzyloxy)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 3.14



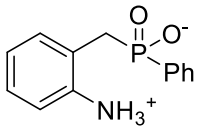
To a round-bottom flask was added benzyl (2-bromobenzyl)phosphonamide **3.16** (2.08 g, 6.11 mmol, 1.0 equiv.), copper(I) bromide (44 mg, 0.31 mmol, 5 mol%), anhydrous K_2CO_3 (1.86g, 13.44 mmol, 2.2 equiv.) in CH_3CN (60 mL) under N_2. N,N'-dimethylethylenediamine (0.33 mL, 3.06 mmol, 0.5 equiv.) was added to the mixture. The reaction was refluxed for 16 h. The reaction mixture was cooled down to r.t., diluted with EtOAc and washed with aq. NH_4Cl (sat.). The aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine (sat.), dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by silica gel chromatography (Hex/EtOAc, 6/4 to 2/8) to afford 2-(benzyloxy)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **3.14** as a white solid (855 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 7.18-7.06 (m, 2H), 6.85 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 5.22-4.98 (m, 2H), 3.19-2.80 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.84 (d, *J* = 22.0 Hz), 136.21 (d, *J* = 5.8 Hz), 128.65, 128.50, 128.31 (d, *J* = 1.3 Hz), 127.96, 127.00 (d, *J* = 17.6 Hz), 121.20 (d, *J* = 5.1 Hz), 120.46 (d, *J* = 1.6 Hz), 111.74 (d, *J* = 13.6 Hz), 67.74 (d, *J* = 6.3 Hz), 26.75 (d, *J* = 119.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.7 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_2P$ 260.0835, found 260.0831.

Synthesis of (2-nitrobenzyl)(phenyl)phosphinic acid 3.18



To a round-bottom flask was added phenylphosphinic acid (1.42 g, 10.0 mmol, 1.00 equiv.) in DCM (25 mL) under N_2. The solution was cooled down to 0 °C and BSA (6.11 mL, 25.0 mmol, 2.50 equiv.) was added dropwise. The solution was stirred for 15 min then 2-nitrobenzyl bromide **3.5** (2.16 g, 10.0 mmol, 1.00 equiv.) was added at 0 °C. The reaction was allowed to warm up to r.t. and stirred for 12 h. MeOH (5 mL) was added to quench the reaction. Solvents were removed under vacuum and the residue was taken up in AcOEt. Aq. sat. $NaHCO_3$ was used to extract. The aqueous layer was then acidified with HCl 6N and extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuum to afford (2- nitrobenzyl)(phenyl)phosphinic acid **3.18** as a light brown solid (2.59 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (s, 1H), 7.82 (d, J = 8.2 Hz), 7.55 – 7.41 (m, 4H), 7.39 – 7.24 (m, 4H), 3.75 (d, J = 18.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.00 (d, J = 6.0 Hz), 133.51 (d, J = 5.1 Hz), 132.92 (d, J = 3.2 Hz), 132.37 (d, J = 2.9 Hz), 131.34 (d, J = 10.3 Hz), 130.32 (d, J = 136.5 Hz), 128.30 (d, J = 13.2 Hz), 127.76 (d, J = 3.4 Hz), 127.33 (d, J = 8.4 Hz), 125.05 (d, J = 2.8 Hz), 35.41 (d, J = 91.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.32. HRMS (ESI+) m/z [M+H]+ calcd for $C_{13}H_{12}NO_4P$ 278.0577, found 278.0574.

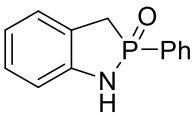
Synthesis of (2-ammoniobenzyl)(phenyl)phosphinate 3.19 [24a]



In a Parr hydrogenation reactor containing Palladium on carbon (10% w/w, 478 mg, 0.45 mmol, 0.05 equiv.) under nitrogen, was added a solution of (2-nitrobenzyl)(phenyl)phosphonic acid **3.18** (2.50 g, 9 mmol, 1.00 equiv.) in EtOH (100 mL). The reactor was mounted on a Parr hydrogenation apparatus. The reactor was placed under vacuum and refilled with hydrogen (50 psi). The reaction mixture was agitated at r.t. for 2 h. The hydrogen

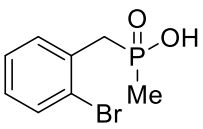
atmosphere was then slowly evacuated with a water aspirator and replaced with nitrogen. The reaction mixture was then filtered over celite. The filtrate was concentrated under vacuum to yield (2-ammoniobenzyl)(phenyl)phosphonic acid **3.19** as a beige solid (2.07g, 93%): ^{1}H NMR (400 MHz, DMSO) δ 7.70 – 7.64 (m, 2H), 7.54 – 7.47 (m, 1H), 7.45 – 7.40 (m, 2H), 6.95 – 6.90 (m, 1H), 6.76 (d, J = 7.8, 2H), 6.54 – 6.54 (m, 1H), 4.79 (bs, 9H), 3.13 (d, J = 16.8 Hz, 2H); ^{31}P NMR (162 MHz, DMSO) δ 35.89.

Synthesis of 2-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 3.17 [24a]



To a round-bottom flask was added methyl (2-ammoniobenzyl)phosphonic acid **3.18** (2.51 g, 10.0 mmol, 1.00 equiv.) in anhydrous DMF (100 mL). The solution was heated at 60 °C until everything is solubilized then EDC.HCl (2.11 g, 11.0 mmol, 1.10 equiv.) was added to the solution. The reaction mixture was then heated at 110 °C for 3 h. DMF was removed under vacuum and the residue was taken up in CH_2Cl_2 and washed with brine. The organic layer was then dried over $MgSO_4$ and concentrated under vacuum to yield 2-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **3.17** as a beige solid (1.79 g, 75%): ^{1}H NMR (400 MHz, DMSO) δ 8.50 (d, *J* = 10.3 Hz, 1H), 7.91 – 7.67 (m, 2H), 7.66 – 7.40 (m, 3H), 7.34 – 7.05 (m, 2H), 6.79 (dd, *J* = 10.5, 7.7 Hz, 2H), 3.33 – 2.99 (m, 2H).

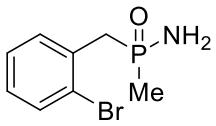
Synthesis of (2-bromobenzyl)(methyl)phosphinic acid 3.21



To a solution of H-phosphonate **3.8** (17.2 g, 65.6 mmol, 1.00 equiv.) in DCM (100 mL) under N_2 at 0 °C was added BSA (19.3 mL, 78.7 mmol, 1.20 equiv.) dropwise. The reaction was stirred at 0 °C for 15 min then iodomethane (4.90 mL, 78.7 mmol,

1.20 equiv.) was added dropwise. The reaction mixture was allowed to warm up to r.t. and was stirred for 12 h. Methanol (5 mL) was added to the reaction mixture to quench it. It was then concentrated under vacuum to remove the solvents. The residue was taken up in DCM, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford phosphinic acid **3.21** as a white solid (16.1 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 7.57 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.46 (ddd, *J* = 7.7, 2.7, 1.8 Hz, 1H), 7.35-7.26 (m, 1H), 7.14-7.09 (m, 1H), 3.37 (d, *J* = 17.6 Hz, 2H), 1.42 (d, *J* = 14.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.04 (d, *J* = 2.9 Hz), 132.20 (d, *J* = 7.2 Hz), 131.99 (d, *J* = 4.7 Hz), 128.56 (d, *J* = 3.4 Hz), 127.71 (d, *J* = 3.3 Hz), 124.64 (d, *J* = 7.4 Hz), 38.10 (d, *J* = 88.7 Hz), 14.45 (d, *J* = 96.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 52.7 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_8H_{10}BrO_2P$ 248.9675, found 248.9671.

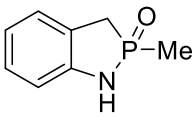
Synthesis of *P*-(2-bromobenzyl)-*P*-methylphosphinic amide 3.22



To a solution of compound **3.21** (15.99 g, 64.2 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) under N_2 was added oxalyl chloride (0.84 mL, 9.77 mmol, 1.2 equiv.) carefully. The reaction mixture was stirred at r.t. for 2 h. This mixture was then added dropwise to a flask containing ammonium hydroxide (28% NH_3 in H_2O, 21.6 mL, 321 mmol, 5.0 equiv.). It was stirred at r.t. for 15 min. The solvent was removed under vacuum. The solid residue was washed with water and dried under vacuum to afford *P*-(2-bromobenzyl)-*P*-methylphosphinic amide **3.22** as a white solid (13.9 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.48-7.45 (m, 1H), 7.34-7.30 (m, 1H), 7.17-7.12 (m, 1H), 3.45 (d, *J* = 17.2 Hz, 2H), 2.74 (s, 2H), 1.51 (d, *J* = 13.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.21 (d, *J* = 2.9 Hz), 132.87 (d, *J* = 7.7 Hz), 131.67 (d, *J* = 4.5 Hz), 128.63 (d, *J* = 3.5 Hz), 127.94 (d, *J* = 3.3 Hz), 124.50 (d, *J* = 7.0

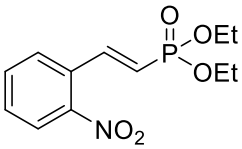
Hz), 39.39 (d, J = 81.0 Hz), 15.99 (d, J = 88.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 34.9 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_8H_{11}BrNOP$ 247.9834, found 247.9827.

Synthesis of 2-methyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 3.20 [24a]



To a round-bottom flask was added phosphonamide **3.22** (7.90 g, 31.8 mmol, 1.00 equiv.), copper(I) bromide (228 mg, 1.60 mmol, 0.05 equiv.), K_2CO_3 (9.67 g, 70.0 mmol, 2.20 equiv.) in CH_3CN (320 mL) under N_2. DMEDA (1.71 mL, 15.9 mmol, 0.50 equiv.) was added to the mixture. The reaction mixture refluxed for 24 h. The solvent was removed under vacuum. The residue was taken up in EtOAc, washed with sat. aq. NH_4Cl. The organic layer was separated. The aqueous layer was extracted with EtOAc (2x). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (AcOEt/MeOH 10:0 to 9:1) to afford 2-methyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **3.20** as a beige solid (3.77 g, 59%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 10.1 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.05 (dd, J = 7.7, 1.4 Hz, 1H), 6.71 (dd, J = 7.4, 1.2 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 3.10 (dd, J = 18.3, 5.6 Hz, 1H), 2.91 (m, 1H), 1.67 (d, J = 14.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 145.82 (d, J = 14.6 Hz), 128.16, 127.46 (d, J = 13.6 Hz), 123.12 (d, J = 2.5 Hz), 119.20, 111.07 (d, J = 11.0 Hz), 31.22 (d, J = 80.8 Hz), 17.47 (d, J = 88.8 Hz); ^{31}P NMR (162 MHz, DMSO-d_6): δ = 53.8 (s).

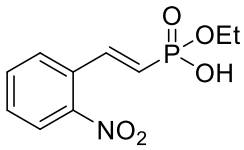
Synthesis of diethyl (E)-(2-nitrostyryl)phosphonate 3.30 [74]



In a round-bottom flask containing tetraethyl methylenediphosphonate **3.29** (4.74 g, 16.4 mmol, 1.00 equiv.) in THF (50 mL) under N_2 at 0 °C was added

NaH (60% suspension in oil, 986 mg, 24.7 mmol, 1.50 equiv.) portionwise. The suspension was stirred for 10 min at 0 °C, then, a solution of 2-nitrobenzaldehyde **3.28** (2.74 g, 18.1 mmol, 1.10 equiv.) in THF (5 mL) was added dropwise at 0 °C. The reactiom mixture was allowed to warm up to r.t. and stirred for 4 h. The reaction mixture was diluted with EtOAc and washed with NH_4Cl (sat. aq.). The aqueous layer was extracted with EtOAc (x2). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hex/EtOAc 6:4 to 3:7) to yield the desired product **3.30** as a yellow oil (3.00 g, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.85 (dd, *J* = 21.9, 17.4 Hz, 1H), 7.70-7.58 (m, 2H), 7.54 (ddd, *J* = 8.27, 7.2, 1.7 Hz, 1H), 6.22 (t, *J* = 17.5 Hz, 1H), 4.18 (dq, *J* = 8.0, 7.1 Hz, 4H), 1.37 (t, *J* = 7.0, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 147.85, 143.65 (d, *J* = 8.0 Hz), 133.71, 131.49 (d, *J* = 24.7 Hz), 130.25, 129.14 (d, *J* = 1.8 Hz), 124.82, 120.24 (d, *J* = 189.0 Hz), 62.31 (d, *J* = 5.7 Hz), 16.39 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 16.5 (s).

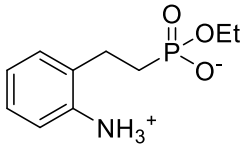
Synthesis of ethyl hydrogen (E)-(2-nitrostyryl)phosphonate 3.31



To a round-bottom flask was added compound **3.30** (3.00 g, 10.5 mmol, 1.00 equiv.) in toluene (10 mL). An aqueous solution of 4N NaOH (42 mL, 42.1 mmol, 4.00 equiv.) was added to the flask. The reaction mixture was then heated at reflux for 24 h. The organic layer and aqueous layer were separated. The aqueous layer was then acidified to pH 1 with aqueous 1N HCl and extracted with DCM (2x). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the desired compound **3.31** as a yellow solid (2.08 g, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* =

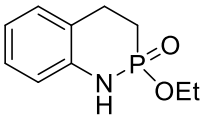
22.3, 17.3 Hz, 1H), 7.66 (d, *J* = 4.1 Hz, 2H), 7.59-7.51 (m, 1H), 6.32 (t, *J* = 17.5 Hz, 1H), 4.25-4.18 (m, 2H), 1.40 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 147.88, 143.19 (d, *J* = 7.9 Hz), 133.64, 131.50 (d, *J* = 25.3 Hz), 130.15, 129.24, 124.79, 120.55 (d, *J* = 194.2 Hz), 62.36 (d, *J* = 5.4 Hz), 16.32 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.6 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_5P$ 258.0526, found 258.0533.

Synthesis of ethyl (2-ammoniophenethyl)phosphonate 3.32



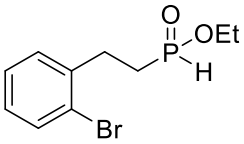
To a Parr hydrogenation reactor containing Palladium on carbon (5% w/w, 331 mg, 0.16 mmol, 2 mol%) under nitrogen, was added a solution of compound **3.31** (2.00 g, 7.78 mmol, 1.00 equiv.) in EtOH (150 mL). The reactor was mounted on a Parr hydrogenation apparatus. The reactor was placed under vacuum and refilled with hydrogen (50 psi). The reaction mixture was agitated at r.t. for 2 h. The hydrogen atmosphere was then slowly evacuated with a water aspirator and replaced with nitrogen. The reaction mixture was then filtered over celite. The filtrate was concentrated under vacuum to yield the desired compound **3.32** as a beige solid (1.77 g, 99 %): ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.03-6.85 (m, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.55-6.52 (m, 1H), 4.89 (s, 3H), 3.92-3.85 (m, 2H), 2.71-2.56 (m, 2H), 1.90-1.72 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-*d*6) δ 145.63, 129.06, 127.19, 126.08 (d, *J* = 15.7 Hz), 117.42, 115.62, 60.21 (d, *J* = 5.7 Hz), 25.84 (d, *J* = 134.2 Hz), 24.59 (d, *J* = 3.8 Hz), 16.94 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, DMSO-*d*6) δ 28.8 (s). HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{16}NO_3P$ 230.0941, found 230.0942.

Synthesis of 2-ethoxy-1,3,4-trihydrobenzo[e][1,2]azaphosphinine 2-oxide 3.24 from 3.32



To a round-bottom flask was added zwitterion **3.24** (1.76 g, 7.68 mmol, 1.00 equiv.) in anhydrous DMF (80 mL). Then EDC.HCl (1.77 g, 9.21 mmol, 1.10 equiv.) was added to the solution. The reaction mixture was then heated at 100 °C for 3h. The solvent was removed under vacuum and the residue was taken up in CH_2Cl_2 and washed with brine. The organic layer was then dried over $MgSO_4$ and concentrated under vacuum to yield compound **3.32** as a beige solid (1.35 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.03 (m, 2H), 6.88-6.84 (m, 1H), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.58 (s, 1H), 4.27-4.05 (m, 2H), 3.33-3.04 (m, 2H), 2.29-2.05 (m, 1H), 2.05-1.88 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.28, 129.32, 127.55 (d, *J* = 2.3 Hz), 122.11 (d, *J* = 9.1 Hz), 120.70, 117.56 (d, *J* = 9.3 Hz), 60.43 (d, *J* = 6.6 Hz), 27.30 (d, *J* = 8.6 Hz), 20.51 (d, *J* = 121.9 Hz), 16.44 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2P$ 212.0835, found 212.0840.

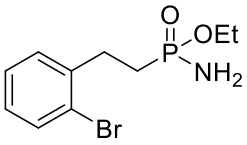
Synthesis of ethyl (2-bromophenethyl)-*H*-phosphinate 3.34 [54]



To a solution of ethyl phosphinate in CH_3CN (0.5 M, 72 mL, 36 mmol, 1.70 equiv.) and 2-bromostyrene **3.33** (3.88 g, 21.2 mmol, 1.00 equiv.) under N_2 was added Pd_2dba_3 (146 mg, 0.16 mmol, 0.75 mol%) and Xantphos (196 mg, 0.34 mmol, 1.6 mol%). The reaction mixture was refluxed for 16 h, then the solvent was removed under vacuum. The residue was taken up in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt, 3:7) to afford the desired product **3.34** as a yellow oil (3.76 g,

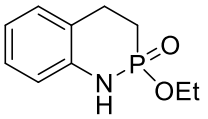
64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.20-7.35 (m, 2H), 7.14 (d, *J* = 533 Hz, 1H), 7.00-7.15 (m, 1H), 4.00-4.25 (m, 2H), 2.90-3.10 (m, 2H), 2.00-2.20 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.59 (d, *J* = 535.0 Hz).

Synthesis of ethyl *P*-(2-bromophenethyl)phosphonamidite 3.35



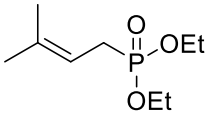
To a round-bottom flask was added *H*-phosphonate **3.34** (1.21 g, 4.37 mmol, 1.00 equiv.) in CCl_4 (4.22 mL, 43.7 mmol, 10 equiv.) and CH_3CN (10 mL) under N_2. The solution was cooled down to 0 °C and Et_3N (1.22 mL, 8.74 mmol, 2.00 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then ammonium hydroxide (28% NH_3 in H_2O, 7.7 mL, 114 mmol, 26.0 equiv.) was added dropwise. The reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. It was then concentrated under vacuum to remove the solvents. The residue was diluted with EtOAc, washed with NH_4Cl, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the desired product **3.35** as an off-white solid (1.01 g, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35-7.20 (m, 2H), 7.09 (ddd, *J* = 7.9, 6.9, 2.2 Hz, 1H), 4.32-3.99 (m, 2H), 3.18-2.96 (m, 2H), 2.87 (d, *J* = 3.4 Hz, 2H), 2.19-1.96 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.47 (d, *J* = 16.9 Hz), 132.95, 130.27, 127.94 (d, *J* = 40.9 Hz), 124.15, 59.87 (d, *J* = 6.6 Hz), 29.78 (d, *J* = 15.1 Hz), 29.13 (d, *J* = 109.8 Hz), 16.52 (d, *J* = 6.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.0 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{15}BrNO_2P$ 292.0097, found 292.0101.

Synthesis of 2-ethoxy-1,3,4-trihydrobenzo[e][1,2]azaphosphinine 2-oxide 3.24 from 3.35



To a round-bottom flask was added compound **3.35** (622 mg, 2.13 mmol, 1.00 equiv.), copper(I) bromide (15 mg, 0.11 mmol, 0.05 equiv.), K_2CO_3 (618 mg, 4.47 mmol, 2.10 equiv.) in CH_3CN (20 mL) under N_2. DMEDA (115 μL, 1.07 mmol, 0.50 equiv.) was added to the mixture. The reaction mixture was refluxed for 24 h. Then, it was concentrated under vacuum to remove the solvent. The residue was taken up in EtOAc, washed with aq. NH_4Cl (sat.). The organic layer was separated. The aqueous layer was extracted with EtOAc (2x). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (Hex/EtOAc 3:7 to 1:9) to afford the desired product **3.24** as a white solid (180 mg, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.03 (m, 2H), 6.88-6.84 (m, 1H), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.58 (s, 1H), 4.27-4.05 (m, 2H), 3.33-3.04 (m, 2H), 2.29-2.05 (m, 1H), 2.05-1.88 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.28, 129.32, 127.55 (d, *J* = 2.3 Hz), 122.11 (d, *J* = 9.1 Hz), 120.70, 117.56 (d, *J* = 9.3 Hz), 60.43 (d, *J* = 6.6 Hz), 27.30 (d, *J* = 8.6 Hz), 20.51 (d, *J* = 121.9 Hz), 16.44 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2P$ 212.0835, found 212.0840.

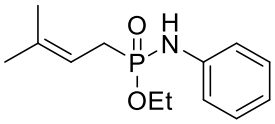
Synthesis of diethyl (3-methylbut-2-en-1-yl)phosphonate 3.36 [56]



In a round-bottom flask was added triethyl phosphite (8.31 g, 50.0 mmol, 1.00 equiv.) and isoprenyl bromide **3.35** (7.45 g, 50.0 mmol, 1.00 equiv.) under N_2. A short-path distillation apparatus was mounted on the flask to trap bromoethane generated during the reaction. The reaction mixture was stirred at 110 °C for 2 h. The reaction yielded diethyl (3-

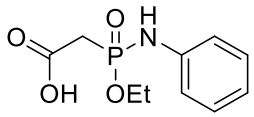
methylbut-2-en-1-yl)phosphonate **3.36** (9.30 g, 91%). The product was used without further purification (NMR purity: 91%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.5 (s)

Synthesis of ethyl *P*-(3-methylbut-2-en-1-yl)-*N*-phenylphosphonamidate 3.37



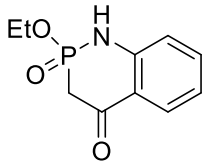
To a solution of compound **3.36** (9.30 g, 45.5 mmol, 1.00 equiv.) in CH_2Cl_2 (15 mL) under N_2 was added oxalyl chloride (5.15 mL, 60.0 mmol, 1.20 equiv.) carefully. DMF (0.40 mL, 5.00 mmol, 0.10 equiv.) was added dropwise and the reaction mixture was stirred at reflux for 24 h. This mixture was then added dropwise to a flask containing aniline (9.10 mL, 100 mmol, 2.20 equiv.) and DIPEA (17.4 mL, 100 mmol, 2.20 equiv.) in DCM (5 mL). It was stirred at r.t. for 12 h. Sat. aq. NH_4Cl was added to the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by silica gel column chromatography (Hex/EtOAc 4:6 to 2:8) to afford ethyl *P*-(3-methylbut-2-en-1-yl)-*N*-phenylphosphonamidate **3.37** (8.76 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 2H), 7.09-6.98 (m, 2H), 6.98-6.82 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.59 (d, *J* = 5.4 Hz, 1H), 5.46-4.95 (m, 1H), 4.34-3.87 (m, 2H), 2.76 (dt, *J* = 7.9, 1.0 Hz, 1H), 2.71 (dt, *J* = 7.7, 1.0 Hz, 1H), 1.65 (dd, *J* = 5.4, 1.4 Hz, 3H), 1.46 (dd, *J* = 4.1, 1.3 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.73, 137.07 (d, *J* = 14.3 Hz), 129.36 (d, *J* = 4.5 Hz), 121.16, 117.25 (d, *J* = 6.1 Hz), 112.27 (d, *J* = 10.1 Hz), 60.17 (d, *J* = 7.1 Hz), 26.68 (d, *J* = 129.1 Hz), 25.77 (d, *J* = 3.2 Hz), 17.88 (d, *J* = 2.8 Hz), 16.24 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}NO_2P$ 254.1304, found 254.1297.

Synthesis of 2-(ethoxy(phenylamino)phosphoryl)acetic acid 3.38



In a round-bottom flask was added compound **3.37** (1.21 g, 4.77 mmol, 1.00 equiv.) in DCM (25 mL). The solution was cooled down to -78 °C and ozone was bubbled in the solution for 15 min. Then, dimethyl sulfide (2.5 mL, 33.4 mmol, 7.00 equiv.) was added to the flask and the reaction mixture was allowed to warm up to r.t. and was stirred for 12 h. The reaction mixture was then concentrated under vacuum and the crude product was dissolved in *t*-BuOH (12.8 mL) and water (6.4 mL). Amylene (1.01 mL, 9.56 mmol, 2.00 equiv.), $NaH_2PO_4.H_2O$ (989 mg, 7.17 mmol, 1.50 equiv.) and $NaOCl_2$ (80% pure, 648 mg, 7.17 mmol, 1.50 equiv.) were added successively to the solution at 0 °C. The reaction mixture was allowed to warm up to r.t. and was stirred for 1 h. The mixture was diluted with EtOAc and washed and washed with 10% aqueous tartaric acid. The aqueous layer was reextracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford 2-(ethoxy(phenylamino)phosphoryl)acetic acid **3.38** (278 mg, 24%). The compound was used without further purification for subsequent steps: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (bs, 1H), 7.47-7.20 (m, 2H), 7.12-6.93 (m, 3H), 6.85 (d, *J* = 5.6 Hz, 1H), 4.38-4.22 (m, 1H), 4.21-3.98 (m, 1H), 3.24-3.00 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.6 (s).

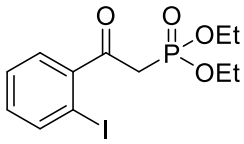
Synthesis of 2-ethoxy-3-hydrobenzo[e][1,2]azaphosphinin-4(1H)-one 2-oxide 3.25



In a round-bottom flask was added compound **3.38** (507 mg, 2.16 mmol, 1.00 equiv.) and cyanuric chloride (637 mg, 3.46 mmol, 1.60 equiv.) in 10 mL of DCM. Pyridine (0.18 mL, 2.16 mmol, 1.00 equiv.) was added dropwise. The solution was stirred at r.t. for 15 min. Then, $AlCl_3$ (864 mg, 6.48 mmol, 3.00 equiv.) was added

portion-wise. The reaction mixture was stirred at r.t. for 5 h. It was then filtered through Celite and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel column chromatography (Hexanes/AcOEt 4:6 to 1:9) to yield the desired product **3.25** (68 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.11-7.77 (m, 1H), 7.63-7.39 (m, 1H), 7.06-7.90 (m, 2H), 4.38-3.98 (m, 2H), 3.43-3.08 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.43 (d, *J* = 5.2 Hz), 143.92 (d, *J* = 3.2 Hz), 135.85, 128.96, 121.47, 118.87 (d, *J* = 11.9 Hz), 61.45 (d, *J* = 6.7 Hz), 40.86 (d, *J* = 114.4 Hz), 16.20 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.6 (s).

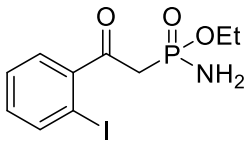
Synthesis of diethyl (2-(2-iodophenyl)-2-oxoethyl)phosphonate 3.40



To a solution of diethyl methylphosphonate (1.75 g, 11.5 mmol, 1.15 equiv.) in THF (10 mL) under N_2 was added *n*-BuLi (2.5 M in hexanes, 4.6 mL, 11.5 mmol, 1.15 equiv.) at -78 °C. The mixture was stirred for 30 min then a solution of methyl 2-iodobenzoate **3.39** (2.62 g, 10.0 mmol, 1.00 equiv.) was added dropwise at -78 °C. The reaction mixture was stirred for 2h at -78 °C. The reaction was diluted with EtOAc and washed with aq. NH_4Cl (sat.) and brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was then purified by silica gel chromatography (Hecanes/AcOEt, 6:4 to 2:8) to afford the desired product **3.40** (2.33g, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.26-7.22 (m, 1H), 6.98-6.94 (m, 1H), 3.93 (dq, *J* = 8.3, 7.1 Hz, 4H), 3.48 (d, *J* = 22.4 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.08 (d, *J* = 6.7 Hz), 142.94 (d, *J* = 1.6 Hz), 140.64, 132.20, 129.35, 127.97, 91.43, 62.53 (d, *J* = 6.5 Hz), 41.12 (d, *J* = 127.5 Hz), 16.20 (d, *J* = 6.3 Hz) ^{31}P

NMR (162 MHz, $CDCl_3$) δ 18.7 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}IO_4P$ 382.9904, found 382.9901.

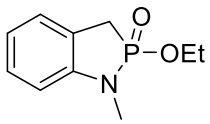
Synthesis of ethyl *P*-(2-(2-iodophenyl)-2-oxoethyl)phosphonamidite 3.41



Compound **3.40** (3.49 g, 9.13 mmol, 1.00 equiv.) was dissolved in $C1H_2Cl_2$ (20 mL) in a flask under N_2. Oxalyl chloride (0.94 mL, 10.9 mmol, 1.20 equiv.) was added cautiously to the solution (bubbles a lot). DMF (70 μL, 0.91 mmol, 10 mol%) was added dropwise to the mixture. The reaction mixture was stirred under N_2 at r.t. for 24 h. The solution was then added dropwise into a flask containing $NH_3.H_2O$ (28% in weight NH_3 in H_2O, 3.5 mL, 5.00 equiv.) and the resulting mixture was stirred at r.t. for 10 min and, then, $NaHSO_4$ (0.5 M) was added until the pH was acidic. The organic layer was washed with $NaHCO_3$ (sat.), brine (sat.), dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by silica gel chromatography (Hex/EtOAc, 3:7 to 0:10) to afford the desired compound **3.41** as a white solid (1.97g, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48-7.44 (m, 1H), 7.17 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 4.12 (dq, *J* = 8.1, 7.1 Hz, 2H), 3.80 (dd, *J* = 20.7, 14.6 Hz, 1H), 3.54 (dd, *J* = 21.3, 14.6 Hz, 1H), 3.26 (d, *J* = 4.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.54 (d, *J* = 7.0 Hz), 143.26 (d, *J* = 3.3 Hz), 141.04, 132.48, 129.24, 128.19, 91.59, 60.73 (d, *J* = 6.7 Hz), 43.51 (d, *J* = 117.1 Hz), 16.32 (d, *J* = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}INO_3P$ 353.9750, found 353.9757.

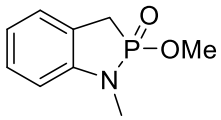
General procedure A: *N*-alkylation of phostams. To a solution of phostam (1.0 equiv.) in THF (0.1M) cooled down to 0°C was added LiHMDS (1.0 M in toluene, 1.1 equiv.) dropwise. The solution was stirred for 5 min at 0 °C then alkyl halide (1.1 equiv.) was added dropwise. The reaction mixture was stirred at r.t. or reflux until completion. Reaction mixture was then diluted with EtOAc and poured onto aq. sat. NH_4Cl. Aqueous layer was extracted with EtOAc (x2). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Crude was purified by silica gel column chromatography.

Synthesis of *N*-methyl-*P*-ethoxy-2,3-dihydro-1*H*-1,2-benzaphosphole 2-oxide 4.1.



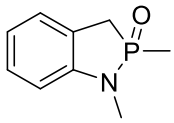
According to *General procedure A*, to a solution of phostam **3.1** (986 mg, 5.00 mmol, 1.00 equiv.) in THF (50 mL) was added LiHMDS (1M in toluene, 5.50 mL, 5.50 mmol, 1.10 equiv.) and then iodomethane (0.34 mL, 5.50 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 1 h. After quenching and working up, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4 to 4:6) to yield the desired product as a beige solid (710 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.07 (m, 1H), 7.04-7.01 (m, 1H), 6.75-6.70 (m, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 3.98 (dq, *J* = 8.0, 7.7 Hz, 2H), 3.00-2.80 (m, 2H), 2.88 (d, *J* = 8.2 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (d, *J* = 27.1 Hz), 128.22 (s), 126.6 (d, *J* = 16.9 Hz), 120.4 (d, *J* = 4.1 Hz), 119.8 (d, *J* = 1.8 Hz), 108.2 (d, *J* = 11.0 Hz), 62.3 (d, *J* = 6.5 Hz), 26.8 (d, *J* = 1.7 Hz), 25.4 (d, *J* = 119.8 Hz), 16.5 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.5 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2P$ 212.0835, found 212.0843

Synthesis of 2-methoxy-1-methyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.2



According to *General procedure A*, to a solution of phostam **3.10** (183 mg, 1.00 mmol, 1.00 equiv.) in THF (20 mL) was added LiHMDS (1M in toluene, 1.10 mL, 1.10 mmol, 1.10 equiv.) and then iodomethane (68 μL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 30 minutes. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 5:5 to 3:7) to yield the desired product **4.2** as a yellowish oil (118 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.86 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 3.74 (dd, J = 11.4, 2.0 Hz, 3H), 3.27 – 2.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.42 (d, J = 27.2 Hz), 128.39, 126.70 (d, J = 16.9 Hz), 120.38 (d, J = 3.9 Hz), 120.07 (d, J = 2.0 Hz), 108.32 (d, J = 11.2 Hz), 52.94 (d, J = 6.6 Hz), 26.98 (d, J = 1.7 Hz), 24.72 (d, J = 119.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.1 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_9H_{12}NO_2P$ 198.0678, found 198.0684.

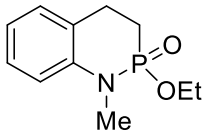
Synthesis of 1,2-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.3



According to *General procedure A*, to a solution of phostam **3.20** (334 mg, 2.00 mmol, 1.00 equiv.) in THF (20 mL) was added LiHMDS (1M in toluene, 2.20 mL, 2.20 mmol, 1.10 equiv.) and then iodomethane (0.14 mL, 2.20 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 30 min. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 4:6 to 1:9) to yield the desired product **4.3** as a beige solid (234 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.13 (m, 2H), 6.83-6.79 (m, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 3.16 (dd, *J* = 18.3 Hz, 1H), 3.01-2.95 (m, 4H), 1.70 (d, *J* = 14.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (d, *J* = 20.4 Hz), 128.4 (s), 126.9 (d, *J* = 13.2 Hz), 121.6 (d, *J* =

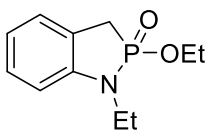
1.6 Hz), 119.6 (d, *J* = 1.5 Hz), 108.2 (d, *J* = 8.9 Hz), 30.1 (d, *J* = 82.6 Hz), 26.9 (d, *J* = 2.7 Hz), 14.9 (d, *J* = 88.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 56.3 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_9H_{12}NOP$ 182.0729, found 182.0724

Synthesis of 2-ethoxy-1-methyl-1,3,4-trihydrobenzo[e][1,2]azaphosphinine 2-oxide 4.4



According to *General procedure A,* to a solution of phostam **3.24** (211 mg, 1.00 mmol, 1.00 equiv.) in THF (5 mL) was added LiHMDS (1M in toluene, 1.10 mL, 1.10 mmol, 1.10 equiv.) and then iodomethane (68 μL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 30 min. After quench, workup and silica gel chromatography (Hexanes/AcOEt 5:5) the desired product **4.4** was obtained as a colorless oil (196 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 9.1, 7.4, 1.7 Hz, 1H), 7.07 (ddd, *J* = 7.5, 1.6, 0.9 Hz, 1H), 6.94-6.79 (m, 2H), 4.13-4.02 (m, 2H), 3.13 (d, *J* = 7.2 Hz, 3H), 3.15-3.01 (m, 2H), 2.18-1.98 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.21 (d, *J* = 3.8 Hz), 128.74 (d, *J* = 1.3 Hz), 127.66, 125.51 (d, *J* = 8.2 Hz), 120.71, 114.33 (d, *J* = 6.0 Hz), 61.53 (d, *J* = 6.4 Hz), 29.69 (d, *J* = 1.4 Hz), 26.65 (d, *J* = 8.4 Hz), 21.87 (d, *J* = 121.7 Hz), 16.54 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0987.

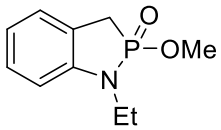
Synthesis of 2-ethoxy-1-ethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.5



According to *General procedure A*, to a solution of phostam **3.1** (197 mg, 1.00 mmol, 1.00 equiv.) in THF (12 mL) was added LiHMDS (1M in toluene, 1.10

mL, 1.10 mmol, 1.10 equiv.) and then iodoethane (88 μL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 6 h. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4) to yield the desired product **4.5** as a colorless oil (144 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.03 (m, 2H), 6.85 – 6.81 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.10 (p, *J* = 7.4 Hz, 2H), 3.51 (ddt, *J* = 17.9, 10.7, 7.2 Hz, 2H), 3.28 – 2.70 (m, 2H), 1.33 (td, *J* = 7.0, 3.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.47 (d, *J* = 27.9 Hz), 128.20, 126.95 (d, *J* = 17.0 Hz), 120.75 (d, *J* = 4.1 Hz), 119.66 (d, *J* = 2.0 Hz), 108.59 (d, *J* = 11.4 Hz), 62.30 (d, *J* = 6.5 Hz), 35.74 (d, *J* = 1.8 Hz), 25.75 (d, *J* = 119.0 Hz), 16.55 (d, *J* = 6.2 Hz), 13.66 (s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0999.

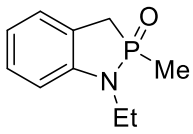
Synthesis of 1-ethyl-2-methoxy-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.6



According to *General procedure A*, to a solution of phostam **3.10** (183 mg, 1.00 mmol, 1.00 equiv.) in THF (12 mL) was added LiHMDS (1M in toluene, 1.10 mL, 1.10 mmol, 1.10 equiv.) and then iodoethane (88 μL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 6 h. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4 to 4:6) to yield the desired product **4.6** as a yellowish oil (127 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.04 (m, 2H), 6.87 – 6.87 (tt, *J* = 7.6, 1.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.73 (d, *J* = 11.6 Hz, 3H), 3.65 – 3.37 (m, 2H), 3.18 – 2.84 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.42 (d, *J* = 27.9 Hz), 128.26, 126.96 (d, *J* = 16.9 Hz), 120.59 (d, *J* = 4.1 Hz), 119.82 (d, *J* = 1.9 Hz), 108.66 (d, *J* = 11.4 Hz), 52.81 (d, *J* = 6.6 Hz), 35.83 (d, *J* = 1.8 Hz), 24.92 (d, *J* = 119.0 Hz), 13.72; ^{31}P NMR (162

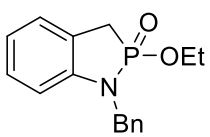
MHz, $CDCl_3$) δ 47.8 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2P$ 212.0835, found 212.0840.

Synthesis of 1-ethyl-2-methyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.7



According to *General procedure A*, to a solution of phostam **3.20** (282 mg, 1.69 mmol, 1.00 equiv.) in THF (12 mL) was added LiHMDS (1M in toluene, 1.86 mL, 1.86 mmol, 1.10 equiv.) and then iodoethane (0.15 mL, 1.86 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 6 h. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 4:6 to 2:8) to yield the desired product **4.7** as a colorless oil (204 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.15 (m, 2H), 6.82-6.79 (m, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 3.65-3.44 (m, 2H), 3.22-3.13 (m, 1H), 2.98 (dd, *J* = 18.1, 5.0 Hz, 1H), 1.74 (d, *J* = 13.9 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (d, *J* = 21.2 Hz), 128.3 (s), 127.2 (d, *J* = 13.5 Hz), 121.8 (d, *J* = 1.8 Hz), 119.4 (d, *J* = 1.3 Hz), 108.5 (d, *J* = 9.0 Hz), 35.7 (d, *J* = 2.8 Hz), 30.3 (d, *J* = 82.3 Hz), 16.1 (d, *J* = 88.5 Hz), 14.0 (d, *J* = 0.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 55.3 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NOP$ 196.0886, found 196.0889.

Synthesis of 1-benzyl-2-ethoxy-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.8



According to *General procedure A*, to a solution of phostam **3.1** (4.00 g, 20.3 mmol, 1.00 equiv.) in THF (12 mL) was added LiHMDS (1M in toluene, 22.3 mL, 22.3 mmol, 1.10 equiv.) and then benzyl bromide (2.66 mL, 22.3 mmol, 1.10 equiv.). The

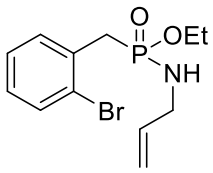
reaction mixture was stirred at reflux for 1 h. After quench and workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4 to 4:6) to yield the desired product **4.8** as a white solid (4.02 g, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 1H), 7.39-7.31 (m, 2H), 7.32-7.23 (m, 1H), 7.18 (d, *J* = 7.4 Hz, 0H), 7.12-7.03 (m, 1H), 6.89-6.79 (m, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.81-4.52 (m, 2H), 4.30-3.94 (m, 2H), 3.55-2.94 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.67 (d, *J* = 27.8 Hz), 136.93 (d, *J* = 2.2 Hz), 128.65, 128.18, 127.32, 127.01, 126.79 (d, *J* = 17.0 Hz), 120.57 (d, *J* = 3.7 Hz), 120.11 (d, *J* = 1.9 Hz), 109.80 (d, *J* = 11.1 Hz), 62.51 (d, *J* = 6.6 Hz), 45.00 (d, *J* = 2.1 Hz), 25.97 (d, *J* = 120.4 Hz), 16.53 (d, *J* = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2P$ 288.1148, found 288.1157.

General procedure B: Chlorination/amination sequence of phosphonate 3.7. To a solution of compound **3.7** (1.0 equiv.) in CH_2Cl_2 (0.5 M) under N_2 was added oxalyl chloride (1.2 equiv.) carefully. DMF (0.1 equiv.) was added dropwise and the reaction mixture was stirred at reflux for 12 h. This mixture was then added dropwise to a flask containing the primary amine (1.2 equiv.) and DIPEA (2.0 equiv.) in DCM (~1M in regard to phosphonate **3.7**). It was stirred at r.t. for 8 h. Sat. aq. NH_4Cl was added to the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford the pure phosphonamides.

General procedure C: Amination of *H*-phosphinate 3.8 via an Atherton-Todd reaction. To a round-bottom flask was added iodoform (1.20 equiv.), DIPEA (2.00 equiv.) and benzylamine (1.20 equiv.) in CH_3CN (0.4 M in regard to *H*-phosphinate **3.8**) under N_2. The mixture was cooled down to 0 °C. A solution of *H*-phosphinate (1.00 equiv.) in CH_3CN (2 M in regard to *H*-phosphinate **3.8**)

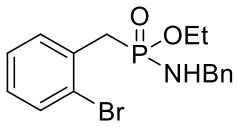
was added dropwise to the mixture via an addition funnel at 0 °C. The reaction mixture was allowed to warm up to r.t. and stirred for 2 h. The reaction mixture was then concentrated under vacuum to remove the solvent. The residue was taken up in EtOAc and washed with aq. sat. NH_4Cl then with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to yield the desired product phosphonamides.

Synthesis of ethyl *N*-allyl-*P*-(2-bromobenzyl)phosphonamidate 4.10



According to *General procedure B*, to a solution of phosphonate **3.7** (2.50 g, 8.14 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) under N_2 was added oxalyl chloride (0.84 mL, 9.77 mmol, 1.2 equiv.) and DMF (63 μL, 0.81 mmol, 0.1 equiv.). After chlorination this mixture was then added to allylamine (0.73 mL, 9.77 mmol, 1.2 equiv.) and DIPEA (2.8 mL, 16.3 mmol, 2.0 equiv.) in DCM (5 mL). After workup, the crude was purified by silica gel column chromatography (Hex/EtOAc 6:4 to 2:8) to afford ethyl N-benzyl-(2-bromobenzyl)phosphonamidate **4.10** (1.39 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (ddd, *J* = 7.7, 2.8, 1.8 Hz, 1H), 7.31-7.25 (m, 1H), 7.11 (dd, *J* = 7.7, 2.0 Hz, 1H), 5.93-5.64 (m, 1H), 5.16 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.05 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.22-3.84 (m, 2H), 3.68-3.31 (m, 2H), 3.41 (dd, *J* = 21.0, 1.9 Hz, 2H), 2.55 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.32 (d, *J* = 5.4 Hz), 132.89 (d, *J* = 2.9 Hz), 132.70 (d, *J* = 8.2 Hz), 131.77 (d, *J* = 4.9 Hz), 128.37 (d, *J* = 3.6 Hz), 127.58 (d, *J* = 3.4 Hz), 124.90 (d, *J* = 8.4 Hz), 115.31, 60.20 (d, *J* = 6.9 Hz), 43.59, 35.28 (d, *J* = 126.2 Hz), 16.36 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}BrNO_2P$ 318.0253, found 318.0261

Synthesis of ethyl *N*-benzyl-*P*-(2-bromobenzyl)phosphonamidate 4.11



According to *General procedure B*, to a solution of phosphonate **3.7** (2.50 g, 8.14 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added oxalyl chloride (0.84 mL, 9.77 mmol, 1.2 equiv.) and DMF (63 μL, 0.81 mmol, 0.1 equiv.). After chlorination this mixture was then added to benzylamine (1.10 mL, 9.77 mmol, 1.2 equiv.) and DIPEA (2.8 mL, 16.3 mmol, 2.0 equiv.) in DCM (5 mL). After workup, the crude was purified by silica gel column chromatography (Hex/EtOAc 6:4 to 2:8) to afford ethyl N-benzyl-(2-bromobenzyl)phosphonamidate **4.11** (1.85 g, 62%).

Or

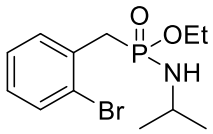
According to *General procedure C*, to solution of iodoform (945 mg, 2.40 mmol, 1.20 equiv.), DIPEA (0.70 mL, 4.00 mmol, 2.00 equiv.) and benzylamine (0.26 mL, 2.40 mmol, 1.20 equiv.) in CH_3CN (5 mL) was added a solution of *H*-phosphonate **3.8** (526 mg, 2.00 mmol, 1.00 equiv.) in CH_3CN (1 mL). After workup, the desired product **4.11** was obtained as an off-white solid (677 mg, 92%).

Or

To a round-bottom flask was added *H*-phosphonate **3.8** (2.63 g, 10 mmol, 1.0 equiv.) in CCl_4 (9.6 mL, 100 mmol, 10 equiv.) and CH_3CN (20 mL) under N_2. The solution was cooled down to 0 °C and Et_3N (2.80 mL, 20.0 mmol, 2.0 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then benzylamine (2.18 mL, 20 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. It was then concentrated under vacuum to remove the solvents. The residue was diluted with EtOAc, washed with NH_4Cl, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the

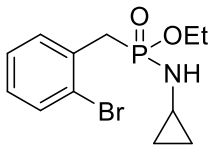
desired phosphonamidate **4.11** as an off-white solid (g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.54 (m, 1H), 7.50 (ddd, *J* = 7.7, 2.7, 1.7 Hz, 1H), 7.36-7.20 (m, 6H), 7.15-7.00 (m, 1H), 4.52-4.05 (m, 2H), 4.05-3.83 (m, 2H), 3.44 (d, *J* = 20.9 Hz, 2H), 2.85 (dt, *J* = 10.7, 7.1 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.86 (d, *J* = 5.8 Hz), 132.92 (d, *J* = 2.9 Hz), 132.69 (d, *J* = 8.3 Hz), 131.83 (d, *J* = 4.9 Hz), 128.57, 128.42 (d, *J* = 3.5 Hz), 127.62 (d, *J* = 3.4 Hz), 127.29, 124.91 (d, *J* = 8.4 Hz), 60.35 (d, *J* = 6.9 Hz), 45.10, 35.37 (d, *J* = 125.5 Hz), 16.35 (d, *J* = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}BrNO_2P$ 368.0410, found 368.0409.

Synthesis of ethyl *P*-(2-bromobenzyl)-*N*-isopropylphosphonamidate 4.12



According to *General procedure C*, to solution of iodoform (7.17 g, 18.2 mmol, 1.2 equiv.), DIPEA (5.30 mL, 30.4 mmol, 2.00 equiv.) and isopropylamine (2.60 mL, 30.4 mmol, 2.00 equiv.) in CH_3CN (45 mL) was added a solution of *H*-phosphonate **3.8** (4.00 g, 15.2 mmol, 1.0 equiv.) in CH_3CN (5 mL). After workup, the desired product **4.12** was obtained as a beige solid (5.07 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 7.20 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.02 (ddd, *J* = 9.7, 4.8, 2.0 Hz, 1H), 4.10-3.73 (m, 2H), 3.50 – 3.22 (m, 1H), 3.30 (d, *J* = 20.8 Hz, 2H), 2.36 (t, *J* = 10.3 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.88 (d, *J* = 8.0 Hz), 132.75 (d, *J* = 2.9 Hz), 131.62 (d, *J* = 5.0 Hz), 128.21 (d, *J* = 3.4 Hz), 127.48 (d, *J* = 3.3 Hz), 124.95 (d, *J* = 8.7 Hz), 59.81 (d, *J* = 6.8 Hz), 43.31, 35.54 (d, *J* = 126.2 Hz), 25.95 (d, *J* = 4.5 Hz), 25.38 (d, *J* = 4.7 Hz), 16.34 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 27.5 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{19}BrNO_2P$ 320.0419, found 320.0391.

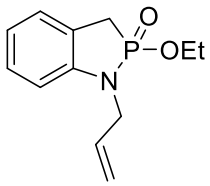
Synthesis of ethyl *P*-(2-bromobenzyl)-*N*-cyclopropylphosphonamidate 4.13



According to *General procedure C*, to solution of iodoform (7.17 g, 18.2 mmol, 1.2 equiv.), DIPEA (5.30 mL, 30.4 mmol, 2.00 equiv.) and cyclopropylamine (2.10 mL, 30.4 mmol, 2.00 equiv.) in CH_3CN (45 mL) was added a solution of *H*-phosphonate **3.8** (4.00 g, 15.2 mmol, 1.0 equiv.) in CH_3CN (5 mL). After workup, the desired product **4.13** was obtained as an off-white solid (5.09 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.24-7.13 (m, 1H), 7.08-7.01 (m, 1H), 4.09-3.78 (m, 2H), 3.55-3.28 (m, 3H), 2.26 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.52 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.82 (d, *J* = 2.7 Hz), 132.65 (d, *J* = 7.7 Hz), 131.68 (d, *J* = 5.0 Hz), 128.25 (d, *J* = 3.3 Hz), 127.47 (d, *J* = 3.2 Hz), 124.99 (d, *J* = 9.0 Hz), 60.00 (d, *J* = 6.8 Hz), 34.61 (d, *J* = 124.6 Hz), 22.88, 16.31 (d, *J* = 6.7 Hz), 7.53 (d, *J* = 4.5 Hz), 6.93 (d, *J* = 4.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.7 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}BrNO_2P$ 318.0253, found 318.0235.

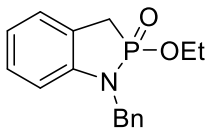
General procedure D: Copper-catalyzed cyclization of phosphinamides. To a mixture of phosphonamide (1.0 equiv.), copper(I) bromide (5 mol%), potassium carbonate (2.2 equiv.) in acetonitrile (0.1 M) under N_2 was added *N*,*N*'-dimethylethylenediamine (0.5 equiv.). The reaction mixture is then stirred at reflux for 24 h. It was then cooled down to r.t. diluted in AcOEt, washed with aq. sat. NH_4Cl and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Crude was purified by silica gel column chromatography to afford the pure phostam.

Synthesis of 1-allyl-2-ethoxy-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.14



According to *General procedure D*, to a mixture of phostam **4.10** (1.39 g, 4.37 mmol, 1.00 equiv.), copper(I) bromide (31 mg, 0.22 mmol, 0.05 equiv.), K_2CO_3 (1.27 g, 9.18 mmol, 2.10 equiv.) in CH_3CN (45 mL) was added DMEDA (54 μL, 0.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/EtOAc 3:7 to 1:9) compound **4** as a beige solid (653 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 2H), 6.86-6.77 (m, 1H), 6.62 (dd, *J* = 7.7, 1.1 Hz, 1H), 5.89 (ddt, J = 17.2, 10.2, 5.0 Hz, 1H), 5.30 (dd, J = 17.2, 1.7 Hz, 1H), 5.21 (dd, J = 10.4, 1.6 Hz, 1H), 4.27-3.85 (m, 4H), 3.34-2.68 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.60 (d, *J* = 27.6 Hz), 133.06 (d, *J* = 1.6 Hz), 128.11, 126.77 (d, *J* = 16.9 Hz), 120.56 (d, *J* = 3.9 Hz), 119.98 (d, *J* = 1.9 Hz), 117.20, 109.53 (d, *J* = 11.1 Hz), 62.32 (d, *J* = 6.6 Hz), 43.53 (d, *J* = 1.9 Hz), 25.77 (d, *J* = 120.2 Hz), 16.51 (d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.0 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}NO_2P$ 238.0991, found 238.0993

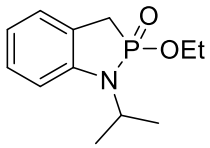
Synthesis of 1-benzyl-2-ethoxy-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.8



According to *General procedure D*, to a mixture of phostam **4.11** (1.86 g, 5.04 mmol, 1.00 equiv.), copper(I) bromide (36 mg, 0.25 mmol, 0.05 equiv.), K_2CO_3 (1.46 g, 10.6 mmol, 2.10 equiv.) in CH_3CN (50 mL) was added DMEDA (0.27 mL, 2.52 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/EtOAc 3:7 to 1:9) to afford compound **4.8** as a white solid (593 mg, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 1H), 7.37-7.31 (m, 1H), 7.30-7.26 (m, 1H), 7.18 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.11-7.02 (m, 1H), 6.84 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.83-4.54

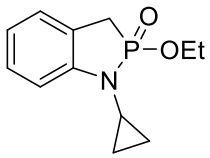
(m, 1H), 4.31-3.99 (m, 1H), 3.26-3.01 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.67 (d, *J* = 27.8 Hz), 136.93 (d, *J* = 2.2 Hz), 128.65, 128.18, 127.32, 127.01, 126.79 (d, *J* = 17.0 Hz), 120.57 (d, *J* = 3.7 Hz), 120.11 (d, *J* = 1.9 Hz), 109.80 (d, *J* = 11.1 Hz), 62.51 (d, *J* = 6.6 Hz), 45.00 (d, *J* = 2.1 Hz), 25.97 (d, *J* = 120.4 Hz), 16.53 (d, *J* = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2P$ 288.1148, found 288.1157.

Synthesis of 2-ethoxy-1-isopropyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.15



According to *General procedure D*, to a mixture of phostam **4.12** (1.71 g, 5.34 mmol, 1.00 equiv.), copper(I) bromide (38 mg, 0.27mmol, 0.05 equiv.), K_2CO_3 (1.62 g, 11.75 mmol, 2.20 equiv.) in CH_3CN (55 mL) was added DMEDA (0.29 mL, 2.67 mmol, 0.50 equiv.). Reaction time: 96 h instead of 24 h. After workup, the crude was purified by silica gel column chromatography (Hexanes/EtOAc 5:5 to 2:8) to afford compound **4.15** as a yellowish oil (497 mg, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-6.99 (m, 2H), 6.79 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 4.07 (ddq, *J* = 12.1, 7.4, 4.7, 3.9 Hz, 2H), 3.95 (dsept, *J* = 13.6, 6.9 Hz, 1H), 3.18-2.76 (m, 2H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.51 (d, *J* = 28.1 Hz), 128.02, 126.97 (d, *J* = 17.0 Hz), 120.70 (d, *J* = 4.0 Hz), 119.36 (d, *J* = 2.0 Hz), 109.65 (d, *J* = 11.4 Hz), 62.13 (d, *J* = 6.3 Hz), 45.84, 26.42 (d, *J* = 118.4 Hz), 21.15 (d, *J* = 1.4 Hz), 20.28 (d, *J* = 2.2 Hz), 16.44 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{18}NO_2P$ 240.1148, found 240.1146

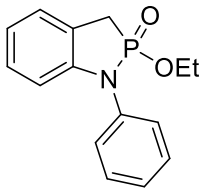
Synthesis of 1-cyclopropyl-2-ethoxy-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.16



According to *General procedure D*, to a mixture of phostam **4.13** (636 mg, 2.00 mmol, 1.00 equiv.), copper(I) bromide (14 mg, 0.10 mmol, 0.05 equiv.), K_2CO_3 (608 mg, 4.40 mmol, 2.20 equiv.) in CH_3CN (20 mL) was added DMEDA (0.11 mL, 1.00 mmol, 0.50 equiv.). Reaction time: 48 h instead of 24 h. After workup, the crude was purified by silica gel column chromatography (Hexanes/EtOAc 5:5 to 2:8) to afford compound **4.16** as a colorless oil (497 mg, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.19 (m, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.16 (dq, *J* = 8.7, 7.0 Hz, 2H), 3.19-2.82 (m, 2H), 2.53-2.48 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.31-1.16 (m, 1H), 0.99-0.83 (m, 2H), 0.84-0.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.94 (d, *J* = 29.1 Hz), 128.14, 126.59 (d, *J* = 16.4 Hz), 120.14 (d, *J* = 2.0 Hz), 119.95 (d, *J* = 3.5 Hz), 109.91 (d, *J* = 10.6 Hz), 62.44 (d, *J* = 6.6 Hz), 26.12 (d, *J* = 118.6 Hz), 23.04, 16.56 (d, *J* = 5.9 Hz), 5.32 (d, *J* = 4.3 Hz), 4.85 (d, *J* = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.3 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}NO_2P$ 238.0991, found 238.1003.

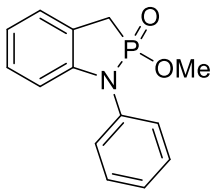
General procedure E: *N*-arylation of phostams. To a mixture of phostam (1.0 equiv.), copper(I) bromide (5 mol%), potassium carbonate (2.10 equiv) in acetonitrile (0.1 M) under N_2 was added aryl iodide (1.2 equiv.) followed by DMEDA (0.5 equiv.). The reaction mixture is then stirred at reflux for 16 h. It was then cooled down to r.t. diluted in AcOEt, washed with aq. sat. NH_4Cl and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude was purified by silica gel column chromatography.

Synthesis of 2-ethoxy-1-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.17



According to *General procedure E*, to a mixture of phostam **3.1** (986 mg, 5.00 mmol, 1.00 equiv.), CuBr (36 mg, 0.25 mmol, 5 mol%) and K_2CO_3 (1.52 g, 11.0 mmol) in CH_3CN (50 mL) was added iodobenzene (0.67 mL, 6.00 mmol, 1.20 equiv.) and DMEDA (0.27 mL, 2.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 5:5) to yield the desired product **4.17** as a yellowish oil (1.07 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 4H), 7.37-7.32 (m, 1H), 7.22-7.20 (m, 1H), 7.13-7.08 (m, 1H), 6.91-6.87 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.18-3.99 (m, 2H), 3.30-3.10 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (d, *J* = 28.6 Hz), 136.1 (s), 129.9 (s), 128.1 (s), 127.3 (d, *J* = 2.9 Hz), 127.3 (s), 127.1 (d, *J* = 17.0 Hz), 120.7 (d, *J* = 1.9 Hz), 120.3 (d, *J* = 3.9 Hz), 110.2 (d, *J* = 9.9 Hz), 62.9 (d, *J* = 6.6 Hz), 26.4 (d, *J* = 120.3 Hz), 16.4 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.8 (s); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}NO_2P$ 274.0991, found 274.1004.

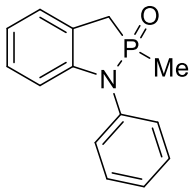
Synthesis of 2-methoxy-1-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.18



According to *General procedure E*, to a mixture of phostam **3.10** (183 mg, 1.00 mmol, 1.00 equiv.), CuBr (7 mg, 0.05 mmol, 5 mol%) and K_2CO_3 (290 mg, 2.10 mmol, 2.10 equiv.) in CH_3CN (10 mL) was added iodobenzene (0.13 mL, 1.20 mmol, 1.20 equiv.) and DMEDA (54 μL, 0.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 5:5 to 1:9) to yield the desired product **4.18** as a colorless oil (62 mg, 24%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.41 (m, 4H), 7.41 – 7.32 (m, 1H), 7.25 – 7.22 (m, 1H), 7.18 – 7.08 (m, 1H), 6.93 – 6.91 (m, 1H), 6.62 (d, *J* =

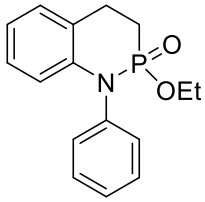
8.0 Hz, 1H), 3.74 (d, *J* = 11.5 Hz, 3H), 3.50 – 3.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.49 (d, *J* = 28.4 Hz), 135.99, 129.96, 128.21, 127.36, 127.24, 127.20 (d, *J* = 2.7 Hz), 127.07, 120.89 (d, *J* = 2.1 Hz), 120.17 (d, *J* = 3.5 Hz), 53.41 (d, *J* = 6.8 Hz), 25.59 (d, *J* = 120.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 44.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_2P$ 260.0835, found 260.0843.

Synthesis of 2-methyl-1-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.19



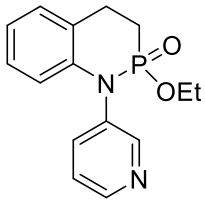
According to *General procedure E*, to a mixture of phostam **3.20** (167 mg, 1.00 mmol, 1.00 equiv.), CuBr (7 mg, 0.05 mmol, 5 mol%) and K_2CO_3 (290 mg, 2.10 mmol, 2.10 equiv.) in CH_3CN (10 mL) was added iodobenzene (0.13 mL, 1.20 mmol, 1.20 equiv.) and DMEDA (54 μL, 0.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 5:5 to 1:9) to yield the desired product **4.19** as a white solid (182 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.1, 1H), 7.35 – 7.32 (m, 1H), 7.30 – 7.20 (m, 3H), 7.15 – 7.10 (m, 3H), 7.01 – 6.97 (m, 1H), 5.37 (d, *J* = 10.5 Hz, 1H), 3.60 (d, *J* = 17.5 Hz, 2H), 1.58 (d, *J* = 13.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.63 (d, *J* = 1.4 Hz), 133.18 (d, *J* = 2.9 Hz), 132.60 (d, *J* = 7.1 Hz), 131.91 (d, *J* = 4.7 Hz), 129.53, 128.74 (d, *J* = 3.4 Hz), 127.96 (d, *J* = 3.3 Hz), 124.42 (d, *J* = 7.0 Hz), 121.96, 118.54 (d, *J* = 5.6 Hz), 37.55 (d, *J* = 81.0 Hz), 14.77 (d, *J* = 88.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 34.7 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NOP$ 244.0886, found 244.0874.

Synthesis of 2-ethoxy-1-phenyl-1,3,4-trihydrobenzo[e][1,2]azaphosphinine 2-oxide 4.21



According to *General procedure E*, to a mixture of phostam **3.24** (211 mg, 1.00 mmol, 1.00 equiv.), CuBr (7 mg, 0.05 mmol, 5 mol%) and K_2CO_3 (290 mg, 2.10 mmol, 2.10 equiv.) in CH_3CN (10 mL) was added iodobenzene (0.13 mL, 1.20 mmol, 1.20 equiv.) and DMEDA (54 μL, 0.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 5:5) to yield the desired product **4.21** as a colorless oil (175 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.40 (m, 2H), 7.40-7.30 (m, 3H), 7.13 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.04-7.02 (m, 1H), 6.90-6.86 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.37-3.81 (m, 2H), 3.37-3.01 (m, 2H), 2.44-2.13 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.47 (d, *J* = 4.8 Hz), 138.94, 129.84 (d, *J* = 2.2 Hz), 129.72, 128.73, 127.46, 127.25, 126.53 (d, *J* = 7.5 Hz), 121.58, 118.83 (d, *J* = 5.2 Hz), 62.10 (d, *J* = 6.4 Hz), 26.68 (d, *J* = 8.4 Hz), 23.66 (d, *J* = 121.7 Hz), 16.44 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2P$ 288.1148, found 288.1158.

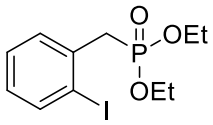
Synthesis of 2-ethoxy-1-(pyridin-3-yl)-1,3,4-trihydrobenzo[e][1,2]azaphosphinine 2-oxide 4.22



According to *General procedure E*, to a mixture of phostam **3.24** (211 mg, 1.00 mmol, 1.00 equiv.), CuBr (7 mg, 0.05 mmol, 5 mol%) and K_2CO_3 (290 mg, 2.10 mmol, 2.10 equiv.) in CH_3CN (10 mL) was added 3-iodopyridine (246 mg, 1.20 mmol, 1.20 equiv.) and DMEDA (54 μL, 0.50 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 4:6) to yield the desired product **4.22** as a yellowish oil (219 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63-8.44 (m, 1H), 7.72

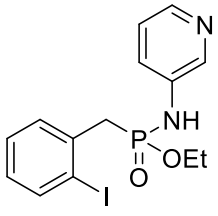
(ddd, J = 8.1, 2.5, 1.3 Hz, 1H), 7.36 (ddd, J = 8.1, 4.8, 0.8 Hz, 1H), 7.13 (dd, J = 7.5, 1.6 Hz, 1H), 7.07-6.98 (m, 1H), 6.93-6.89 (m, 1H), 6.41 (dd, J = 8.2, 0.9 Hz, 1H), 4.24-3.91 (m, 2H), 3.36-3.02 (m, 2H), 2.41-2.19 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.49 (d, J = 2.5 Hz), 147.83, 143.64 (d, J = 4.0 Hz), 136.96 (d, J = 2.1 Hz), 136.23, 129.00 (d, J = 1.3 Hz), 127.71, 127.15 (d, J = 7.5 Hz), 124.18, 122.42, 119.01 (d, J = 4.8 Hz), 62.20 (d, J = 6.4 Hz), 26.57 (d, J = 8.4 Hz), 23.62 (d, J = 122.1 Hz), 16.41 (d, J = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_2P$ 289.1100, found 289.1111.

Synthesis of diethyl (2-iodobenzyl)phosphonate 4.24 [73]



In a round-bottom flask was added triethyl phosphite (2.42 g, 14.6 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **4.23** (4.33 g, 14.6 mmol, 1.0 equiv.) under N_2. A short-path distillation apparatus was mounted on the flask to trap iodoethane generated during the reaction. The reaction mixture was stirred at 110 °C for 2 h. The reaction yielded diethyl (2-iodobenzyl)phosphonate **4.24** (4.96 g, 96%) as a clear oil. Product was used without further purification (NMR purity: 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1H), 7.39-7.30 (m, 1H), 7.20-7.10 (m, 1H), 6.86-6.65 (m, 1H), 3.91 (dq, J = 8.1, 7.1 Hz, 4H), 3.38-3.14 (m, 2H), 1.13 (t, J = 7.1 Hz, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 25.1 (s).

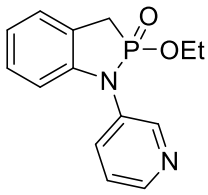
Synthesis of ethyl *P*-(2-iodobenzyl)-*N*-(pyridin-3-yl)phosphonamidite 4.25 [73]



Diethyl (2-iobenzyl)phosphonate **4.24** (4.96 g, 14.6 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (40 mL) in a flask under N_2. Oxalyl chloride (1.50 mL,

17.5 mmol, 1.20 equiv.) was added cautiously to the solution (bubbles a lot). DMF (0.12 mL, 1.50 mmol, 10 mol%) was added dropwise to the mixture. The reaction mixture was stirred under N_2 at r.t. for 24 h. The solution was then added dropwise into a flask containing 3-aminopyridine (2.75 g, 29.2 mmol, 2.00 equiv.) and DIPEA (5.10 mL, 29.2 mmol, 2.00 equiv.) in CH_2Cl_2 (10 mL). the resulting mixture was stirred at r.t. for 10 h. Then, NH_4Cl (aq. sat.) was added to quench the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by silica gel chromatography (EtOAc) to afford ethyl *P*-(2-iodobenzyl)-*N*-(pyridin-3-yl)phosphonamidite **4.25** as a beige solid (3.46 g, 59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.8 Hz, 1H), 8.24-8.01 (m, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.49-7.33 (m, 2H), 7.25-7.18 (m, 1H), 7.14 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.95-6.72 (m, 2H), 4.19 (dq, *J* = 10.1, 7.2 Hz, 1H), 4.01 (dq, *J* = 10.1, 7.2 Hz, 1H), 3.77-3.21 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.7 (s).

Synthesis of 2-ethoxy-1-(pyridin-3-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.20

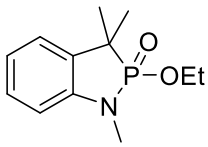


In a round-bottom flask was added compound **4.25** (810 mg, 2.00 mmol, 1.00 equiv.), copper(I) iodide (381 mg, 2.00 mmol, 1.00 equiv.) and Cs_2CO_3 (1.95 g, 6.00 mmol, 3.00 equiv.) in a mixture of dioxane (20 mL) and toluene (20 mL) under N_2. The reaction mixture was refluxed for 24 h. Then, it was diluted with EtOAc, washed with NH_4Cl (aq. sat.), brine, dried over MgSO4 and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt 3:7 to 0:10) to afford 2-ethoxy-1-(pyridin-3-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **4.20** (268 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.5 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89-7.75 (m, 1H), 7.43

(dd, *J* = 8.2, 4.8 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.15-7.06 (m, 1H), 7.02-6.79 (m, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 4.24-3.94 (m, 2H), 3.43-3.02 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.64 (d, *J* = 2.7 Hz), 148.24, 144.73 (d, *J* = 27.8 Hz), 134.89 (d, *J* = 2.5 Hz), 133.21, 128.34, 127.42 (d, *J* = 17.0 Hz), 124.46, 121.48 (d, *J* = 2.1 Hz), 120.44 (d, *J* = 3.0 Hz), 109.98 (d, *J* = 9.8 Hz), 63.20 (d, *J* = 6.7 Hz), 26.41 (d, *J* = 120.4 Hz), 16.50 (d, *J* = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 43.1 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_2P$ 275.0944, found 275.0959.

General procedure F: Benzylic dimethylation of *N*-substituted phostams. In a round-bottom flask was added *N*-substituted phostam (1.00 equiv.) in THF (0.2M) under N_2. The solution was cooled down to 0 °C and LiHMDS (1M in toluene, 2.1 equiv.) was added dropwise. The reaction was stirred for 5 min at 0 °C then iodomethame was added dropwise (2.1 equiv.). The reaction mixture was allowed to warm up to r.t. and stirred for 45 min. The reaction mixture was then diluted with EtOAc and poured onto aq. sat. NH_4Cl. Aqueous layer was extracted with EtOAc (x2). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Crude was either pure enough after workup or purified by silica gel column chromatography to afford pure gem-dimethyl phostams.

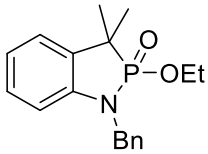
Synthesis of 2-ethoxy-1,3,3-trimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.26



According to *General procedure F*, to a solution of *N*-methyl phostam **4.1**, (343 mg, 1.62 mmol, 1.00 equiv.) in THF (10 mL) was added LiHMDS (1M in toluene, 3.41 mL, 3.41 mmol, 2.10 equiv.) and then iodomethane (0.21 mL, 3.41 mmol, 2.10

equiv.). The reaction mixture was stirred at r.t. for 45 min. After quench and workup, the desired product **4.26** was obtained as a colorless oil (357 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.59 – 4.04 (m, 2H), 2.98 (d, *J* = 8.2 Hz, 3H), 1.46 (dd, *J* = 16.5, 11.4 Hz, 6H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.06 (d, *J* = 25.6 Hz), 133.15 (d, *J* = 8.9 Hz), 128.01 (d, *J* = 1.2 Hz), 122.82 (d, *J* = 12.8 Hz), 120.32 (d, *J* = 1.4 Hz), 108.23 (d, *J* = 10.0 Hz), 62.79 (d, *J* = 7.1 Hz), 34.64 (d, *J* = 123.4 Hz), 26.93, 25.50, 21.43 (d, *J* = 3.0 Hz), 16.71 (d, *J* = 5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 52.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{18}NO_2P$ 238.1148, found 238.1145.

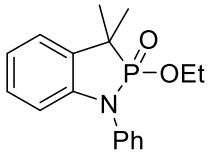
Synthesis of 1-benzyl-2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.27



According to *General procedure F*, to a solution of phostam **4.8** (250 mg, 0.87 mmol, 1.00 equiv.) in THF (5 mL) was added LiHMDS (1M in toluene, 1.83 mL, 1.83 mmol, 2.10 equiv.) and then iodomethane (0.11 mL, 1.83 mmol, 2.10 equiv.). The reaction mixture was stirred at r.t. for 45 min. After quench and workup, the desired product **4.27** (216 mg, 79%) was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.39 (m, 2H), 7.39-7.30 (m, 2H), 7.30-7.22 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.11-7.00 (m, 1H), 6.97-6.81 (m, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 4.83-4.59 (m, 2H), 4.31-3.98 (m, 2H), 1.56 (dd, *J* = 16.5, 9.2 Hz, 6H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.16 (d, *J* = 26.2 Hz), 137.20 (d, *J* = 2.5 Hz), 133.25 (d, *J* = 8.6 Hz), 128.62, 127.87 (d, *J* = 1.3 Hz), 127.27, 127.03, 122.94 (d, *J* = 12.7 Hz), 120.51 (d, *J* = 1.4 Hz), 109.83 (d, *J* = 10.0 Hz), 62.88 (d, *J* = 7.2 Hz), 44.90, 34.86 (d, *J* =

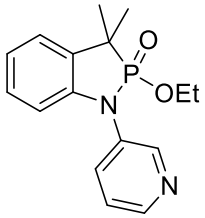
123.6 Hz), 25.70, 21.71 (d, J = 2.9 Hz), 16.69 (d, J = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 52.0 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{22}NO_2P$ 316.1461, found 316.1469.

Synthesis of 2-ethoxy-3,3-dimethyl-1-phenyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.28



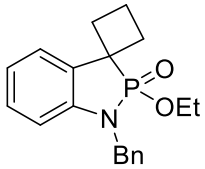
According to *General procedure F*, to a solution of N-phenyl phostam **4.17** (977 mg, 3.58 mmol, 1.00 equiv.) in THF (18 mL) was added LiHMDS (1M in toluene, 7.51 mL, 7.51 mmol, 2.10 equiv.) and then iodomethane (0.47 mL, 7.51 mmol, 2.10 equiv.). The reaction mixture was stirred at r.t. for 45 min. After quench and workup, the desired product **4.28** was obtained as a yellowish oil (358 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.40 (m, 4H), 7.40-7.30 (m, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.11 (dddd, J = 8.2, 7.6, 1.5, 0.8 Hz, 1H), 7.03-6.89 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.43-3.96 (m, 3H), 1.59 (dd, J = 16.7, 4.1 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.02 (d, J = 26.7 Hz), 136.59, 133.13 (d, J = 8.3 Hz), 129.77, 127.84, 127.06 (d, J = 2.7 Hz), 126.96, 123.29 (d, J = 12.7 Hz), 121.23, 110.51 (d, J = 8.9 Hz), 63.17 (d, J = 7.4 Hz), 35.20 (d, J = 123.5 Hz), 25.41, 22.02 (d, J = 2.9 Hz), 16.58 (d, J = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 48.8 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}NO_2P$ 302.1304, found 302.1317.

Synthesis of 2-ethoxy-3,3-dimethyl-1-(pyridin-3-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.29



According to *General procedure F*, to a solution of phostam **4.20** (274 mg, 1.00 mmol, 1.00 equiv.) in THF (10 mL) was added LiHMDS (1M in toluene, 2.10 mL, 2.10 mmol, 2.10 equiv.) and then iodomethane (0.13 mL, 2.10 mmol, 2.10 equiv.). The reaction mixture was stirred at r.t. for 45 min. After quench and workup, the desired product **4.29** was obtained as a colorless oil (253 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (bs, 1H), 8.58 (bs, 1H), 7.77 (ddd, *J* = 8.1, 2.5, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.7 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16-7.08 (m, 1H), 7.01-6.97 (m, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.42-4.04 (m, 2H), 1.58 (d, *J* = 17.0 Hz, 6H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.05 (d, *J* = 41.9 Hz), 142.14 (d, *J* = 26.0 Hz), 134.34 (d, *J* = 2.6 Hz), 133.76 (bs), 133.28 (d, *J* = 7.9 Hz), 128.04 (d, *J* = 1.1 Hz), 124.36 (bs), 123.60 (d, *J* = 12.7 Hz), 122.01 (d, *J* = 1.5 Hz), 110.37 (d, *J* = 8.5 Hz), 63.40 (d, *J* = 7.3 Hz), 35.42 (d, *J* = 123.2 Hz), 25.38, 21.88 (d, *J* = 2.9 Hz), 16.61 (d, *J* = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 49.1 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_2P$ 303.1257, found 303.1247.

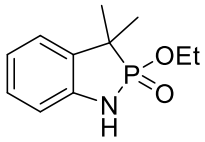
Synthesis of 1-benzyl-2-ethoxy-1H-spiro[benzo[d][1,2]azaphosphole-3,1'-cyclobutane] 2-oxide 4.31



According to *General procedure F*, to a solution of phostam **4.8** (250 mg, 0.87 mmol, 1.00 equiv.) in THF (5 mL) was added LiHMDS (1M in toluene, 1.83 mL, 1.83 mmol, 2.10 equiv.) and then 1,3-dibromopropane (97 μL, 0.96 mmol, 1.10 equiv.). The reaction mixture was stirred at r.t. for 45 min. After quench, workup and

purification by silica gel chromatography (Hexanes/EtOAc 5:5 to 2:8) the desired product **4.31** was obtained as a colorless oil (140 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.42-7.39 (m, 2H), 7.33 (ddd, *J* = 7.5, 6.7, 1.3 Hz, 2H), 7.28-7.25 (m, 1H), 7.09-7.02 (m, 1H), 6.92 (m, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 4.82-4.53 (m, 2H), 4.26-4.02 (m, 2H), 3.16-3.00 (m, 1H), 2.87-2.69 (m, 1H), 2.65-2.49 (m, 1H), 2.38-2.15 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.73 (d, *J* = 27.1 Hz), 137.12 (d, *J* = 1.9 Hz), 131.36 (d, *J* = 12.3 Hz), 128.61, 128.13 (d, *J* = 1.3 Hz), 127.24, 127.00, 123.84 (d, *J* = 14.0 Hz), 120.54 (d, *J* = 1.5 Hz), 109.30 (d, *J* = 10.3 Hz), 62.87 (d, *J* = 7.1 Hz), 45.08 (d, *J* = 1.4 Hz), 40.04 (d, *J* = 123.0 Hz), 32.55 (d, *J* = 3.7 Hz), 28.94 (d, *J* = 5.3 Hz), 17.38 (d, *J* = 6.5 Hz), 16.62 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 50.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_2P$ 328.1461, found 328.1472.

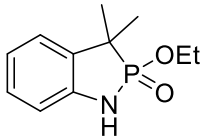
Synthesis of 2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.32 via NBS/AIBN promoted debenzylation (Table 4.7, entry 4)



In a round-bottom flask was added, under argon, phostam **4.27** (50 mg, 0.16 mmol, 1.00 equiv.) in chlorobenzene (5 mL) under argon. NBS (28 mg, 0.16 mmol, 1.00 equiv.) was added followed by AIBN (3 mg, 0.01 mmol, 0.1 equiv.). The mixture was refluxed for 3 h then more NBS (28 mg, 0.16 mmol, 1.00 equiv.) and more AIBN (3 mg, 0.01 mmol, 0.1 equiv.) were added. The reaction mixture was refluxed for 17h. IT was then cooled down to r.t. and diethyl ether (5 mL) and water (7 mL) were added to the solution, which was stirred for 4 h, then the organic layer was separated, dried over anhydrous $MgSO_4$, and evaporated and the crude product was purified by silica gel chromatography (Hexanes/AcOEt, 3:7) to give 1-benzyl-2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **4.32** (17 mg, 48%)

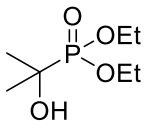
Or

Synthesis of 2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.32 via lithium naphthalenide promoted debenzylation (Table 4.7, entry 8)



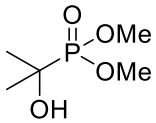
In a round-bottom flask was added, under argon, naphthalene (1.10 g, 8.59 mmol, 1.00 equiv.) in THF (50 mL) under argon. Lithium (596 mg, 859 mmol, 10.0 equiv.) was added portionwise in the solution at r.t. The mixture was stirred at r.t. until it turned into a deep green color (~ 45 min). The solution was cooled down to 0 °C and a solution of phostam **4.27** (2.71 g, 8.59 mmol, 1.00 equiv.) in THF (15 mL) was added. The reaction mixture was allowed to warm up to r.t. and was stirred for 2 h. The reaction mixture was then filtered over celite to remove excess lithium. The filtrate was diluted with EtOAc and washed with NH_4Cl (aq. sat.). The aqueous layer was extracted with EtOAc (x3). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/EtOAc 3:7) to afford 1-benzyl-2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide **4.32** (1.00 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-6.99 (m, 2H), 6.98-6.84 (m, 1H), 6.82-6.70 (m, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 4.17 (dq, *J* = 8.0, 7.1 Hz, 2H), 1.50 (dd, *J* = 16.4, 12.0 Hz, 6H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.53 (d, *J* = 20.5 Hz), 133.75 (d, *J* = 10.2 Hz), 127.91 (d, *J* = 1.7 Hz), 123.26 (d, *J* = 13.2 Hz), 120.71, 111.84 (d, *J* = 12.2 Hz), 62.37 (d, *J* = 7.3 Hz), 35.71 (d, *J* = 124.2 Hz), 25.52, 21.34 (d, *J* = 3.1 Hz), 16.55 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 52.4 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0992.

Synthesis of diethyl (2-hydroxypropan-2-yl)phosphonate 4.37 [76]



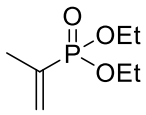
A solution of diethyl phosphite **4.35** (2.76g, 20.0 mmol, 1.00 equiv.) and acetone (2.20 mL, 30.0 mmol, 1.50 equiv.) in CH_3CN (20 mL) under N_2 was cooled down to 0 °C. DBU (3.29 mL, 22.0 mmol, 1.10 equiv.) was added dropwise to the solution. The reaction mixture was allowed to warm up to r.t. and stirred for 4 h. It was then concentrated *in vacuo* to remove the solvent. The residue was dissolved in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the desired product **4.37** as a colorless oil (3.56 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (bs, 1H), 4.11-4.01 (m, 4H), 1.32 (d, *J* = 15.3 Hz, 6H) , 1.21 (t, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.6 (s).

Synthesis of dimethyl (2-hydroxypropan-2-yl)phosphonate 4.38 [77]



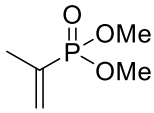
A solution of dimethyl phosphite **4.36** (5.50 g, 50.0 mmol, 1.00 equiv.) and acetone (5.50 mL, 75.0 mmol, 1.50 equiv.) in CH_3CN (50 mL) under N_2 was cooled down to 0 °C. DBU (8.23 mL, 55.0 mmol, 1.10 equiv.) was added dropwise to the solution. The reaction mixture was allowed to warm up to r.t. and stirred for 4 h. It was then concentrated *in vacuo* to remove the solvent. The residue was dissolved in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the desired product **4.38** as a white solid (7.72 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (d, *J* = 10.2 Hz, 6H), 3.57 (bs, 1H), 1.45 (d, *J* = 15.4 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.7 (s).

Synthesis of diethyl prop-1-en-2-ylphosphonate 4.39.[78]



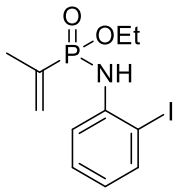
In a round-bottom flask was added compound **4.37** (3.56 g, 18.1 mmol, 1.00 equiv.) and pyridine (1.61 mL, 19.9 mmol, 1.10 equiv.) in chloroform (30 mL) under N_2. Thionyl chloride (1.45 mL, 19.9 mmol, 1.10 equiv.) was added dropwise to the solution. The reaction mixture was stirred at 60 °C for 4 h and was then cooled down to r.t. and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the desired product as a yellow oil **4.39** (2.58 g, 80%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78-5.44 (m, 2H), 3.90-3.84 (m, 4H), 1.91 (d, *J* = 14.0 Hz), 1.09 (t, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.1 (s).

Synthesis of dimethyl prop-1-en-2-ylphosphonate 4.40 [79]



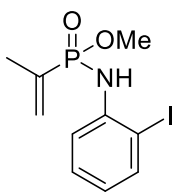
In a round-bottom flask was added compound **4.38** (4.86 g, 28.9 mmol, 1.00 equiv.) and pyridine (2.57 mL, 31.8 mmol, 1.10 equiv.) in chloroform (60 mL) under N_2. Thionyl chloride (2.32 mL, 31.8 mmol, 1.10 equiv.) was added dropwise to the solution. The reaction mixture was stirred at 60 °C for 4 h and was then cooled down to r.t. and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the desired product **4.40** (3.40 g, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.51 (m, 2H), 3.51 (d, *J* = 10.2 Hz, 6H), 1.70 (d, *J* = 14.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.9 (s).

Synthesis of ethyl *N*-(2-iodophenyl)-*P*-(prop-1-en-2-yl)phosphonamidite 4.41



In a flask under N_2 was added compound **4.39** (2.90 g, 16.3 mmol, 1.00 equiv.) in DCM (30 mL). Oxalyl chloride (1.68 mL, 19.5 mmol, 1.20 equiv.) was added slowly followed by DMF (0.13 mL, 1.63 mmol, 0.10 equiv.) dropwise. The reaction mixture was refluxed overnight. It was then cooled down to r.t. and added dropwise to a solution of 2-iodoaniline (7.14 g, 32.6 mmol, 2.00 equiv.) and DIPEA (5.69 mL, 32.6 mmol, 2.00 equiv.) in DCM (10 mL). The reaction mixture was refluxed for 10 h. It was then cooled down to r.t. and washed with aq. NH_4Cl (sat.). Organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4 to 1:9) to afford the desired product **4.41** as a beige solid (4.23 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.71 (m, *J* = 7.9, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.2, 1.6, 0.7 Hz, 1H), 7.21 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.67 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 6.00 (ddq, *J* = 22.2, 1.2, 1.2 Hz, 1H), 5.79 (ddq, *J* = 47.9, 1.6, 1.5 Hz, 1H), 5.40 (d, *J* = 5.5 Hz, 1H), 4.34-4.04 (m, 2H), 1.95 (ddd, *J* = 14.4, 1.7, 1.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.68 (d, *J* = 3.8 Hz), 139.18, 135.71 (d, *J* = 162.0 Hz), 130.42 (d, *J* = 9.5 Hz), 129.43, 123.26, 117.08 (d, *J* = 2.3 Hz), 89.09 (d, *J* = 10.5 Hz), 61.26 (d, *J* = 6.1 Hz), 18.65 (d, *J* = 12.9 Hz), 16.35 (d, *J* = 6.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 17.7 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}INO_2P$ 351.9958, found 351.9967.

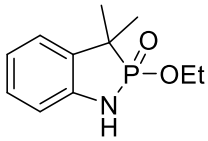
Synthesis of methyl *N*-(2-iodophenyl)-*P*-(prop-1-en-2-yl)phosphonamidite 4.42



In a flask under N_2 was added compound **4.40** (2.20 g, 14.7 mmol, 1.00 equiv.) in DCM (30 mL). Oxalyl chloride (1.50 mL, 17.6 mmol, 1.20 equiv.) was added

slowly followed by DMF (0.11 mL, 1.47 mmol, 0.10 equiv.) dropwise. The reaction mixture was refluxed overnight. It was then cooled down to r.t. and added dropwise to a solution of 2-iodoaniline (6.44 g, 29.4 mmol, 2.00 equiv.) and DIPEA (5.12 mL, 29.4 mmol, 2.00 equiv.) in DCM (10 mL). The reaction mixture was refluxed for 10 h. It was then cooled down to r.t. and washed with aq. NH_4Cl (sat.). Organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by silical gel column chromatography (Hexanes/AcOEt, 5:5 to 2:8) to afford the desired product **4.42** as a white solid (2.77 g, 56%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.72 (m, 1H), 7.31 (ddd, *J* = 8.2, 1.6, 0.6 Hz, 1H), 7.26-7.20 (m, 1H), 6.70 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.01 (ddq, *J* = 22.3, 1.2, 1.1 Hz, 1H), 5.82 (ddq, *J* = 48.1, 1.6, 1.6 Hz, 1H), 5.41 (d, *J* = 5.6 Hz, 1H), 3.82 (d, *J* = 11.3 Hz, 3H), 1.97 (ddd, *J* = 14.5, 1.7, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.51 (d, *J* = 3.7 Hz), 139.23, 135.22 (d, *J* = 162.0 Hz), 130.75 (d, *J* = 9.5 Hz), 129.52, 123.42, 117.08 (d, *J* = 2.2 Hz), 89.19 (d, *J* = 10.5 Hz), 51.45 (d, *J* = 6.1 Hz), 18.68 (d, *J* = 12.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.3 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}INO_2P$ 337.9801, found 337.9799.

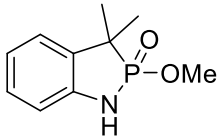
Synthesis of 2-ethoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.32



In a sealed tube flushed with N_2 was added compound **4.41** (2.30 g, 6.35 mmol, 1.00 equiv.), $Pd(OAc)_2$ (28 mg, 0.13 mmol, 2 mol%), sodium formate (518 mg, 7.62 mmol, 1.20 equiv.), TBAB (2.46 g, 7.62 mmol, 1.20 equiv.) in DMA (40 mL). Cy_2NMe (3.40 mL, 15.9 mmol, 2.50 equiv.) was then added. The tube was sealed and heated at 110 °C for 4 h. It was cooled down to r.t. and the solvent was removed under reduced pressure. The residue was taken up in EtOAc to dissolve and washed with brine. The organic layer was dried $MgSO_4$ and

concentrated under vacuum. The crude was then filtered over a pad of silica (Hexanes/AcOEt 5:5 to 3:7) to afford a mixture of compound **4.32** and Cy_2NMe which was then recrystallized from a mixture of DCM and hexanes to afford pure compound **4.32** as white crystals (1.27 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-6.99 (m, 2H), 6.98-6.84 (m, 1H), 6.82-6.70 (m, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 4.17 (dq, *J* = 8.0, 7.1 Hz, 2H), 1.50 (dd, *J* = 16.4, 12.0 Hz, 6H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.53 (d, *J* = 20.5 Hz), 133.75 (d, *J* = 10.2 Hz), 127.91 (d, *J* = 1.7 Hz), 123.26 (d, *J* = 13.2 Hz), 120.71, 111.84 (d, *J* = 12.2 Hz), 62.37 (d, *J* = 7.3 Hz), 35.71 (d, *J* = 124.2 Hz), 25.52, 21.34 (d, *J* = 3.1 Hz), 16.55 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 52.4 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0992.

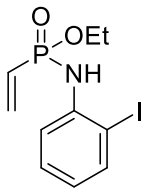
Synthesis of 2-methoxy-3,3-dimethyl-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.33



In a sealed tube flushed with N_2 was added compound **4.42** (2.50 g, 7.41 mmol, 1.00 equiv.), $Pd(OAc)_2$ (33 mg, 0.15 mmol, 2 mol%), sodium formate (605 mg, 8.90 mmol, 1.20 equiv.), TBAB (2.87 g, 8.90 mmol, 1.20 equiv.) in DMA (50 mL). Cy_2NMe (4.0 mL, 18.5 mmol, 2.50 equiv.) was then added. The tube was sealed and heated at 110 °C for 4 h. It was cooled down to r.t. and the solvent was removed under reduced pressure. The residue was taken up in EtOAc to dissolve and washed with brine. The organic layer was dried $MgSO_4$ and concentrated under vacuum. The crude was then filtered over a pad of silica (Hexanes/AcOEt, 4:6) to afford a mixture of compound **4.33** and Cy_2NMe which was then recrystallized from a mixture of DCM and hexanes to afford pure compound **4.33** as white crystals (798 mg, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.06 (m, 2H), 6.98-6.85 (m, 1H), 6.77 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.02 (d, *J* = 7.1 Hz, 1H), 3.81 (d, *J* = 10.8 Hz, 3H), 1.51 (dd, *J* = 16.5, 12.4 Hz, 6H); ^{13}C NMR (100

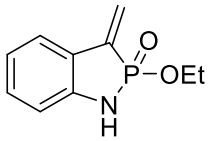
MHz, $CDCl_3$) δ 140.18 (d, *J* = 20.4 Hz), 133.75 (d, *J* = 9.9 Hz), 127.98 (d, *J* = 1.7 Hz), 123.32 (d, *J* = 13.2 Hz), 121.02, 111.89 (d, *J* = 12.0 Hz), 52.96 (d, *J* = 7.3 Hz), 35.89 (d, *J* = 124.1 Hz), 25.61, 21.01 (d, *J* = 3.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 53.5 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2P$ 212.0835, found 212.0843.

Synthesis of ethyl *N*-(2-iodophenyl)-*P*-vinylphosphonamidate 4.42



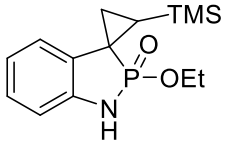
To a solution of diethyl vinylphosphonate **4.44** (5.85 g, 35.6 mmol, 1.00 equiv.) in DCM (70 mL) under N_2, was added oxalyl chloride (3.67 mL, 42.8 mmol, 1.20 equiv.) and DMF (0.28 mL, 3.56 mmol, 0.10 equiv.). The reaction mixture was stirred at reflux for 12 h. Then it was cooled down to r.t. and added dropwise to a solution of 2-iodoaniline (15.6 g, 71.2 mmol, 2.00 equiv.) and DIPEA (12.4 mL, 71.2 mmol, 2.00 equiv.) in DCM (20 mL). The mixture was refluxed for 12 h; then, cooled down to r.t. and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt, 5:5 to 1:9) to afford the desired compound **4.42** as a white solid (11.04 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.32-7.26 (m, 1H), 7.22 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.67 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.42-6.04 (m, 3H), 5.46 (d, *J* = 5.5 Hz, 1H), 4.30-4.04 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.50 (d, *J* = 3.3 Hz), 139.29, 135.38 (d, *J* = 1.8 Hz), 129.42, 127.29 (d, *J* = 171.8 Hz), 123.35, 116.99 (d, *J* = 2.1 Hz), 89.28 (d, *J* = 10.7 Hz), 61.15 (d, *J* = 6.0 Hz), 16.32 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}INO_2P$ 337.9801, found 337.9810.

Synthesis of 2-ethoxy-3-methylene-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.43



To a flask under N_2 was added compound **4.42** (7.60 g, 22.5 mmol, 1.00 equiv.), $Pd(OAc)_2$ (101 mg, 0.5 mmol, 2 mol%), $P(o\text{-}tolyl)_3$ (342 mg, 1.1 mmol, 5 mol%) in DMF (80 mL) then Et_3N (6.27 mL, 45.0 mmol, 2.00 equiv.) was added. The reaction mixture was heated at 100 °C for 4 h. It was then cooled down to r.t. and the solvent was removed under vacuum. The residue was taken up in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt, 4:6) to afford the desired compound **4.43** as a white solid (2.40 g, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (ddd, *J* = 7.7, 1.3, 0.6 Hz, 1H), 7.25-7.11 (m, 1H), 6.96-6.84 (m, 1H), 6.79 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 6.31 (dd, *J* = 46.0, 1.0 Hz, 1H), 6.02 (d, *J* = 21.5 Hz, 1H), 4.11-3.85 (m, 2H), 1.32 (td, *J* = 7.1, 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.59 (d, *J* = 17.8 Hz), 134.21 (d, *J* = 155.2 Hz), 130.97 (d, *J* = 2.5 Hz), 122.26 (d, *J* = 27.1 Hz), 121.16 (d, *J* = 13.6 Hz), 120.43, 119.30 (d, *J* = 8.4 Hz), 112.67 (d, *J* = 11.3 Hz), 62.73 (d, *J* = 6.4 Hz), 16.22 (d, *J* = 7.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.8 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_2P$ 210.0678, found 210.0686.

Synthesis of 2-ethoxy-2'-(trimethylsilyl)-1H-spiro[benzo[d][1,2]azaphosphole-3,1'-cyclopropane]2-oxide 4.45

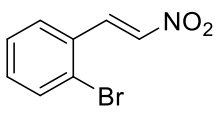


To a solution of compound **4.43** (570 mg, 2.72 mmol, 1.00 equiv.) in THF (9.0 mL) under N_2 was added $TMSCHN_2$ (0.6 M in hexane, 9.0 mL, 5.44 mmol, 2.0 equiv.) dropwise over 30 minutes at r.t. The reaction was stirred at r.t. for 16 h. The solvent and excess $TMSCHN_2$ were removed under vacuum. The residue was taken up

in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt, 5:5 to 0:10) to afford the desired compound **4.45** as a yellow oil (803 mg, 67%): Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-6.99 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.85-6.77 (m, 1H), 6.75 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.62 (dd, *J* = 7.6, 1.3 Hz, 1H), 4.11-3.87 (m, 2H), 1.58 (ddd, *J* = 13.0, 9.2, 3.6 Hz, 1H), 1.48 (ddd, *J* = 10.6, 6.2, 3.6 Hz, 1H), 1.30 (td, *J* = 7.1, 0.6 Hz, 3H), 0.66 (ddd, *J* = 13.9, 10.6, 9.2 Hz, 1H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.00 (d, *J* = 17.3 Hz), 130.52 (d, *J* = 22.6 Hz), 126.70 (d, *J* = 2.1 Hz), 120.04, 118.66 (d, *J* = 11.9 Hz), 111.31 (d, *J* = 11.7 Hz), 62.29 (d, *J* = 7.2 Hz), 21.61 (d, *J* = 172.0 Hz), 21.10 (d, *J* = 2.9 Hz), 19.91 (d, *J* = 3.1 Hz), 16.31 (d, *J* = 6.9 Hz), -1.27; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.4 (s); Diastereomers 2&3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (qt, *J* = 7.7, 1.0 Hz, 2H, diastereomers 2&3), 6.89-6.71 (m, 5H, diastereomers 2&3), 6.72-6.61 (m, 2H, diastereomer 2), 6.48 (d, *J* = 8.1 Hz, 1H, diastereomer 3), 4.19 – 4.04 (m, 2H, diastereomer 2), 3.98 (dq, *J* = 8.1, 7.1 Hz, 1H, diastereomer 3), 1.84 (ddd, *J* = 15.6, 11.1, 4.3 Hz, 1H, diastereomer 3), 1.69 (ddd, *J* = 13.8, 9.3, 3.4 Hz, 1H, diastereomer 2), 1.55 (ddd, *J* = 11.4, 9.3, 4.4 Hz, 1H, diastereomer 3), 1.32 (t, *J* = 7.1 Hz, 3H, diastereomer 2), 1.26 (t, *J* = 7.1 Hz, 3H, diastereomer 3), 1.19 (ddd, *J* = 10.5, 6.4, 3.4 Hz, 1H, diastereomer 2), 1.10 (ddd, *J* = 19.0, 11.1, 9.3 Hz, 1H, diastereomer 3), 0.84 (ddd, *J* = 14.7, 10.5, 9.3 Hz, 1H, diastereomer 2), 0.20 (s, 9H, diastereomer 2), -0.05 (s, 9H, diastereomer 3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2 (s, 40%), 45.5 (s, 60%); Diastereomer 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.00 (m, 1H), 6.87-6.68 (m, 3H), 6.15 (d, J = 6.8 Hz, 1H), 4.08-3.89 (m, 2H), 2.20-2.02 (m, 1H), 1.32 (td, J = 7.0, 0.7 Hz, 3H), 1.29-1.19 (m, 1H), 0.82 (ddd, J = 18.7, 11.2, 9.6 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.61 (d, *J* = 19.0 Hz), 127.27 (d, *J* = 21.3 Hz), 127.02, 121.88 (d, *J* = 14.1 Hz), 119.83, 111.58 (d, *J* = 11.8 Hz), 62.59 (d, *J* = 7.1 Hz), 22.57 (d, *J* = 163.0 Hz), 20.10 (d, *J* = 2.8 Hz), 16.33

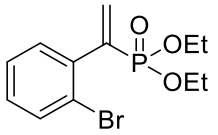
(d, J = 7.1 Hz), 15.51 (d, J = 3.4 Hz), -0.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.6 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{22}NO_2PSi$ 296.1230, found 296.1238.

Synthesis of *trans*-2-bromo-β-nitrostyrene 4.47.[68]



To a round-bottom flask was added 2-bromobenzaldehyde **4.46** (2.44 g, 12.3 mmol, 1.00 equiv.) and ammonium acetate (1.89 g, 24.5 mmol, 2.00 equiv.) in AcOH (25 mL) under N_2. The suspension was stirred for 15 min at r.t., then, nitromethane (2.66 mL, 49.0 mmol, 4.00 equiv.) was added. The resulting mixture was stirred at reflux for 4 h. Water (35 mL) was added to quench the reaction mixture. It was then extracted with DCM (x3). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was recrystallized from DCM/Hexanes to afford pure *trans*-2-bromo-β-nitrostyrene **4.47** as a yellow solid (2.34 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 13.6 Hz, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 7.60 (dd, J = 7.7, 1.9 Hz, 1H), 7.56 (d, J = 13.6 Hz, 1H), 7.44 – 7.33 (m, 2H).

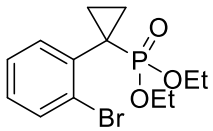
Synthesis of diethyl (1-(2-bromophenyl)vinyl)phosphonate 4.48



To a round-bottom flask was added nitrostyrene **4.47** (4.35 g, 19.1 mmol, 1.00 equiv.) in CH_3CN (200 mL) under N_2. Diethyl phosphite (3.05 mL, 23.7 mmol, 1.24 equiv.) was added dropwise at r.t. to the solution followed by DBU (3.54 mL, 23.7 mmol, 1.24 equiv.). The reaction mixture was stirred at r.t. for 12 h. Reaction mixture was diluted with EtOAc and washed with aq. sat. NH_4Cl then brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography

(Hexanes/AcOEt 7:3 to 4:6) to afford diethyl (1-(2-bromophenyl)vinyl)phosphonate **4.48** as a colorless oil (3.17 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 1H), 7.27 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.15 (ddd, *J* = 8.8, 7.3, 1.4 Hz, 1H), 6.53 (dd, *J* = 22.3, 1.3 Hz, 2H), 5.98 (dd, *J* = 46.5, 1.3 Hz, 2H), 4.11 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.95 (d, *J* = 180.7 Hz), 137.60 (d, *J* = 10.7 Hz), 135.37 (d, *J* = 7.5 Hz), 133.08, 130.58 (d, *J* = 3.3 Hz), 129.29 (d, *J* = 2.1 Hz), 126.95 (d, *J* = 1.8 Hz), 122.88 (d, *J* = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.8 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}BrO_3P$ 319.0093, found 319.0104.

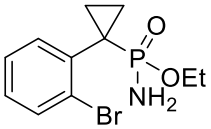
Synthesis of diethyl (1-(2-bromophenyl)cyclopropyl)phosphonate 4.49



To a round-bottom flask was added NaH (60% suspension in mineral oil, 326 mg, 8.15 mmol, 1.25 equiv.) in anhydrous DMF (45 mL) under N_2. Trimethylsulfonium iodide (1.73 g, 8.47 mmol, 1.30 equiv.) was added portion wise at r.t. and the suspension was stirred for 15 min. Then, a solution of phosphonate **4.48** (2.08 g, 6.52 mmol, 1.00 equiv.) in DMF (40 mL) was added dropwise to the flask via an addition funnel. The reaction mixture was stirred at r.t. for 10 h. the reaction mixture was quenched with aq. sat. NH_4Cl and was extracted with AcOEt. Organic layer was washed with brine (x4), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography (Hexanes/AcOEt 6:4 to 3:7) to yield diethyl (1-(2-bromophenyl)cyclopropyl)phosphonate **4.49** as a colorless oil (1.66 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 1H), 7.43-7.33 (m, 1H), 7.27-7.16 (m, 1H), 7.08-6.97 (m, 1H), 4.46-3.75 (m, 4H), 1.91-1.49 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 7H), 1.12-1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.79, 134.77 (d, *J* = 3.6 Hz), 133.19

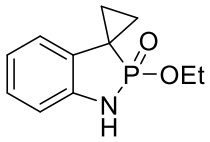
(d, *J* = 2.5 Hz), 128.76 (d, *J* = 2.9 Hz), 127.07 (d, *J* = 2.6 Hz), 126.55 (d, *J* = 4.4 Hz), 62.43 (d, *J* = 6.6 Hz), 22.14 (d, *J* = 193.3 Hz), 16.38 (d, *J* = 6.2 Hz), 13.95 (d, *J* = 2.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}BrO_3P$ 333.0250, found 333.0241.

Synthesis of ethyl *P*-(1-(2-bromophenyl)cyclopropyl)phosphonamidite 4.50



To a solution of compound **4.49** (1.66 g, 4.98 mmol, 1.00 equiv.) in CH_2Cl_2 (25 mL) under N_2 was added oxalyl chloride (0.51 mL, 5.98 mmol, 1.20 equiv.) carefully. DMF (40 μL, 0.50 mmol, 0.10 equiv.) was added dropwise and the reaction mixture was stirred at reflux for 5 days. This mixture was then added dropwise to a flask containing ammonium hydroxide (28% NH_3 in H_2O, 1.7 mL, 24.9 mmol, 5.00 equiv.). It was stirred at r.t. for 15 min. Sat. aq. NH_4Cl was added to the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by silica gel column chromatography (Hex/EtOAc 6:4 to 0:10) to afford ethyl P-(1-(2-bromophenyl)cyclopropyl)phosphonamidite **4.50** as a yellowish oil (544 mg, 36%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.36 (m, 2H), 7.31-7.13 (m, 1H), 7.11-6.98 (m, 1H), 4.20-3.78 (m, 2H), 3.04 (d, *J* = 4.8 Hz, 2H), 1.84-1.40 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.14-0.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.57 (d, *J* = 3.0 Hz), 134.99 (d, *J* = 3.3 Hz), 133.28 (d, *J* = 2.3 Hz), 128.73 (d, *J* = 2.7 Hz), 127.30 (d, *J* = 2.4 Hz), 126.41 (d, *J* = 4.3 Hz), 60.59 (d, *J* = 6.6 Hz), 24.30 (d, *J* = 172.1 Hz), 16.39 (d, *J* = 6.6 Hz), 14.17 (d, *J* = 2.9 Hz), 13.98 (d, *J* = 1.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.3 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}BrNO_2P$ 304.0097, found 304.0101.

Synthesis of 2-ethoxy-1H-spiro[benzo[d][1,2]azaphosphole-3,1'-cyclopropane] 2-oxide 4.30



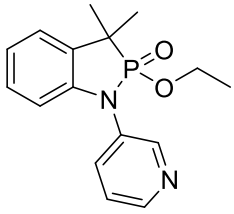
To a round-bottom flask was added phosphonamide **4.50** (540 mg, 1.78 mmol, 1.00 equiv.), copper(I) bromide (13 mg, 0.09 mmol, 0.05 equiv.), K_2CO_3 (515 mg, 3.73 mmol, 2.10 equiv.) in CH_3CN (18 mL) under N_2. DMEDA (0.10 mL, 0.89 mmol, 0.50 equiv.) was added to the mixture. The reaction mixture refluxed for 24 h. The solvent was removed under vacuum. The residue was taken up in EtOAc, washed with sat. aq. NH_4Cl. The organic layer was separated. The aqueous layer was extracted with EtOAc (2x). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (AcOEt/MeOH 10:0 to 9:1) to afford 2-ethoxy-1H-spiro[benzo[d][1,2]azaphosphole-3,1'-cyclopropane] 2-oxide **4.30** as a white solid (290 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.92-6.71 (m, 2H), 6.60 (d, *J* = 7.7 Hz, 1H), 4.11-3.80 (m, 2H), 1.85 (dddd, *J* = 15.5, 9.8, 7.3, 4.5 Hz, 1H), 1.62 (dddd, *J* = 15.4, 9.7, 7.3, 4.8 Hz, 1H), 1.52-1.38 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24-1.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.39 (d, *J* = 18.4 Hz), 128.67 (d, *J* = 19.9 Hz), 127.05 (d, *J* = 1.8 Hz), 120.20, 118.90 (d, *J* = 12.8 Hz), 111.41 (d, *J* = 12.3 Hz), 62.40 (d, *J* = 6.9 Hz), 17.92, 17.57 (d, *J* = 2.4 Hz), 16.30 (d, *J* = 7.2 Hz), 13.84 (d, *J* = 2.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{14}NO_2P$ 224.0835, found 224.0835.

General procedure G: Heteroarylation of phostam 4.32 with CuBr. To a mixture of phostam **4.32** (1.0 equiv.), copper(I) bromide (10 mol%), potassium carbonate (2.1 equiv) in acetonitrile (0.1 M) under N_2 was added heteroaryl halide (1.2 equiv.) followed by *N,N'*-dimethylethylenediamine (0.5 equiv.). The reaction mixture is then stirred at reflux for 20 h.

It was then cooled down to r.t. diluted in AcOEt, washed with aq. sat. NH_4Cl and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Crude was purified by silica gel column chromatography to afford the pure compound.

General procedure H: Heteroarylation of phostam 4.32 with CuI. To a mixture of phostam **4.32** (1.0 equiv.), copper(I) iodide (25 mol%), potassium carbonate (3.0 equiv) in acetonitrile (0.1 M) under N_2 was added heteroaryl halide (1.3 equiv.) followed by *N,N'*-dimethylethylenediamine (0.25 equiv.). The reaction mixture is then stirred at reflux for 20 h. It was then cooled down to r.t. diluted in AcOEt, washed with aq. sat. NH_4Cl and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Crude was purified by silica gel column chromatography to afford the pure compound

Synthesis of 2-ethoxy-3,3-dimethyl-1-(pyridin-3-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.29



According to *General procedure G*, to a mixture of phostam **4.32** (45 mg, 0.20 mmol, 1.00 equiv.), CuBr (3 mg, 0.02 mmol, 10 mol%) and K_2CO_3 (58 mg, 0.42 mmol, 2.10 equiv.) in CH_3CN (2 mL) was added 3-iodopyridine (49 mg, 0.24 mmol, 1.20 equiv.) and DMEDA (11 μL, 0.10 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 3:7) to yield the desired product **4.29** as a colorless oil (51 mg, 85%).

Or

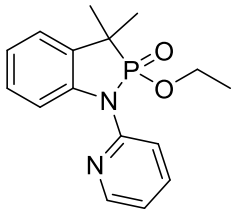
According to *General procedure G*, to a mixture of phostam **4.32** (45 mg, 0.20 mmol, 1.00 equiv.), CuBr (3 mg, 0.02 mmol, 10 mol%) and K_2CO_3 (58 mg, 0.42 mmol, 2.10 equiv.) in CH_3CN (2 mL)

was added 3-bromopyridine (23 μL, 0.24 mmol, 1.20 equiv.) and DMEDA (11 μL, 0.10 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 3:7) to yield the desired product **4.29** as a colorless oil (49 mg, 81%).

Or

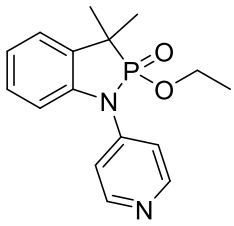
According to *General procedure H*, to a mixture of phostam **4.32** (45 mg, 0.20 mmol, 1.00 equiv.), CuI (10 mg, 0.05 mmol, 25 mol%) and K_2CO_3 (83 mg, 0.60 mmol, 3.00 equiv.) in CH_3CN (2 mL) was added 3-bromopyridine (25 μL, 0.26 mmol, 1.30 equiv.) and DMEDA (5 μL, 0.05 mmol, 0.25 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 3:7) to yield the desired product **4.29** as a colorless oil (49 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (bs, 1H), 8.58 (bs, 1H), 7.77 (ddd, *J* = 8.1, 2.5, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.7 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16-7.08 (m, 1H), 7.01-6.97 (m, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.42-4.04 (m, 2H), 1.58 (d, *J* = 17.0 Hz, 6H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.05 (d, *J* = 41.9 Hz), 142.14 (d, *J* = 26.0 Hz), 134.34 (d, *J* = 2.6 Hz), 133.76 (bs), 133.28 (d, *J* = 7.9 Hz), 128.04 (d, *J* = 1.1 Hz), 124.36 (bs), 123.60 (d, *J* = 12.7 Hz), 122.01 (d, *J* = 1.5 Hz), 110.37 (d, *J* = 8.5 Hz), 63.40 (d, *J* = 7.3 Hz), 35.42 (d, *J* = 123.2 Hz), 25.38, 21.88 (d, *J* = 2.9 Hz), 16.61 (d, *J* = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 49.1 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_2P$ 303.1257, found 303.1247.

Synthesis of 2-ethoxy-3,3-dimethyl-1-(pyridin-2-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.56



According to *General procedure G*, to a mixture of phostam **4.32** (100 mg, 0.44 mmol, 1.00 equiv.), CuBr (6 mg, 0.04 mmol, 10 mol%) and K_2CO_3 (128 mg, 0.92 mmol, 2.10 equiv.) in CH_3CN (4.5 mL) was added 2-iodopyridine (57 μL, 0.53 mmol, 1.20 equiv.) and DMEDA (24 μL, 0.22 mmol, 0.50 equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 4:6) to yield the desired product **4.56** as a colorless oil (107 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.73 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.27-7.15 (m, 2H), 7.10 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.04 (m, 1H), 4.74-3.89 (m, 2H), 1.55 (dd, *J* = 17.0, 13.5 Hz, 6H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.84 (d, *J* = 2.7 Hz), 148.91, 139.84 (d, *J* = 24.4 Hz), 138.12, 133.97 (d, *J* = 6.8 Hz), 127.73, 123.37 (d, *J* = 12.4 Hz), 122.66, 119.83, 116.23 (d, *J* = 2.9 Hz), 113.27 (d, *J* = 8.0 Hz), 63.50 (d, *J* = 7.7 Hz), 35.25 (d, *J* = 126.6 Hz), 25.63, 20.91 (d, *J* = 3.3 Hz), 16.37 (d, *J* = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.2 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_2P$ 303.1257, found 303.1247.

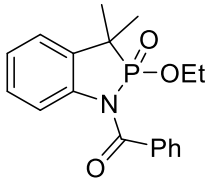
Synthesis of 2-ethoxy-3,3-dimethyl-1-(pyridin-4-yl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.57



According to *General procedure G*, to a mixture of phostam **4.32** (100 mg, 0.44 mmol, 1.00 equiv.), CuBr (6 mg, 0.04 mmol, 10 mol%) and K_2CO_3 (128 mg, 0.92 mmol, 2.10 equiv.) in CH_3CN (4.5 mL) was added 4-iodopyridine (109 mg, 0.53 mmol, 1.20 equiv.) and DMEDA (24 μL, 0.22 mmol, 0.50

equiv.). After workup, the crude was purified by silica gel column chromatography (Hexanes/AcOEt 4:6) to yield the desired product **4.57** as a yellowish oil (107 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.4 Hz, 2H), 7.34 (d, *J* = 6.9 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.09-7.00 (m, 2H), 4.56-3.69 (m, 2H), 1.51 (dd, *J* = 21.4, 17.4 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.05, 145.95 (d, *J* = 2.1 Hz), 139.60 (d, *J* = 24.8 Hz), 134.49 (d, *J* = 6.6 Hz), 127.98, 123.87 (d, *J* = 12.4 Hz), 123.34, 117.36 (d, *J* = 3.3 Hz), 112.89 (d, *J* = 7.8 Hz), 63.39 (d, *J* = 7.5 Hz), 35.67 (d, *J* = 124.5 Hz), 25.24, 21.13 (d, *J* = 3.1 Hz), 16.45 (d, *J* = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.5 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_2P$ 303.1257, found 303.1248.

Synthesis of (2-ethoxy-3,3-dimethyl-2-oxido-3-hydrobenzo[d][1,2]azaphosphol-1-yl)(phenyl)methanone 4.59



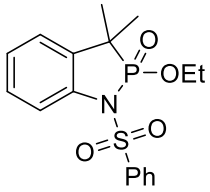
To a solution of phostam **4.32** (50 mg, 0.22 mmol, 1.00 equiv.) and Et_3N (37 μL, 0.27 mmol, 1.20 equiv.) in DCM (5 mL) under N_2 was added BzCl (31 μL, 0.27 mmol, 1.20 equiv.). The reaction mixture was stirred at r.t. for 1 h. Sat. aq. NH_4Cl was added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by silica gel chromatography (Hexanes/AcOEt, 7:3 to 5:5) to afford the desired compound **4.59** as a white solid (59 mg, 82%)

Or

To a solution of phostam **4.32** (50 mg, 0.22 mmol, 1.00 equiv.) in THF (5 mL) under N_2 was added LiHMDS (1M in toluene, 28 μL, 0.24 mmol, 1.10 equiv.). The solution was stirred at r.t. for 5 min. Then, BzCl (28 μL, 0.24 mmol, 2.1 equiv.) was added. The reaction mixture was stirred at

r.t. for 1 h. Sat. aq. NH_4Cl was added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by silica gel chromatography (Hexanes/AcOEt, 7:3 to 6:4) to afford the desired compound **4.59** as a white solid (62 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 2H), 7.63 – 7.54 (m, 1H), 7.53 – 7.44 (m, 2H), 7.39 – 7.35 (m, 1H), 7.29 – 7.12 (m, 3H), 4.50 – 3.93 (m, 1H), 3.73 (ddq, *J* = 10.3, 9.3, 7.1 Hz, 1H), 1.58 (d, *J* = 17.7 Hz, 3H), 1.47 (d, *J* = 17.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.34 (d, *J* = 2.8 Hz), 137.64 (d, *J* = 24.0 Hz), 135.46, 134.14 (d, *J* = 6.3 Hz), 132.27, 128.91, 128.41, 127.93, 125.04, 123.31 (d, *J* = 12.5 Hz), 118.98 (d, *J* = 7.0 Hz), 64.01 (d, *J* = 6.9 Hz), 36.05 (d, *J* = 124.5 Hz), 23.69 (dd, *J* = 35.0, 2.1 Hz), 16.20 (d, *J* = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 45.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_3P$ 330.1254, found 330.1266.

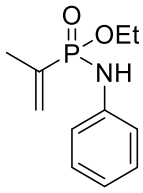
Synthesis of 2-ethoxy-3,3-dimethyl-1-(phenylsulfonyl)-1,3-dihydrobenzo[d][1,2]azaphosphole 2-oxide 4.60



To a solution of phostam **4.32** (225 mg, 1.00 mmol, 1.00 equiv.) in THF (10 mL) under N_2 was added LiHMDS (1M in toluene, 1.10 mL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred for 5 min at r.t. Then, $PhSO_2Cl$ (0.15 mL, 1.20 mmol, 1.20 equiv.) was added at r.t. The reaction mixture was stirred at r.t. for 1 h. Sat. aq. NH_4Cl was added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by silica gel chromatography (Hexanes/AcOEt, 6:4 to 5:5) to afford the desired compound **4.60** as a colorless oil (222 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 2H), 7.67 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.61 – 7.54 (m,

1H), 7.53 – 7.43 (m, 2H), 7.26 – 7.18 (m, 1H), 7.18 – 7.07 (m, 2H), 4.83 – 4.25 (m, 2H), 1.48 (d, *J* = 17.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 17.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.75, 135.79 (d, *J* = 22.7 Hz), 133.80 (d, *J* = 6.6 Hz), 133.64, 129.02, 128.37, 127.90, 124.93 (d, *J* = 1.4 Hz), 123.61 (d, *J* = 13.3 Hz), 115.44 (d, *J* = 6.4 Hz), 64.21 (d, *J* = 8.1 Hz), 35.55 (d, *J* = 126.3 Hz), 25.39 (d, *J* = 1.3 Hz), 22.01 (d, *J* = 3.5 Hz), 16.25 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.4 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}NO_4PS$ 366.0923, found 366.0935.

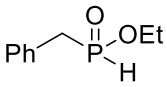
Synthesis of ethyl *N*-phenyl-*P*-(prop-1-en-2-yl)phosphonamidite 5.1



In a flask under N_2 was added compound **4.39** (1.00 g, 5.61 mmol, 1.00 equiv.) in DCM (28 mL). Oxalyl chloride (0.58 mL, 6.74 mmol, 1.20 equiv.) was added slowly followed by DMF (43 μL, 0.56 mmol, 0.10 equiv.) dropwise. The reaction mixture was refluxed for 20 h. It was then cooled down to r.t. and added dropwise to a solution of aniline (2.56 mL, 28.1 mmol, 5.00 equiv.) and DIPEA (1.95 mL, 11.2 mmol, 2.00 equiv.) in DCM (10 mL). The reaction mixture was refluxed for 10 h. It was then cooled down to r.t. and washed with aq. NH_4Cl (sat.). Organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (Hexanes/AcOEt, 6:4 to 1:9) to afford the desired product **5.1** as a yellowish solid (846 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 2H), 7.03 – 6.85 (m, 3H), 6.11 (d, *J* = 5.5 Hz, 1H), 6.03 – 5.88 (m, 1H), 5.88 – 5.63 (m, 1H), 4.28 – 4.05 (m, 2H), 1.98 (dt, *J* = 14.3, 1.4 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.25, 135.98 (d, *J* = 163.7 Hz), 129.52 (d, *J* = 9.3 Hz), 129.26, 121.40, 117.27 (d, *J* = 6.4 Hz), 60.68 (d, *J* = 6.3 Hz), 18.69 (d, *J* = 13.1 Hz), 16.25 (d, *J* = 6.8 Hz);

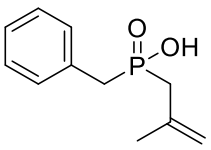
^{31}P NMR (162 MHz, $CDCl_3$) δ 18.0 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0997.

Synthesis of ethyl benzyl *H*-phosphinate 5.5 [49]



To a solution of ethyl phosphinate (0.5M in CH_3CN, 90 mmol, 180 mL, 1.0 equiv.) was added benzyl bromide (16.9 g, 99 mmol, 1.1 equiv.). The solution was then cooled down to 0 °C and DBU (14.8 mL, 99 mmol, 1.1 equiv.) was added dropwise via an addition funnel. Reaction mixture was allowed to warm up to r.t. and was stirred for 2 h. Reaction mixture was concentrated *in vacuo* to remove CH_3CN. Residue was taken up in AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by silica gel column chromatography (Hexanes/AcOEt 3:7) to yield the desired product **5.5** as a colorless oil (13.8 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dt, *J* = 545.0, 1.9 Hz, 1H), 7.44 – 7.18 (m, 5H), 4.27 – 3.97 (m, 2H), 3.29 – 3.11 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 36.5 (d, *J* = 544 Hz).

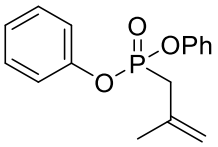
Synthesis of benzyl(2-methylallyl)phosphinic acid 5.3



To a round-bottom flask was added *H*-phosphinate **5.5** (1.84 g, 10.0 mmol, 1.00 equiv.) in DCM (20 mL) under N_2. The solution was cooled down to 0 °C and BSA (4.89 mL, 20 mmol, 2.0 equiv.) was added dropwise. The solution was stirred for 15 min then methallyl bromide (1.21 mL, 12.0 mmol, 1.2 equiv.) was added at 0 °C. The reaction was allowed to warm up to r.t. and stirred for 12 h. MeOH (5 mL) was added to quench the reaction. Solvents were removed under vacuum and the residue was taken up in AcOEt.

Aq. sat. $NaHCO_3$ was used to extract. The aqueous layer was then acidified with HCl 6N and extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuum to afford benzyl(2-methylallyl)phosphinic acid **5.3** as a white solid (1.49 g, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.36 – 7.19 (m, 5H), 4.95 (dp, *J* = 4.7, 1.6 Hz, 1H), 4.83 (ddq, *J* = 4.8, 1.8, 0.9 Hz, 1H), 3.06 (d, *J* = 16.7 Hz, 2H), 2.42 (dd, *J* = 17.5, 1.0 Hz, 2H), 1.90 – 1.75 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.48 (d, *J* = 9.5 Hz), 131.65 (d, *J* = 7.7 Hz), 130.10 (d, *J* = 5.7 Hz), 128.54 (d, *J* = 2.6 Hz), 126.77 (d, *J* = 3.2 Hz), 115.73 (d, *J* = 10.7 Hz), 37.75 (d, *J* = 89.5 Hz), 36.22 (d, *J* = 88.3 Hz), 24.00 (d, *J* = 2.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.9; HRMS (ESI+) m/z [M+H]+ calcd for $C_{11}H_{15}O_2P$ 211.0882, found 211.0875.

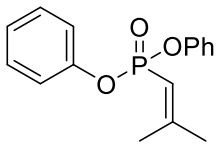
Synthesis of diphenyl (2-methylallyl)phosphonate 5.6



To a solution of diphenyl phosphite **5.7** (16.9 mL, 88 mmol, 1.0 equiv.) in CH_3CN (200 mL) was added methallyl bromide (9.8 mL, 97 mmol, 1.1 equiv.). The solution was then cooled down to 0 °C and DBU (14.5 mL, 97 mmol, 1.1 equiv.) was added dropwise via an addition funnel. Reaction mixture was allowed to warm up to r.t. and was stirred for 2 h. Reaction mixture was concentrated *in vacuo* to remove CH_3CN. Residue was taken up in AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by silica gel column chromatography (Hexanes/AcOEt 9:1 to 7:3) to yield the desired product **5.6** as a white solid (16.6 g, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 7.24 – 7.09 (m, 6H), 5.09 (dp, *J* = 4.7, 1.5 Hz, 1H), 5.08 – 5.00 (m, 1H), 3.02 – 2.89 (m, 2H), 2.01 – 1.98 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.40 (d, *J* = 9.3 Hz), 135.03 (d, *J* = 11.5 Hz), 129.77, 125.14 (d, *J* = 1.3 Hz), 120.59 (d, *J* = 4.4 Hz), 116.89 (d, *J* = 13.1 Hz), 35.53 (d,

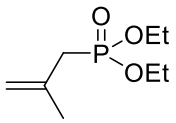
J = 138.2 Hz), 23.78 (d, *J* = 3.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.3 (s); HRMS (ESI+) m/z [M+H]+ calcd for $C_{16}H_{17}O_3P$ 289.0988, found 289.0983.

Synthesis of diphenyl (2-methylprop-1-en-1-yl)phosphonate 5.8



To a solution of compound **5.6** (1.44 g, 5.0 mmol, 1.0 equiv.) in CH_3CN (10 mL) was added DBU (1.50 mL, 10.0 mmol, 2.0 equiv.). Reaction mixture was stirred for 18 h at r.t.. Reaction mixture was concentrated *in vacuo* to remove CH_3CN. Residue was taken up in AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford desired compound **5.8** as a yellow oil (1.11g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 7.28 – 7.12 (m, 7H), 5.75 – 5.55 (m, 1H), 2.17 (dd, *J* = 3.4, 1.1 Hz, 3H), 1.98 (t, *J* = 1.2 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 10.6 (s).

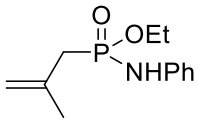
Synthesis of diethyl (2-methylallyl)phosphonate 5.11.[80]



To a round-bottom flask was added diethyl phosphite (2.76 g, 20.0 mmol, 1.00 equiv.) in DCM (40 mL) under N_2. The solution was cooled down to 0 °C and BSA (7.33 mL, 30 mmol, 1.5 equiv.) was added dropwise. The solution was stirred for 15 min then methallyl bromide (2.22 mL, 22.0 mmol, 1.10 equiv.) was added at 0 °C. The reaction was allowed to warm up to r.t. and stirred for 12 h. MeOH (8 mL) was added to quench the reaction. Solvents were removed under vacuum and the residue was taken up in AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum to afford phosphonate **5.11** as a colorless oil (2.84 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (dq, *J* = 4.9, 1.5 Hz, 1H), 4.90

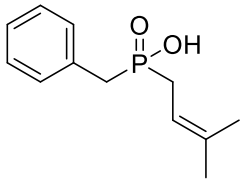
(ddt, *J* = 5.9, 2.1, 1.1 Hz, 1H), 4.45 – 3.95 (m, 4H), 2.76 – 2.43 (m, 2H), 1.90 (dt, *J* = 3.0, 1.2 Hz, 3H), 1.33 (t, *J* = 7.0, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.2 (s).

Synthesis of ethyl *P*-(2-methylallyl)-*N*-phenylphosphonamidate 5.9



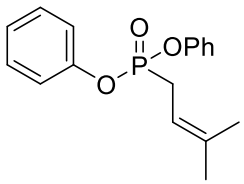
In a flask under N_2 was added compound **5.11** (484 mg, 2.52 mmol, 1.00 equiv.) in DCM (13 mL). Oxalyl chloride (0.26 mL, 3.02 mmol, 1.20 equiv.) was added slowly followed by DMF (19 μL, 0.25 mmol, 0.10 equiv.) dropwise. The reaction mixture was refluxed for 20 h. It was then cooled down to r.t. and added dropwise to a solution of aniline (1.15 mL, 12.6 mmol, 5.00 equiv.) and DIPEA (0.88 mL, 5.04 mmol, 2.00 equiv.) in DCM (5 mL). The reaction mixture was refluxed for 10 h. It was then cooled down to r.t. and washed with aq. NH_4Cl (sat.). Organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (Hexanes/AcOEt, 1:9 to 5:5) to afford the desired product **5.9** as a yellowish oil (428 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 2H), 7.11 – 6.77 (m, 3H), 6.06 (d, *J* = 5.6 Hz, 1H), 4.90 (dp, *J* = 4.8, 1.6 Hz, 1H), 4.75 (ddt, *J* = 6.6, 2.0, 1.0 Hz, 1H), 4.38 – 4.01 (m, 2H), 2.90 – 2.61 (m, 2H), 1.88 (dt, *J* = 3.2, 1.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.46, 136.16 (d, *J* = 10.6 Hz), 129.51, 121.46, 117.26 (d, *J* = 6.1 Hz), 115.71 (d, *J* = 12.1 Hz), 60.40 (d, *J* = 7.3 Hz), 35.28 (d, *J* = 124.9 Hz), 23.94 (d, *J* = 2.7 Hz), 16.23 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.9 (s); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{18}NO_2P$ 240.1148, found 240.1153.

Synthesis of benzyl(3-methylbut-2-en-1-yl)phosphinic acid 5.12



To a round-bottom flask was added *H*-phosphinate **5.5** (1.84 g, 10.0 mmol, 1.00 equiv.) in DCM (20 mL) under N_2. The solution was cooled down to 0 °C and BSA (4.89 mL, 20 mmol, 2.0 equiv.) was added dropwise. The solution was stirred for 15 min then prenyl bromide (1.39 mL, 12.0 mmol, 1.2 equiv.) was added at 0 °C. The reaction was allowed to warm up to r.t. and stirred for 12 h. MeOH (5 mL) was added to quench the reaction. Solvents were removed under vacuum and the residue was taken up in AcOEt. Aq. sat. $NaHCO_3$ was used to extract. The aqueous layer was then acidified with HCl 6N and extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuum to afford phosphinic acid **5.12** as a white solid (1.97 g, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.49 – 6.81 (m, 5H), 5.24 – 5.02 (m, 1H), 3.01 (d, *J* = 16.8 Hz, 2H), 2.38 (dd, *J* = 17.8, 7.7 Hz, 2H), 1.75 (dd, *J* = 4.8, 1.4 Hz, 3H), 1.57 (dd, *J* = 3.7, 1.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.03 (d, *J* = 13.3 Hz), 131.75 (d, *J* = 7.4 Hz), 129.95 (d, *J* = 5.7 Hz), 128.52 (d, *J* = 2.6 Hz), 126.71 (d, *J* = 3.3 Hz), 112.47 (d, *J* = 8.5 Hz), 36.21 (d, *J* = 86.9 Hz), 28.84 (d, *J* = 93.2 Hz), 25.90 (d, *J* = 2.9 Hz), 18.12 (d, *J* = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.2; HRMS (ESI+) m/z [M+H]+ calcd for $C_{12}H_{17}O_2P$ 225.1039, found 225.1049.

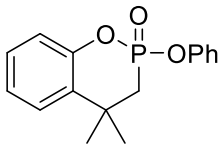
Synthesis of diphenyl (3-methylbut-2-en-1-yl)phosphonate 5.13



To a solution of diphenyl phosphite **5.7** (2.34 g, 10 mmol, 1.0 equiv.) in CH_3CN (20 mL) was added prenyl bromide (1.27 mL, 11 mmol, 1.1 equiv.). The solution was then cooled down to 0 °C and DBU (1.65 mL, 11 mmol, 1.1 equiv.) was added dropwise via an addition funnel. Reaction mixture was allowed to warm up to

r.t. and was stirred for 2 h. Reaction mixture was concentrated *in vacuo* to remove CH_3CN. Residue was taken up in AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by silica gel column chromatography (Hexanes/AcOEt 9:1) to yield the desired product **5.13** as a colorless oil (2.18 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 4H), 7.25 – 7.06 (m, 6H), 5.32 (tdt, *J* = 7.8, 4.8, 1.5 Hz, 1H), 3.25 – 2.32 (m, 2H), 1.80 (dq, *J* = 5.9, 1.3 Hz, 3H), 1.67 (dd, *J* = 4.4, 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.48 (d, *J* = 9.0 Hz), 138.17 (d, *J* = 15.4 Hz), 129.75, 125.07 (d, *J* = 1.3 Hz), 120.57 (d, *J* = 4.4 Hz), 111.33 (d, *J* = 11.7 Hz), 26.59 (d, *J* = 140.4 Hz), 25.86 (d, *J* = 3.3 Hz), 18.10 (d, *J* = 2.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.0 (s); HRMS (ESI+) m/z [M+H]+ calcd for $C_{17}H_{19}O_3P$ 303.1145, found 303.1138.

Synthesis of 4,4-dimethyl-2-phenoxy-3,4-dihydrobenzo[e][1,2]oxaphosphinine 2-oxide 5.14



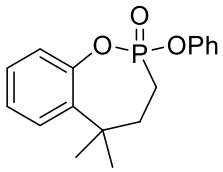
In a flask was added phosphonate **5.6** (228 mg, 1.0 mmol. 1.0 equiv) in sulfuric acid (5 mL). The reaction mixture was stirred at r.t. for 2 h. IT was then cooled down to 0 °C and poured into ice-cold brine. The solution was extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired heterocycle **5.14** (176 mg, 61%)

Or

In a flask was added phosphonate **5.8** (228 mg, 1.0 mmol. 1.0 equiv) in sulfuric acid (5 mL). The reaction mixture was stirred at r.t. for 2 h. It was then cooled down to 0 °C and poured into ice-cold brine. The solution was extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired heterocycle **5.14** (190 mg,

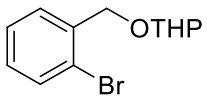
66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 77.46 – 7.32 (m, 3H), 7.30 – 7.14 (m, 5H), 7.06 (dd, *J* = 8.1, 1.4 Hz, 1H), 2.36 (dq, *J* = 17.0, 15.3 Hz, 2H), 1.57 – 1.55 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.3 (s); HRMS (ESI+) m/z [M+H]+ calcd for $C_{16}H_{17}O_3P$ 289.0988, found 289.0991.

Synthesis of 5,5-dimethyl-2-phenoxy-3,4,5-trihydrobenzo[f][1,2]oxaphosphepine 2-oxide 5.17



In a flask was added phosphonate **5.13** (302 mg, 1.0 mmol. 1.0 equiv) in sulfuric acid (5 mL). the reaction was stirred at r.t. for 2 h. It was then cooled down to 0 °C and poured into ice-cold brine. The solution was extracted with DCM (x2). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired heterocycle **6.17** (166 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 3H), 7.23 – 7.13 (m, 5H), 6.99 (ddd, *J* = 6.4, 3.0, 1.8 Hz, 1H), 2.58 – 2.25 (m, 2H), 2.19 – 1.90 (m, 2H), 1.49 (d, *J* = 2.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.14 (d, *J* = 8.9 Hz), 148.79 (d, *J* = 7.3 Hz), 138.96 (d, *J* = 2.4 Hz), 129.74, 128.12 (d, *J* = 1.7 Hz), 127.29 (d, *J* = 1.6 Hz), 125.66 (d, *J* = 1.8 Hz), 125.12, 123.29 (d, *J* = 3.8 Hz), 120.41 (d, *J* = 4.7 Hz), 37.27, 34.87 (d, *J* = 7.1 Hz), 29.26, 28.63, 23.05 (d, *J* = 134.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.5 (s); HRMS (ESI+) m/z [M+H]+ calcd for $C_{17}H_{19}O_3P$ 303.1145, found 303.1149.

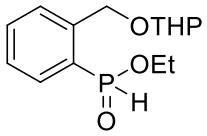
Synthesis of 2-((2-bromobenzyl)oxy)tetrahydro-2H-pyran 5.22 [81]



In a flask was added 2-bromobenzyl alcohol **6.21** (18.7 g, 100 mmol, 1.0 equiv.) in DCM (250 mL) under N_2. Dihydropyran (13.7 mL, 150 mmol, 1.5 equiv.)

was added at r.t. followed by PPTS (2.51 g, 10 mmol, 0.1 equiv.). The reaction mixture was stirred for 4 h at r.t. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (Hexanes/AcOEt 95:5) to afford pure protected alcohol **5.22** (27.1 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (td, *J* = 7.8, 1.5 Hz, 2H), 7.34 (td, *J* = 7.5, 1.3 Hz, 1H), 7.17 (ddd, *J* = 9.1, 7.4, 1.7 Hz, 1H), 4.86 (d, *J* = 13.3 Hz, 1H), 4.81 (t, *J* = 3.5 Hz, 1H), 4.60 (d, *J* = 13.3 Hz, 1H), 3.96 (ddd, *J* = 11.4, 8.7, 3.2 Hz, 1H), 3.69 – 3.53 (m, 1H), 2.08 – 1.86 (m, 1H), 1.86 – 1.50 (m, 5H).

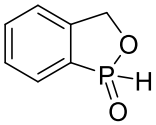
Synthesis of ethyl (2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)phosphinate 5.23



To a solution of compound **5.22** (26.6 g, 98 mmol, 1.00 equiv.) in THF (400 mL) under N_2 cooled down to -78 °C was added *n*-BuLi (2.5 M in hexanes, 39.2 mL, 98 mmol, 1.00 equiv.) dropwise over 30 min via an addition funnel. The mixture was stirred for 3 h at -78 °C. Then a solution of chlorodiethylphosphine (14.1 mL, 98 mmol, 1.00 equiv.) in THF (40 mL) was cannulated over 30 min at -78 °C in the reaction mixture. The reaction was then stirred at -78 °C for 1 h. It was then warmed up to r.t. and the solvent was removed under vacuum. Diethyl ether (200 mL) was added to the flask and stirred for 1 h. The white precipitate (lithium salts) was filtered, washed with diethyl ether (twice 30 mL) and then the diethyl ether solutions were concentrated under vacuum to afford a white oil. The white oil was purified by silica gel column chromatography (Hexanes/AcOEt 9:1 to 5:5) to afford *H*-phosphinate **5.23** as a clear oil (20.6 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers 50:50) δ 7.77 (d, *J* = 574.6 Hz, 1H), 7.76 (d, *J* = 573.4 Hz, 1H), 7.95 (dddd, *J* = 14.6, 7.2, 5.7, 1.4 Hz, 2H), 7.61 – 7.50 (m, 4H), 7.48 – 7.42 (m, 4H), 5.08 – 4.88 (m, 2H), 4.84 – 4.72 (m, 4H), 4.27 – 4.03 (m, 4H), 3.95 – 3.86 (m, 2H), 3.64 – 3.52 (m, 2H), 1.94 – 1.50 (m, 12H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.2

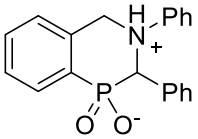
Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of diastereomers 50:50) δ 141.52, 133.00, 132.63, 129.18 (d, *J* = 15.7 Hz), 128.95, 127.69 (d, *J* = 12.7 Hz), 98.42, 67.10, 62.32 (d, *J* = 23.4 Hz), 30.47, 25.39, 19.35 (d, *J* = 19.2 Hz), 16.35; ^{31}P NMR (162 MHz, $CDCl_3$) (mixture of diastereomers 50:50) δ 23.9 (d, *J* = 577 Hz), 23.6 (d, *J* = 577 Hz); HRMS (ESI+) m/z [M+H]+ calcd for $C_{17}H_{19}O_3P$ 303.1145, found 303.1149.

Synthesis of 3H-benzo[c][1,2]oxaphosphole 1-oxide 5.20



In a flask was added *H*-phosphinate **5.23** (12.4 g, 43.6 mmol, 1.00 equiv) and PPTS (1.05 g, 4.4 mmol, 0.10 equiv.) in EtOH (130 mL). The mixture was stirred at 50 °C for 4 h. Then the solution was concentrated under high vacuum for 2 h at 40 °C. The resulting oil was triturated with hexanes to afford the desired compound **5.20** in 80% purity by NMR. ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.5 (d, *J* = 596.9 Hz).

Synthesis of 2,3-diphenyl-2,3,4-trihydrobenzo[d][1,3]azaphosphinin-3-ium-1-olate 1-oxide 5.24



In a flask was added *H*-phosphinate **5.20** (80% pure by ^{31}P NMR, g, mmol, 1.00 equiv.) and *N*-benzylideneaniline (g, mmol, 1.10 equiv) in CH_3CN (mL). DBU (mL, mmol, 1.10 equiv.) was added dropwise at r.t. The reaction mixture was stirred at r.t. for 2 h. The white precipitate was filtered off, washed with CH_3CN and Et_2O and dried under vacuum to afford pure compound **5.24** (mg, %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.56 – 7.42 (m, 1H), 7.41 – 7.24 (m, 6H), 7.18 – 7.05 (m, 2H), 6.81 – 6.68 (m, 1H), 6.69 – 6.53 (m, 2H), 5.36 (dd, *J* = 13.8, 4.6 Hz, 1H), 5.08 – 4.80 (m, 3H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 146.43 (d, *J* = 13.6 Hz), 144.90 (d, *J* = 20.9 Hz), 135.00 (d, *J* = 4.0 Hz), 133.40 (d, *J* = 2.7 Hz), 129.30, 129.20, 129.18, 128.95 (d, *J* = 11.8 Hz), 128.70 (d, *J* = 2.8 Hz), 128.05 (d, *J* = 3.3 Hz), 127.62 (d, *J* = 4.8 Hz), 125.24 (d, *J* = 120.4 Hz), 122.18 (d, *J* = 11.2 Hz), 118.88, 114.37, 72.74 (d, *J* = 1.5 Hz), 59.29 (d, *J* = 104.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 55.7; HRMS (ESI+) m/z [M+Na]+ calcd for $C_{20}H_{18}NO_2P$ 358.0967, found 358.0960.

REFERENCES

1) (a) Corbridge, D. E. C. *Phosphorus word. Chemistry: Biochemistry and Technology* 2005.

(b) Beatty, R. *Phosphorus*. 2000

2) Van Wazer, J.R. *Phosphorus and its compounds,* Vol 1., Wiley, 1958

3) (a) "Ueber das Verhalten der Jodalkyle gegen die sogen. Phosphorigsäureester oder O-Phosphine" Michaelis, A.; Kaehne, R. *Berichte*. **1898**, *31*, 1048–1055. DOI:10.1002/cber.189803101190.

(b) Arbuzov, A. E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.

(c) Arbuzov, A. E. *Chem. Zentr. II*, **1906**, 1639

4) For good reviews on phosphine-catalyzed reactions:

(a) "Phosphine Organocatalysis" Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. *Chem. Rev.* **2018**, *118*, 10049-10293. DOI:10.1021/acs.chemrev.8b000

(b) "Phosphine-Catalyzed Asymmetric Organic Reactions" Ni, H., Chan, W.-L., Lu, Y. (2018). *Chem. Rev.* **2018**, *118*, 9344-9411. DOI:10.1021/acs.chemrev.8b0026

(5) Phosphine Ligand Application Guide – Sigma-Aldrich [Online] https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Datasheet/1/phosphine-ligand-application-guide.pdf (Accessed September 17, 2020).

(6) (a) "Highly Active Palladium Catalysts for Suzuki Coupling Reactions", Wolfe J.P.; Singer, R.A.; Yang, B.H.; Buchwald, S.L. *J. Am. Chem. Soc*. **1999**, *121*, 9550-9561. DOI:10.1021/ja992130h

(b) "New Ammonia Equivalents for the Pd-Catalyzed Amination of Aryl Halides", Huang, X.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 3417-3419. DOI:10.1021/ol0166808

(c) “Monodentate Phosphines Provide Highly Active Catalysts for Pd-Catalyzed *C-N* Bond-Forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heterocycles”, Anderson, K.W.; Tundel, R.E.; Ikawa, T.; Altman, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed*. **2006**, *118*, 6673-6677. DOI:10.1002/ange.200601612

(d) “Significantly Improved Method for the Pd-Catalyzed Coupling of Phenols with Aryl Halides: Understanding Ligand Effects.” Burgos, C.H.; Barder, T.E.; Huang, X.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326. DOI:10.1002/anie.200601253

(e) “General Catalysts for the Suzuki-Miyaura and Sonogashira Coupling Reactions of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water”, Anderson, K.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2005**, *44*, 6173-6177. DOI:10.1002/anie.200502017

(7) (a) “A P,N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions” Lundgren, R.; Peters, B.; Alsabeh, P.; Stradiotto, M. *Angew. Chem. Int. Ed*. **2010**, *49*, 4071-4074. DOI:10.1002/anie.201000526

(b) “Palladium-Catalyzed Mono-α-Arylation of Acetone with Aryl Halides and Tosylates”, Hesp, K.D.; Lundgren, R.J.; Stradiotto, M. *J. Am. Chem. Soc*. **2011**, *133*, 5194-5197. DOI:10.1021/ja200009c

(8) “The Wittig and Related Reactions in Natural Product Synthesis”, K. C. Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebiegs Ann. Recl.* **1997**, 1283-1301. DOI:10.1002/jlac.199719970704

(9) The IRAC Mode of Action Classification Online. https://irac-online.org/modes-of-action/ (Accessed April 28, 2020).

(10) “New Insights on Glyphosate Mode of Action in Nodular Metabolism: Role of Shikimate Accumulation”, de María, N.; Becerril, J. M.; García-Plazaola, J. I.; Hernández, A.; de Felipe, M. R.; Fernández-Pascual, M. *J. Agric. Food Chem.* **2006**, *54*, 2621-2628. DOI:10.1021/jf058166c

(11) “Fosfomycin: Pharmacological, Clinical and Future Perspectives”, Dijkmans, A. C.; Ortiz Zacarías, N. V.;Burggraaf, J.; Mouton, J. W.; Wilms, E. B.; van Nieuwkoop, C.; Touw, D. J.; Stevens, J.; Kamerling, I. M. C. *Antibiotics* **2017**, *6*, 24-41. DOI:10.3390/antibiotics6040024

(12) (a) “Phosphine Oxides (−POMe$_2$) for Medicinal Chemistry: Synthesis, Properties, and Applications” Stambirskyi, M.V.; Kostiuk, T.; Sirobaba, S.H.; Rudnichenko, A.; Titikaiev, D.L. Dmytriv, Y.V.; Kuznietsova, H.; Pishel, I.; Borysko, P.; Mykhailiuk, P.K.; *J. Org. Chem.* **2021,** *86*, 12783-12801. DOI: 10.1021/acs.joc.1c01413

(b) “A comprehensive Review on Brigatinib – A Wonder Drug for Targeted Cancer Therapy in Non-Small Cell Lung Cancer” Bedi, S.; Khan, S.A.; AbuKhader, M.A.; Alam, P.; Siddiqui, N.A.; Husain, A. *Saudi Pharm. J.* **2018**, *26*, 755-763. DOI: 10.1016/j.jsps.2018.04.010

(13) “Application of 1-Hydroxyethylidene-1, 1-Diphosphonic Acid in Boiler Water for Industrial Boilers” Zeng, B.; Li, M.; Zhu, Z.; Zhao, J.; Zhang, H. *Water, Science and Technologies*, **2013**, *67*, 1544-1550. DOI: 10.2166/wst.2013.021

(14) (a) Wilkinson, W.D. *Uranium Metallurgy, 1st Ed.*; Interscience Publishers: New York, 1962

(b) “A ^{31}P and ^{15}N Study of the Extraction of Uranyl Nitrate by Di-2-ethylhexyl Phosphoric Acid” Lemire, A.E.; Janzen, A.F.; Marat, K. *Inorg. Chim. Acta*, **1985**, *110*, 234-241. DOI: 10.1016/S0020-1693(00)82312-9

(15) Fyrolflex® RDP-HP (High purity) product page ICL: https://www.icl-ip.com/product/fyrolflex-rdp/ (Accessed, September 17th, 2021)

(16) “An Overview of Some Recent Advances in DOPO-derivatives: Chemistry and Flame

Retardant Applications" Salmeia, K. A., & Gaan, S. *Polymer Degradation and Stability*, **2015,** *113*, 119-134. DOI: 10.1016/j.polymdegradstab.2014.12.014.

(17) (a) "Enantioselective Brønsted Acid Catalyzed Transfer Hydrogenation:? Organocatalytic Reduction of Imines" Rueping, M.; Sugiono, E., Azap, C., Theissmann, T., Bolte, M. *Org. Lett.* **2005**, *7*, 3781-3783. DOI: 10.1021/ol0515964

(b) "A Powerful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines", Hoffmann, S.; Seayad, A.M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427. DOI: 10.1002/anie.200503062

(c) "Enantioselective Organocatalytic Reductive Amination", Storer, R.I.; Carrera, D.E.; Ni Y.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2006**, *128*, 84-86. DOI: 10.1021/ja057222n

(d) "Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes", Jain, P.; Antilla, J.C.; *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886. DOI: 10.1021/ja104956s

(e) "Direct Synthesis of Chiral 1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazines via a Catalytic Asymmetric Intramolecular Aza-Friedel-Crafts Reaction", He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J.C. *Org. Lett.* **2011**, *13*, 4490-4493. DOI: 10.1021/ol2018328

(18) Press release: The Nobel Prize in Chemistry 2021. https://www.nobelprize.org/prizes/chemistry/2021/press-release/ (Accessed November 9th, 2021)

(19) (a) "Applications of Lawesson's Reagent in Organic and Organometallic Syntheses", Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis (Review)*, **2003**, *13*, 1929–1958. DOI: 10.1055/s-2003-41447

(b) "Thionation reactions of Lawesson's reagents" Cava, M. P.; Levinson, M. I. *Tetrahedron.* **1985**, *41*, 5061–5087. DOI: 10.1016/S0040-4020(01)96753-5

(20) "Ifosfamide" The American Society of Health-System Pharmacists. https://www.drugs.com/monograph/ifosfamide.html (Accessed September 17th, 2021)

(21) "Development of Insecticidal Cyclic Phosphoryl Compounds Through Chemical and Biochemical Approaches" Eto, M. *Pesticides, Food Contaminants, and Agricultural Wastes* **1983**, *18*, 119-145. DOI: 10.1080/03601238309372360

(22) "Novel Phosphoinositide 3-Kinase Inhibitor, Preparation Method and Application", Long, Z.; Guowei, S. PCT Int. Appl. WO 2019228404, Dec 5, 2019

(23) "Phosphorus-Carbon Bond Formation: Palladium-Catalyzed Cross-Coupling of H-Phosphinates and Other P(O)H-Containing Compounds", Berger, O.; Petit, C.; Deal, E.L.; Montchamp, J.-L. *Adv. Synth. Cat.* **2013**, *355*, 1361-1373. DOI: 10.1002/adsc.201300069

(24) (a) "Organophosphorus Compounds XVI. Synthesis of some novel 2,3-dihydro-1H-1,2-Benzazaphosphole 2-Oxides and -Sulphides", Collins, D. J.; Drygala, P. F.; Swan, J. M. *Tetrahedron Lett.* **1982**, *23*, 1117−1120. DOI: 10.1016/S0040-4039(00)87037-9

(b) "Organophosphorus Compounds. XVIII. Synthesis of 2-Phenyl-2,3-dihydro-1H-1,2-Benzazaphosphole 2-Sulfide by Pyrolysis of (2-Aminobenzyl)-Phenyldithiophosphinic Acid", Collins, D.; Drygala, P.; Swan, J. *Aust. J. Chem.* **1983**, *36*, 2095−2110. DOI: 10.1071/CH9832095

(c) "Organophosphorus Compounds. XIX. Synthesis of 2,3-Dihydro-1 H-1,2-Benzazaphosphole 2-Oxides, Variously Substituted on Nitrogen and Phosphorus, by *N-P* Cyclizationof Zwitterionic Intermediates", Collins, D.; Drygala, P.; Swan, J. *Aust. J. Chem.* **1983**, *36*, 2517−2536. DOI: 10.1071/CH9832517

(d) “Organophosphorus Compounds. XX. Approaches to the Synthesis of 2,3-Dihydro-1H-1,2-Benzazaphospholes Involving *C-C* and *C-P* Ring Closure”, Collins, D.; Drygala, P.; Swan, J. *Aust. J. Chem.* **1984**, *37*, 1009−1021. DOI: 10.1071/CH9841009

(e) “Organophosphorus Compounds. XXI. Solvolysis and C3-Substitution Reactions of Some 2,3-Dihydro-1H-1,2-Benzazaphosphole 2-Oxides and 2-Sulfides”, Collins, D.; Drygala, P.; Swan, J. *Aust. J. Chem.* **1984**, *37*, 1349−1356. DOI: 10.1071/CH9841349

(25) “Synthesis of 2-Oxophosphorindolines via the Copper-Catalyzed Intramolecular Aromatic C−H Insertion of Diazophosphonamidates” Huang, P.; Xu, J. *RSC Adv.* **2016**, *6*, 63736−63748. DOI: 10.1039/C6RA10555F

(26) “Reactions of Carbene Intermediates from the Reaction of Trialkyl Phosphites with Dialkyl Benzoylphosphonates: Preparation and Reactions of Dimethyl 2-(*N*-tert-butyl-N-methylamino) Benzoylphosphonate and Dimethyl 2-(methylamino)benzoylphosphonate”, Griffiths, D. V.; Harris, J. E.; Whitehead, B. J. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2545−2548. DOI: 10.1039/A701147D

(27) “On the Cost of Academic Methodologies” Berger, O.; Winters, K. R.; Sabourin, A.; Dzyuba, S. V.; Montchamp, J.-L. *Org. Chem. Front.* **2019**, *6*, 2095−2108. DOI: 10.1039/C9QO00200F

(28) M. Fleisher, USGS Circular 285, *Recent estimates of the abundances of elements in the earth's crust*, 1953. DOI: 10.3133/cir285.

(29) Extraction du Scandium. Ressources et Métallurgie Extractive du Scandium. https://www.techniques-ingenieur.fr/base-documentaire/materiaux-th11/elaboration-et-recyclage-des-metaux-de-transition-42649210/ressources-et-metallurgie-extractive-du-scandium-

m2357/extraction-du-scandium-m2357niv10005.html (in French) (Accessed September 21st, 2021)

(30) The Nobel Prize in Chemistry 2010. https://www.nobelprize.org/prizes/chemistry/2010/summary/ (Accessed September 21st, 2021)

(31) (a) "Phosphinate Chemistry in the 21st Century: A Viable Alternative to the Use of Phosphorus Trichloride in Organophosphorus Synthesis" Montchamp, J.-L. *Acc. Chem. Res.*, **2014**, *47*, 77-87. DOI: 10.1021/ar400071v

(b) "Organophosphorus Synthesis Without Phosphorus Trichloride: The Case for the Hypophosphorous Pathway", Montchamp, J.-L. *Phosphorus, Sulfur Silicon Relat. Elem.*, **2013**, *188*, 66-75. DOI: 10.1080/10426507.2012.727925

(32) "Olefination of Carbonyl Compounds: Modern and Classical Methods" Korotchenko, V.N.; Nenajdenko, V. G.; Balenkova, E. S.; Shastin, A. V. *Russ. Chem. Rev.*, **2004**, *73*, 957-989. DOI: 10.1070/RC2004v073n10ABEH000895

(33) (a) "The Wittig Reaction Using Potassium-tert-butoxide High Yield Methylenations of Sterically Hindered Ketones" Fitjer, L.; Quabeck, U. *Synth. Commun.*, **1985**, *15*, 855-864. DOI: 10.1080/00397918508063883

(b) "The Wittig Reaction in Industrial Practice" Pommer, H. *Angew. Chem. Int. Ed.*, **1977**, *7*, 423-492. DOI: 10.1002/anie.197704233

(c) "The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects" Maryanoff, B.E.; Reitz, A. B. *Chem. Rev.*, **1989**, *89*, 863-927. DOI: 10.1021/cr00094a007

(34) (a) “Carbonyl Methylenation of Easily Enolizable Ketones” Hibino, J.-I.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.*, **1985**, *26*, 5579. DOI: 10.1016/S0040-4039(01)80892-3

(b) “Titanium Reagents for the Alkylidenation of Carboxylic Acid and Carbonic Acid Derivatives” Hartley, R. C.; McKiernan, G.J.; *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2763-2793. DOI: 10.1039/B009709H

(35) (a) “Hydrophosphinylation of Unactivated Terminal Alkenes Catalyzed by Nickel Chloride” Ortial, S.; Fisher, H.C.; Montchamp, J.-L. *J. Org. Chem.*, **2013**, *78*, 6599-6608. DOI: 10.1021/jo4008749

(b) “AIBN-Initiated Radical Reactions of Ethyl Phosphinate” Antczak, M.I.; Montchamp, J.-L. *Synthesis*, **2006**, *18*, 3080-3084. DOI: 10.1055/s-2006-950203.

(c) “Triethylborane-Initiated Room Temperature Radical Addition of Hypophosphites to Olefins: Synthesis of Monosubstituted Phosphinic Acids and EstersDeprèle” S. ; Montchamp, J.-L. *J. Org. Chem.*, **2001**, ***66***, 6745-6755. DOI: 10.1021/jo015876i

(d) “Palladium-Catalyzed Hydrophosphinylation of Alkenes and Alkynes” Deprèle, S. Montchamp, J.-L. *J. Am. Chem. Soc.*, **2002**, *124*, 9386-9387. DOI: 10.1021/ja0261978

(e) “Environmentally Benign Synthesis of *H*-Phosphinic Acids Using a Water-Tolerant, Recyclable Polymer-Supported Catalyst” Deprèle, S.; J.-L. Montchamp, J.-L. *Org. Lett.*, **2004**, *6*, 3805-3808. DOI: 10.1021/ol0484198

(36) Hill, M.; Dietz, M.; Krause, W.; Sicken, M. “Method For Producing Mono-Carboxy-Functionalized Dialkylphosphinic Acids, Esters And Salts Using A Vinyl Ether And The Use Thereof”, US Patent 8,987,489B2 (March 2015).

(37) “Manganese-Mediated Homolytic Aromatic Substitution with Phosphinylidenes” Berger, O.; Montchamp, J.-L. *Chem. Rec.* **2017**, *17*, 1203-1212. DOI: 10.1002/tcr.201700021 and references herein

(38) “Phosphorus Chemistry” Montchamp, J.-L. *Top. Curr. Chem.*, **2015**, *361*, 217-252. And references herein

(39) “Oxidative Phosphonylation of Aromatic Compounds” Effenberger, F.; Kottman, H. *Tetrahedron*, **1985**, *41*, 4171-4182. DOI: 10.1016/S0040-4020(01)97192-3

(40) “Manganese(III)-Promoted Reactions for Formation of Carbon-Heteroatom Bonds.” Pan, X.Q.; Zou, J.P.; Zhang, W. *Mol. Divers.* **2009**, *13*, 421–438. DOI: s11030-009-9144-x

(41) “Hydrophosphorylation of Alkenes with Dialkyl Phosphites Catalyzed by Mn(III) under Air” Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.*, 2004, **69**, 5494-5496. DOI: 10.1021/jo049657j

(42) (a) “Manganese-Mediated Intermolecular Arylation of *H*-Phosphinates and Related Compounds” Berger, O.; Montchamp, J.-L. *Chem. Eur. J.*, **2014**, *20*, 12385-12388. DOI: Manganese-Mediated Intermolecular Arylation of H-Phosphinates and Related Compounds

(b) “Manganese-Catalyzed and Promoted Reactions of *H*-Phosphinate Esters” Fisher, H.C.; Gelat, F.; Montchamp, J.-L. *Adv. Synth. Catal.*, **2014**, *356*, 1199-1204. DOI: 10.1002/adsc.201301157

(43) (a) “Pyridine-Directed Palladium-Catalyzed Phosphonation of C(sp2)-H Bonds”Li, C.; Yano, T.; Ishida, N.; Murakami, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 9801–9804. DOI: 10.1002/anie.201305202

(b) “Pd(II)-Catalyzed Phosphorylation of Aryl C–H Bonds” Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322–9325. DOI: 10.1021/ja404526x

(44) “A Direct and New Convenient Oxidation: Synthesis of Substituted Arylphosphonates from Aromatics” Siméon, F. ; Jaffrès, P.-A.; Villemin, D. *Tetrahedron,* **1998**, *54*, 10111-10118. DOI: 10.1016/S0040-4020(98)00601-2

(45) “Synthesis of Arenephosphonates by Copper(I) Iodide-Promoted Arylation of Phosphite Anions” Osuka, A.; Ohmasa, N.; Yoshida, Y.; Suzuki, H. *Synthesis* **1983**, 69-71. DOI: 10.1055/s-1983-30229

(46) “Visible-Light-Induced External Oxidant-Free Oxidative Phosphonylation of C(sp2)–H Bonds” Niu, L.; Liu, J.; Yi, H.; Wang, S.; Liang, X.-A.; Singh, A.-K.; Chiang C.-W.; Lei, A. *ACS Catal.*, **2017**, *7*, 7412-7416. DOI: 10.1021/acscatal.7b02418

(47) (a) “Oxindole: A Chemical Prism Carrying Plethora of Therapeutic Benefits” Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. *Eur. J. Med. Chem.* **2016**, *123*, 858−894. DOI: 10.1016/j.ejmech.2016.08.011

(b) “Multicomponent Reactions (MCRs): a Useful Access to the Synthesis of Benzo-Fused γ-Lactams” Martínez de Marigorta, E.; de Los Santos, J. M.; Ochoa de Retana, A. M.; Vicario, J.; Palacios, F. *Beilstein J. Org. Chem.* **2019**, *15*, 1065−1085. DOI: 10.3762/bjoc.15.104

(48) “Recent Advances in Catalytic Synthesis of Benzosultams.” Zhao, Q.-Q.; Hu, X.-Q. *Molecules* **2020**, *25*, 4367−4388. DOI: 10.3390/molecules25194367

(49) “DBU-Promoted Alkylation of Alkyl Phosphinates and *H*-Phosphonates” Gavara, L.; Petit, C.; Montchamp, J.-L. *Tetrahedron Lett.* **2012**, *53*, 5000−5003. DOI: 10.1016/j.tetlet.2012.07.019

(50) “Atherton–Todd Reaction: Mechanism, Scope and Applications” Le Corre, S. S.; Berchel, M.; Couthon-Gourvès, H.; Haelters, J.-P.; Jaffrès, P.-A.; *Beilstein J. Org. Chem.* **2014**, *10*, 1166–1196. DOI: 10.3762/bjoc.10.117

(51) IRAC Mode of Action Classification. https://irac-online.org/ (Accessed October 2nd, 2021)

(52) Unpublished results from Montchamps laboratory

(53) “Synthesis of Allenes by Double Horner−Wadsworth−Emmons Reaction” Inoue, H.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **2002**, *58*, 83−90. DOI: 10.1016/S0040-4020(01)01089-4

(54) “Facile *P,N*-Heterocycle Synthesis via Tandem Aminomethylation-Cyclization of *H*-Phosphinate Building Blocks” Queffelec, C.; Montchamp, J.-L. *Org. Biomol. Chem.* **2010**, *8*, 267-273. DOI: 10.1039/b917428a

(55) “5,8-Quinolinedione Scaffold as a Promising Moiety of Bioactive Agents” Kadela-Tomanek, M.; Bębenek, E.; Chrobak, E.; Boryczka, S. *Molecules* **2019**, *24*, 4115. DOI: 10.3390/molecules24224115

(56) “Synthesis and In Vitro Evaluation of Aspartate Transcarbamoylase inhibitors” Coudray, L.; Pennebaker, A. F.; Montchamp, J.-L.. *Bioorg. Med. Chem.* **2009**, 17, 7680-7689. DOI: 10.1016/j.bmc.2009.09.045

(57) “Mild, Efficient Friedel-Crafts Acylations from Carboxylic Acids Using Cyanuric Chloride and $AlCl_3$” Kangani, C. O.; Day, B. W. *Org. Lett.* **2008**, 10, 2645-2648. DOI: 10.1021/ol800752v

(58) “A Practical Preparation of Aryl β-Ketophosphonates” Milburn, R.; McRae, K.; Chan, J.; Tedrow, J.; Larsen, R.; Faul, M. *Tetrahedron Lett.* **2009**, 50, 870-872. DOI: 10.1016/j.tetlet.2008.11.112

(59) (a) “The “Cyclopropyl Fragment” Is a Versatile Player That Frequently Appears in Preclinical/Clinical Drug Molecules” Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712−8756. DOI: 10.1021/acs.jmedchem.6b00472

(b) “Syntheses of Biologically Active 2-Arylcyclopropylamines” Miyamura, S.; Itami, K.; Yamaguchi, J. *Synthesis* **2017**, *49*, 1131−1149. DOI: 10.1055/s-0036-1588390

(c) “Small Ring Chemistry in Crop Protection” Lamberth, C. *Tetrahedron* **2019**, 75, 4365−4383. DOI: doi.org/10.1016/j.tet.2019.06.043

(60) (a) “Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides” Wolfe, J.; Buchwald, S. *J. Org. Chem.* **2000**, 65, 1144-1157. DOI: 10.1021/jo9916986

(b) “Elucidating Reactivity Differences in Palladium- Catalyzed Coupling Processes: The Chemistry of Palladium Hydrides” Hills, I.; Fu, G. *J. Am. Chem. Soc.* **2004**, 126, 13178-13179. DOI: 10.1021/ja0471424

(c) “Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery that Xantphos Can Be Trans-Chelating in a Palladium Complex” Yin, J.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 6043-6048. DOI: 10.1021/ja012610k

(d) “Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational and Synthetic Investigation” Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, *129*, 13001-13007. DOI: 10.1021/ja0717414

(e) “Mild Pd-Catalyzed *N*-Arylation of Methanesulfonides and Related Nucleophiles: Avoiding Potentially Genotoxic Reagents and Byproducts” Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. *Org. Lett.* **2011**, *13*, 2564-2567. DOI: 10.1021/ol200660s

(f) “Cascade Palladium-Catalyzed Alkenyl Aminocarbonylation/ Intramolecular Aryl Amidation: An Aminative Synthesis of 2-Quinolones” Tadd, A.C.; Matsuno, A.; Fielding, M.R.; Willis, M.C. *Org. Lett.* **2009**, *11*, 583-586. DOI: 10.1021/ol802624e

(g) “Palladium-Catalyzed Site-Selective Amidation of Dichloroazines” Young, I.S.; Glass, A.-L.; Cravillion, T.; Han, C.; Zhang, H.; Gosselin, F. *Org. Lett.* **2018**, *20*, 3902-3906. DOI: acs.orglett.8b01483

(61) (a) “The Chan-Evans-Lam N-Arylation of Phosphonic/Phosphinic Amides” Xu, Y.; Su, Q.; Dong, W.; Peng, Z.; An, D. *Tetrahedron* **2017**, *73*, 4602-4609. DOI: 10.1016/j.tet.2017.06.028

(b) “Cu-Catalyzed Arylation of Phosphinic Amide Facilitated by (±)-trans-cyclohexane-1,2-diamine” Li, J.; Zhang, S. L.; Tao C. Z.; Fu, Y.; Guo Q. X. *Chinese Chem. Lett.* **2007**, *18*, 1033-1036. DOI : 10.1016/j.cclet.2007.07.028

(c) “A Simple Copper-Catalyzed Synthesis of Tertiary Acyclic Amides” Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818-2821. DOI: 10.1021/ol200750p

(d) “Structure-Activity Relationships of Norepinephrine Reuptake Inhibitors with Benzothiadiazine Dioxide or Dihydrosulfostyril Cores” Fensome, A.; Goldberg, J.; McComas, C. C.; Trybulski, E. J.; Woodworth R. P.; Deecher, C.; Whiteside, G.T.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1555-1558. DOI: 10.1016/j.bmcl.2010.01.056

(e) “Copper-Catalyzed *N*-Arylation of Sulfonamides with Aryl Bromides Under Mild Conditions” Wang, X.; Guram, A.; Ronk, M.; Milne, J. E.; Tedrow, J. S.; Faul, M.M. *Tetrahedron Lett.* **2012**, *53*, 7-10. DOI: 10.1016/j.tetlet.2011.10.113

(f) “Synthetic Studies Toward Mycobacterium Tuberculosis Sulfolipid-I” Lei, C. D.; Bertozzi, C.R. *J. Org. Chem.* **2008**, *73*, 1008-1017. DOI: 10.1021/jo702032c

(62) (a) “An Organocatalytic Enantioselective Vinylogous Mannich Reaction of α,α-Dicyanoolefins with Isatin N-Boc Ketimines” Zhu, Y.; Li, Y.; Meng, Q.; Li, X. *Org. Chem. Front.* **2016**, 3, 709-713. DOI: 10.1039/C6QO00038J

(b) “A Convenient Enantioselective Synthesis of 3-Asymmetrically Substituted Oxindoles as Progesterone Receptor Antagonists” Alluria, S.; Fenga, H.; Livingsa, M.; Sampa, L.; Biswasa, D.;Lamb, T. W.; Lobkovskyc, E.; Gangulya, A. K. *Tetrahedron Lett.* **2011**, 52, 3945–3948. DOI: 10.1016/j.tetlet.2011.05.120

(c) “Copper-Mediated Fluoroalkylation Reactions with Iododifluoroacetamides: Controlling the Selectivity among Cross-Coupling, Intramolecular Cyclization, and Homocoupling Reactions” Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, 16, 5505-5512. DOI: 10.1021/jo1005262

(d) “Oxidative Debenzylation of *N*-Benzyl Amides and *O*-Benzyl Ethers Using Alkali Metal Bromide” Moriyama, K.; Nakamura, Y.; Togo, H. *Org. Lett.* **2014**, 16, 3812-3815. DOI: 10.1021/ol501703y

(e) “Room-Temperature Debenzylation of N-Benzylcarboxamides by N-Bromosuccinimide” Kuang, L.; Zhou, J.; Chen, S.; Ding, K. *Synthesis* **2007**, 20, 3129-3124. DOI: 10.1055/s-2007-990795

(63) (a) “Palladium-Catalyzed Divergent Cyclopropanation by Regioselective Solvent-Driven C(sp3)−H Bond Activation” Chung, D. S.; Lee, J. S.; Ryu, H.; Park, J.; Kim, H.; Lee, J. H.; Kim, U. B.; Lee, W. K.; Baik, M.-H.; Lee, S.-G. *Angew. Chem. Int. Ed.* **2018**, 57, 15460-15464. DOI: 10.1002/anie.201809133

(b) “Synthesis of 3,3-Dimethyl Aza- and Diazaindolines Using a Palladium-Catalysed Intramolecular Reductive Cyclisation” Day, J.; Frederickson, M. Hogg, C.; Johnson, C. N.; Meek, A.; Northern, J.; Reader, M.; Reid, G. *Synlett*, **2015**, 26, 2570-2574. DOI: 10.1055/s-0035-1560320

(c) “Synthesis of Heterocycles via Ligand-Free Palladium Catalyzed Reductive Heck Cyclization” Liu, P; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul, M. M. *Tet. Let.* 2007, 48, 2307-2310. DOI: 10.1016/j.tetlet.2007.01.156

(64) (a) “Norcarane [Bicyclo[4.1.0]heptane]” Smith, R. D.; Simmons, H. E. *Org. Synth., Coll. Vol.* **1973**, 855. DOI: 10.15227/orgsyn.041.0072

(b) “Synthesis of 1-Arylcyclopropylphosphonates” Gulyukina, N. S.; Varakuta, A. V.; Beletskaya, I. P.. *Russ. Chem. Bull.* **2007**, 56, 1884-1890. DOI: 10.1007/s11172-007-0290-y

(65) “Unusual 1,2-Aryl Migration and Depalladation of Alkylpalladium Intermediates Containing a syn-β-Hydrogen Atom” Youn, S. W.; Lee, S. R.; Kim, Y. A.; Kang, D. Y.; Jang, M. J. *Chem. Select* **2016**, 1, 5749-5757. DOI: 10.1002/slct.201601382

(66) (a) University of Winsconsin – Department of Chemistry. Bordwell pKa Tables. https://www.chem.wisc.edu/areas/reich/pkatable/ (Accessed October 5th, 2021)

(b) “Concerning the Deprotonation of the Trimethylsulfonium Ion by the Dimethylsulfinyl Anion” Haiss, P.; Zeller, K.-P. *Org. Biomol. Chem.* **2011**, 9, 7748-7754

(67) (a) US Patent Application 20050261322

(b) “Synthesis of Substituted Naphthalenes via a Catalytic Ring-Expansion Rearrangement” Glass, A. C.; Morris, B. B.; Zakharov, L. N.; Liu, S.-Y. *Org. Lett.* **2008**, *10,* 4855–4857. doi:10.1021/ol8019617

(c) “Synthesis of Silicon Substituted Cyclopropylmethyl Alcohols in Optically Active Form via Asymmetric Simmons-Smith Reaction of γ-Silicon Substituted Allylic Alcohols” Ukaji, Y. *Chem. Lett.* **1993**, *7*, 1227-1230. DOI: 10.1246/cl.1993.1227

(d) “Catalytic Asymmetric Intramolecular Cyclopropanation of α-Diazo-α-Silyl Acetate” Nakada, M.; Inoue, S.; Nagatani, K.; Tezuka, H.; Hoshino, Y. *Synlett* **2017**, *28*, 1065–1070. doi:10.1055/s-0036-1588414

(68) “Stereoselective Synthesis of Indolines via Organocatalytic Thioester Enolate Addition Reactions” Kolarovic, A.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, 16, 4236-4239. DOI: 10.1021/ol501936n

(69) “Synthesis of Terminal Vinylphosphonates via DBU-Promoted Tandem Phospha-Michael/Elimination Reactions” Chen, H.-X.; Huang, L.-J.; Liu, J.-B.; Weng, J.; Lu, G. *Phosphorus, Sulfur, and Silicon and Rel. Elem.* **2014**, 189, 1858-1866. DOI: 10.1080/10426507.2014.906422

(70) (a) “Reversible and Efficient Inhibition of UDP-Galactopyranose Mutase by Electrophilic, Constrained and Unsaturated UDP-Galactitol Analogues” Ansiaux, C.; N’Go, I.; Vincent, S. P. *Chem. Eur. J.* **2012**, 18, 14860–14866. DOI: 10.1002/chem.201202302

(b) “Lewis Acid Triggered Vinylcyclopropane–Cyclopentene Rearrangement” Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I.I.; Trushkov, I. V. *J. Org. Chem.* **2018**, 83, 543-560. DOI: 10.1021/acs.joc.7b02351

(71) “1,3,8-Triazaspiro[4.5]decane-2,4-diones as Efficacious Pan-Inhibitors of Hypoxia-Inducible Factor Prolyl Hydroxylase 1−3 (HIF PHD1−3) for the Treatment of Anemia” Vachal, P.; Miao, S.; Pierce; J. M.; Guiadeen, D.; Colandrea, V. J.; Wyvratt, M. J.; Hale, J. J. *J. Med. Chem.* **2012**, 55, 2945-2959. DOI: 10.1021/jm201542d

(72) (a) “Cyclization of β-Hydroxyalkylphosphine Oxides - Mechanism Elucidation Using Experimental and DFT Methods” Włodarczyk, K.; Borowski, P.; Drach, M.; Stankevič, M. *Tetrahedron* **2017**, *73*, 239–251. doi:10.1016/j.tet.2016.12.008

(b) “Intramolecular Cationic Cyclization of β-Hydroxyalkylphosphine Oxides—a Route Towards the Benzophosphorinane Core” Włodarczyk, K.; Stankevič, M. *Tetrahedron* **2016**, *72*, 5074–5090. doi:10.1016/j.tet.2016.06.070

(73) “Synthesis and Evaluation of Stilbene Derivatives as a Potential Imaging Agent of Amyloid Plaques” Hong, M. C.; Kim, Y. K.; Choi, J. Y.; Yang, S. Q.; Rhee, H.; Ryu, Y. H.; Choi, T. H.; Cheon, G. J.; An, G. I.; Kim, H. Y.; Kim, Y.; Kim, D. J.; Lee, J.-S.; Chang, Y.-T.; Lee, K. C. *Bioorg. Med. Chem.* **2010**, *18*, 7724−7730. DOI: 10.1016/j.bmc.2010.06.044

(74) “Synthesis of Diethyl 2-(Aryl)Vinylphosphonates by the Heck Reaction CatalyZed by Well-Defined Palladium Complexes” Al-Maksoud, W.; Mesnager, J.; Jaber, F.; Pinel, C.; Djakovitch, L. *J. Organomet. Chem.* **2009**, *694*, 3222−3231. DOI: 10.1016/j.jorganchem.2009.06.020

(75) “Lewis Acid-Mediated Michaelis−Arbuzov Reaction at Room Temperature: A Facile Preparation of Arylmethyl/Heteroarylmethyl Phosphonates” Rajeshwaran, G. G.; Nandakumar, M.; Sureshbabu, R.; Mohanakrishnan, A. K. *Org. Lett.* **2011**, *3*, 1270−1273. DOI: 10.1021/ol1029436

(76) “The Preparation of Dialkyl 1-Hydroxyalkylphosphonates in the Reaction of Trialkyl Phosphites with Oxonium Salts Derived from Aldehydes or Ketones” Soroka, M.; Goldeman, W. *Synthesis* **2006**, *18*, 3019–3024. DOI: 10.1055/s-2006-950200

(77) Nesterov, L.; Krepysheva, N.; Martynov, A. *Zhurnal Obshchei Khimii*, **1982**, 52, 429-430

(78) “Microwave-Assisted Palladium-Catalyzed Cross-Coupling of Aryl and Vinyl Halides with H-Phosphonate Diesters” Kalek, M., Ziadi, A., & Stawinski, J. *Org. Lett.* **2008**, *10*, 4637–4640. DOI: 10.1021/ol801935r

(79) “Reaction of Dimethyl 1-Hydroxyalkylphosphonates with Some Chlorides” Mitsuji, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 812-814.

(80) “Total Synthesis of (+)-Erogorgiaene and the Pseudopterosin A-F Aglycone via Enantioselective Cobalt-Catalyzed Hydrovinylation” Movahhed, S., Westphal, J., Kempa, A., Schumacher, C. E., Sperlich, J., Neudörfl, J.; Schmalz, H. *Chem. Eur. J.* **2021**, 27, 11574–11579. DOI: 10.1002/chem.202101863

(81) “Preparation of Enantioenriched Chiral Organic Molecules by Dynamic Asymmetric Induction from an Outer Chiral Source” Igawa, K.; Kawasaki, Y.; Ano, Y.; Kashiwagi, T.; Ogawa, K.; Hayashi, J.; Tomooka, K. *Chem. Lett.* **2019**, *48*, 726–729. DOI: 10.1246/cl.190170

VITA

Axel Sabourin was born and raised in Versailles, France. After his preparatory classes in Sceaux, he enrolled in the National Graduate School of Chemistry of Montpellier where he received his Bachelor of Science in 2013 and his Master of Science in 2016. In January 2017, Axel began his doctoral studies at Texas Christian University in Fort Worth, Texas under the supervision of Dr. Jean-Luc Montchamp. The first three years of his Ph.D program were sponsored by Bayer SAS. During his graduate studies at TCU, Axel received the TCU College of Science & Engineering Dean Teaching Award in 2019 as well as the 2017, 2018 and 2019 TCU Chemistry & Biochemistry Outstanding Teaching Awards. In December 2021, Axel obtained the Doctor of Philosophy degree in Chemistry.

ABSTRACT

DEVELOPMENT AND REACTIVITY
OF NOVEL BENZO-FUSED PHOSPHORUS-CONTAINING
HETEROCYCLES

by
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The work presented in this dissertation consists in the development of syntheses towards novel benzo-fused phosphorus-containing heterocycles. Special emphasis is given to benzophostam structures. A review of the most relevant literature in terms of preparation of known and related phosphorus-containing heterocycles is provided in Chapter I. The following chapter introduces a new concept invented by Montchamp and coworkers, the cost of academic methodologies (CAM), to evaluate and compare various methodologies according to a cost-based approach. The third chapter details the different strategies developed to synthesize the different *P*-substituted 5- and 6-membered benzophostams and they are evaluated through the CAM lense. Chapter IV is a direct continuation of chapter III with the development of methods to access various *N*- and *C*-substituted benzophostams by arylation or alkylation reactions with various electrophiles of phostams previously synthesized in chapter III or from completely new strategies, such as a reductive Heck approach. Finally, in chapter V, two new strategies are presented to access other type of *P*-heterocycles. The first one is based on the cyclization of unsaturated phosphorus compounds under Friedel-Crafts conditions to access electron rich benzo-fused phosphorus-containing heterocycles while the second approach relies on [4+2] addition process of a benzooxaphosphole oxide with

various permanent dipoles to deliver a series of 6-membered benzo-fused phosphorus-containing heterocycles.