NEW METHODOLOGIES FOR THE SYNTHESIS OF CHIRAL PHOSPHORUS ACIDS AND RELATED COMPOUNDS

by

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

Doctor of Philosophy

December 2021

APPROVAL

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Dissertation approved:

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For the College of Science and Engineering

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and appreciation to my research advisor, Professor Jean-Luc Montchamp. I was inspired to work with you because of your enthusiasm and dedication to research. As my "academic father", you encouraged me to always do my best every day. Your vast knowledge of phosphorus chemistry and science helped create a stimulating environment that gave me the freedom to learn and grow as a scientist. Thank you for all our many discussions, for allowing me to blast my music in the lab, and for having your door open and being available. Most of all, thank you for believing in me.

I would like to extend my appreciation to my committee members Dr. David Minter, Dr. Youngha Ryu, and Dr. Sergei Dzyuba. Thank you for all your invaluable support, advice, and insight throughout my doctoral career.

I want to acknowledge Chloe Ricke for being a fantastic student to work with, and for her contribution to the projects described in this dissertation. I also want to thank Dr. Olivier Berger for being a great friend and scientist to bounce ideas off. I would like to recognize Dr. Axel Sabourin. During the past 5 years you became my coworker, my teacher, my partner, my therapist, and my best friend. I learned so much from you, thank you for those years.

I also want to thank the rest of my colleagues and friends. Your continuous encouragement and friendship have had a true impact on my life. All our Starbucks breaks, chats in the hallways, discussions during lunch, movie nights, happy hours, hikes, and everything in-between means the world to me.

To my friend Andrea Guedez Peña, we have come so far since the first day we met at orientation. Throughout the doctoral program, we grew together and tackled every challenge and obstacle with ease because of the support and warmth we provided each other. You are a

wonderful scientist, woman, and mother. I am so blessed to have you as my friend.

To my wonderful sisters Rebecca Winters and Lee Schwiebert, and my brother-in-law Dennis Schwiebert. I am so lucky to have such awesome siblings and best friends! Our facetime calls, Snapchats, group messages, family vacations, and countless adventures have all kept me going. Our craziness fills my heart up with the best energy and keeps me motivated. Thank you for being amazing role models and the best siblings a girl could ask for.

To my parents Gregory and Kathy Winters. I want to thank my Dad, to whom I owe my scientific brain, creative spirit, and thirst for knowledge. You always challenged and pushed me to become the best version of myself. I am very fortunate to have your support and love. Lastly, I want to thank my Mom, to whom I owe my heart and spirit. You raised a confident and happy daughter. You taught me to believe in myself, helped me remain optimistic and bright, and to look for the good in others. Thanks for answering my hundreds of phone calls.

This thesis is dedicated to my mom,

who has lifted me up every day

since July 17th, 1994.

AUTHOR'S DECLARATION

Part of this dissertation appeared in the following publications:

1) Winters, K. R; Montchamp, J.-L. Evaluation and Development of Methodologies for the Synthesis of Thiophosphinic Acids. *J. Org. Chem.* **2020**, *85*, 14545−14558.
2) Winters, K. R; Ricke, C.; Montchamp, J.-L. Synthesis of Adamantyl *H*-Phosphinate Esters. *Eur. J. Org. Chem.* **2021**

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Å	Angstroms
Ac	Acetyl
Ad	Adamantyl
ACN	Acetonitrile
AHP	Anilinium hypophosphite
AIBN	2,2′-Azobis(2-methylpropionitrile)
Alk	Alkyl
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	tert-Butyl carbamate
BSA	N, O-Bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
C	Carbon
°C	degree Celsius
cat.	Catalytic
Cin	Cinnamyl
conc.	Concentrated
CPA	Chiral Phosphorus Acid

CPME	Cyclopentylmethyl ether
Cy	Cyclohexyl
D	Deuterium
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBB	di-*t*-butylbiphenylide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N′-Dicyclohexylcarbodiimide
DCE	N,N’-Dichloroethane
DCM	Dichloromethane
DOPO	6H-Dibenzo[c,e][1,2λ5]- oxaphosphinine 6-oxide
dd	doublet of doublets
de	Diastereomeric excess
dr	Diastereomeric ratio
DFT	Density functional theory
DIC	N,N′-Diisopropylcarbodiimide
DIPA	Diisopropylamine
DIPEA	N,N’-Diisopropylethylamine
dm	doublet of multiplets
DMAP	4-Dimethylaminopyridine
DMF	N,N’-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1’-Bis(diphenylphosphino)ferrocene

dppp	1,3-Bis(diphenylphosphino)propane
dt	doublet of triplets
EAS	Electrophilic aromatic substitution
EDC	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
equiv	Equivalent(s)
EDG	electron donating group
Et	ethyl
Et_3N	Triethylamine
EWG	electron withdrawing group
GC	gas chromatography
h	hours
Hex	hexyl
HPLC	High pressure liquid chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i-Pr	isopropyl
LiHMDS	Lithium bis(trimethylsilyl)amide
M	metal
m	meta
Me	methyl
min	minute
MS	mass spectroscopy

MS	molecular sieves
NMR	nuclear magnetic resonance
Nu	Nucleophile
Np	Naphthyl
o	ortho
Oct	octyl
p	para
Pd	palladium
Ph	phenyl
Pht	phthalimide
Piv	pivaloyl
PEG	Poly(ethylene glycol)
Ph	Phenyl
PPA	Polyphosphoric acid
Ppm	part per million
Pr	Propyl
PS	Polystyrene
Pyr	Pyridine
R	generic organic substituent
rac	racemic
RCM	Ring-closing metathesis
rt	Room temperature
SM	Starting material

SPINOL	1,1′-spirobiindane-7,7′-diol
t	triplet
td	triplet of doublets
Temp	Temperature
tm	triplet of multiplets
tt	triplet of triplets
T3P	Propylphosphonic anhydride
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols
TBDMS	tert-butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Trityl
TRIP	2,4,6-triisopropylphenyl
Ts	Tosylate
VAPOL	4,4′-dihydroxy-2,2′-diphenyl-3,3′-biphenanthryl
xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

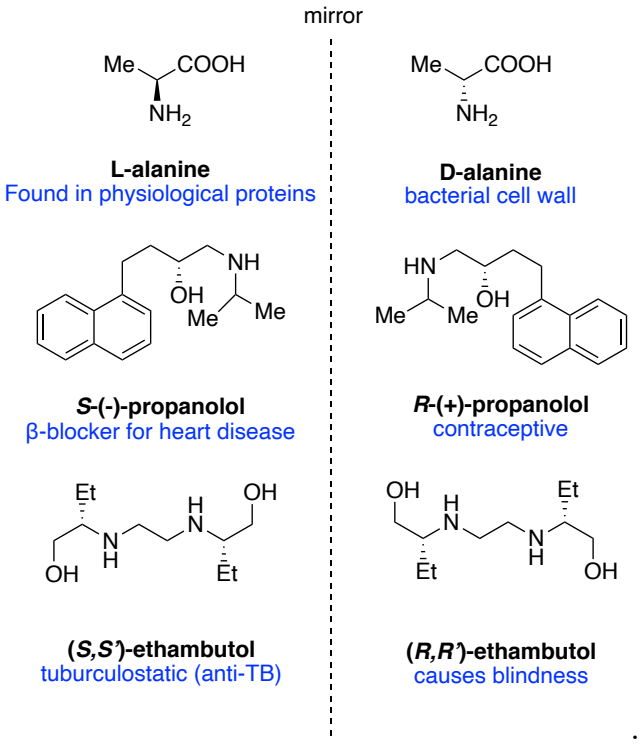
CHAPTER 1

CHIRAL PHOSPHORUS ACIDS IN ORGANOCATALYSIS

1.1 Introduction to Chirality

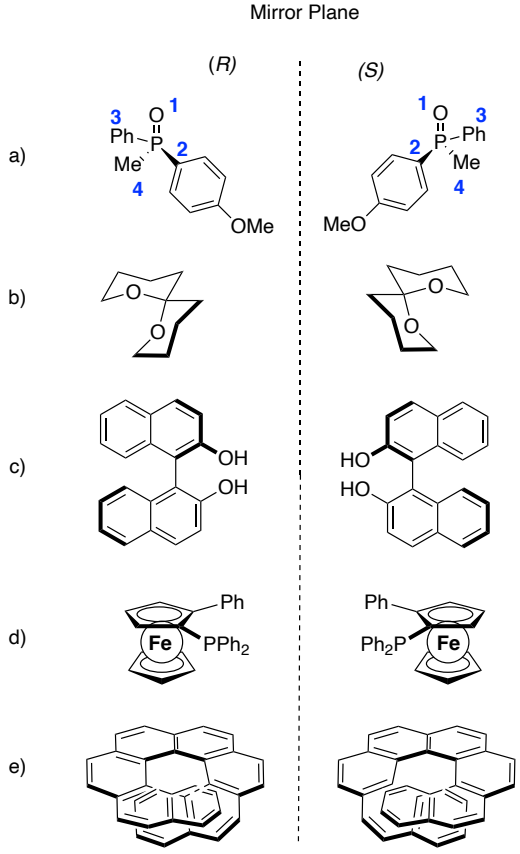
Chirality is a fundamental property of molecules and materials in nature, in which a compound is not identical to its mirror image. Chiral compounds have identical chemical properties but vastly different biological activities (Scheme 1.1). For example, L- and D-alanine are the two isomeric forms of amino acids that are found in nature, where L-alanine is used by the cells for protein synthesis whereas D-alanine is found in cell walls of bacteria. This is also important in pharmaceuticals because chirality plays a significant role in drug pharmacology.[1]

Scheme 1.1 Examples of chiral compounds



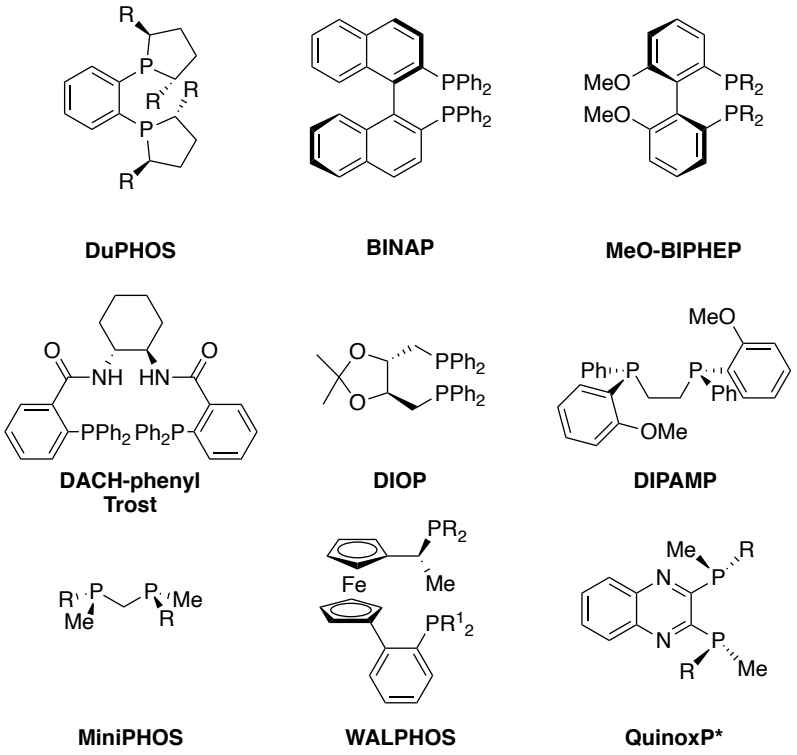
Chirality goes beyond the traditional sp^3 hybridization with four different substituents (Scheme 1.2). Axial chirality does not possess a stereogenic center but instead consists of a nonplanar arrangement of four groups around an axis, such as spiro-compounds or 1,1'-bi-2-naphthol (BINOL). These molecules have restricted rotation around the bond or axis connecting the two substituents. Another form of chirality includes planar chirality, which results from the arrangement of two out-of-plane groups that exist in different planes but cannot rotate due to steric or rotational strain. The inability to rotate or form different conformations leads to a source of stereochemistry. Lastly, helical chirality is seen in molecules that have a right or left-handed helix.

Scheme 1.2 a) point chirality in (4-methoxyphenyl)methylphenyl phosphine oxide; b) axial chirality in 1,7-dioxaspiro[5.5]undecane; c) axial chirality in BINOL; d) planar chirality in 2-phenyl-1-(diphenylphorphanyl)ferrocene; e) helical chirality in [8]helicene

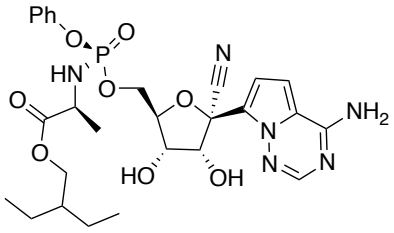


Chiral phosphorus compounds are critically important in the synthesis of pharmaceuticals, herbicides, pesticides, and phosphine ligands.[2] For example, many asymmetric reactions utilize chiral phosphine ligands for transition metal complexes (Scheme 1.3).[3, 4] Another example includes biologically active pharmaceuticals, such as remdesivir, which is a nucleotide analog prodrug approved as an antiviral treatment of Covid (Scheme 1.4).[4] The importance of *P*-stereogenic compounds has driven scientists to continue developing new strategies for the asymmetric synthesis of organophosphorus compounds.

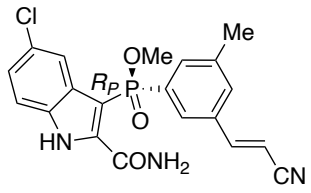
Scheme 1.3 Examples of chiral phosphorus ligands



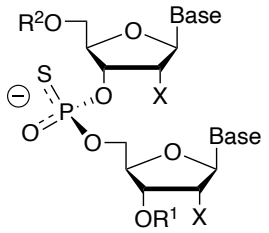
Scheme 1.4 Examples of bioactive chiral phosphorus compounds



Remdesivir
Prodrug of ATP analog; Antiviral agent



IDX899
HIV-1 non-nucleoside
reverse transcriptase inhibitor

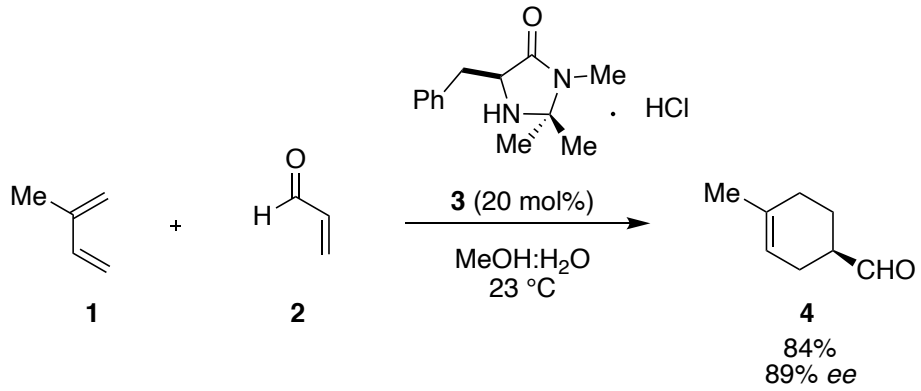


***P*-chiral phosphorothioate**
oligonucleotides

1.2 Asymmetric Synthesis Background

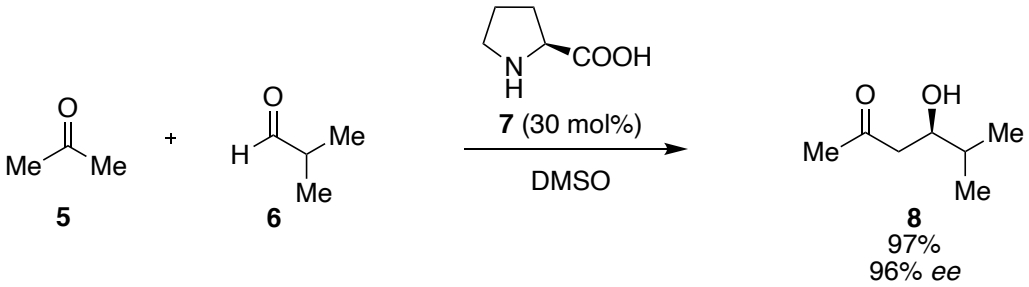
Asymmetric catalysis is a type of transformation in which a chiral catalyst directs the formation of a chiral compound, such that the formation of one specific stereoisomer is favored.[5] This field was notably recognized with the Nobel prize in chemistry; awarded to William Knowles, Ryoji Noyori, and Barry Sharpless (2001), and David MacMillan and Benjamin List (2021).[6] In 2000, MacMillan and coworkers reported the first highly enantioselective organocatalytic Diels-Alder reaction using chiral amine derivatives (Scheme 1.5). The imidazolidinone catalyst **3** led to condensation with **2** to form an iminium ion intermediate, which then would react with the diene **1**. Next, Diels-Alder cycloaddition would occur to give intermediate iminium ion, and upon hydrolysis, regenerate the catalyst and the enantioenriched cycloaddition product **4** in 84% yield and 89% *ee*. Using chiral imidazolidinone with a large benzyl group on the catalyst framework shields the *re* face dienophile, leaving the *si* face exposed to cycloaddition.[7]

Scheme 1.5 Organocatalyzed Diels-Alder reaction between acrolein and 1,3-butadiene reported by MacMillan and coworkers[7]



During the same year, List and coworkers reported an L-proline-catalyzed intermolecular asymmetric aldol condensation (Scheme 1.6).[8] The reaction proceeds via an enamine intermediate, by forming the iminium species through a nucleophilic attack from the proline catalyst **7** on acetone **5**, followed by the carbon-carbon bond-forming step with the starting aldehyde **6**. Lastly, hydrolysis of the iminium-aldol intermediate gives the final aldol product **8** in a 97 % yield and 96 % *ee*.

Scheme 1.6 Proline catalyzed aldol condensation reported by List and coworkers[8]

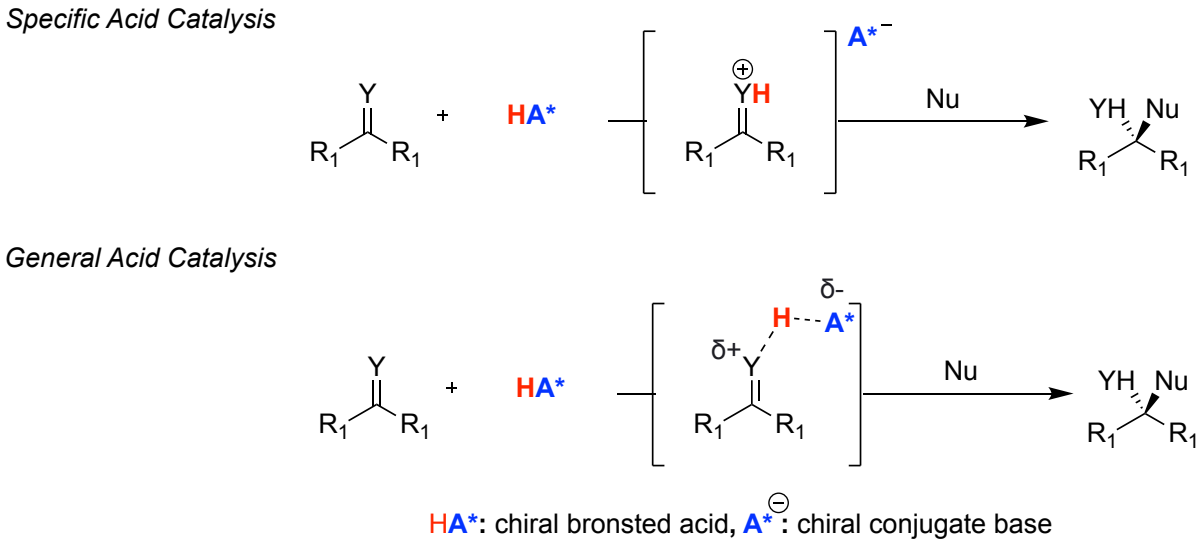


Since these discoveries, activation by chiral hydrogen-bond donors has emerged as a frontier of research in the field of asymmetric catalysis. Numerous reactions and catalysts have been developed and new modes of organocatalysis are being discovered.

1.3 Brønsted Acid Catalysis

In 2004, List introduced a classification system for organocatalysts based on Lewis and Brønsted acid-base theories.[9] Most, but not all, organocatalysts can be broadly classified as Lewis bases (electron donors), Lewis acids (electron acceptors), Brønsted bases (proton acceptors), and Brønsted acids (proton donors). Chiral Brønsted acid catalysis occurs when an enantioenriched product is obtained by using a catalytic amount of a chiral organic molecule bearing an acidic functionality.[10] In 2006, Jacobsen elaborated that this type of catalysis proceeds by either two fundamental mechanisms: 1) reversible protonation of the electrophile in a pre-equilibrium step, before nucleophilic attack (*specific* acid catalysis), or 2) a hydrogen bond is donated from the catalyst to the electrophile during the transition state in the rate-determining step (*general* acid catalysis) (Scheme 1.7).[11]

Scheme 1.7 Jacobsen's principle of specific and general chiral Brønsted acid catalysis[11]

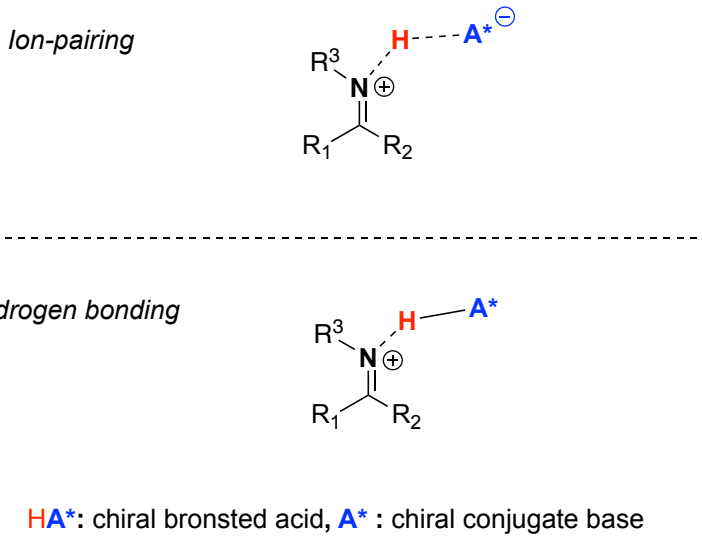


This mechanism of catalysis can be elaborated into the mode of activation, as there are different interactions that can occur between the catalyst and substrates. Many organocatalysts

utilize modes simultaneously and have shown to be successful due to what is now known as *mono* or *dual activation* mode.[5]

Mono-activation from a catalyst can either occur via ion-pairing or hydrogen bonding with a substrate (Scheme 1.8).[5] For example, when looking at an imine species, it was found that the nature of the imine substituents plays a role, as electron-rich imines preferred ion-pairing; whereas electron-poor imines preferred more hydrogen-bonding interactions.[12] The acidity of the catalyst and solvents can also play a role, and both species may be present during the reaction.

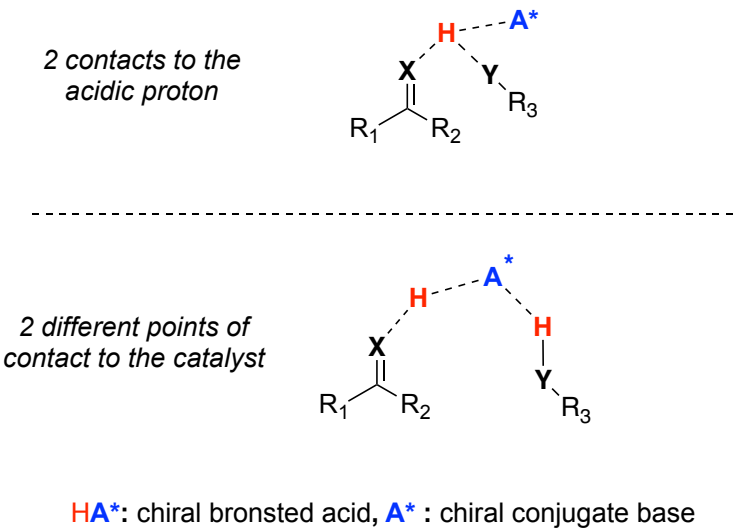
Scheme 1.8 Mono activation through ion- pairing or hydrogen bonding



HA*: chiral bronsted acid, A* : chiral conjugate base

Dual activation (bifunctional) involves activations of electrophilic-reacting partners through two points of contact to the catalyst from the substrate(s) (Scheme 1.9). This can either occur through two contacts to the acidic proton on the catalyst or through an interaction with the acidic proton and a basic site on the catalyst simultaneously.

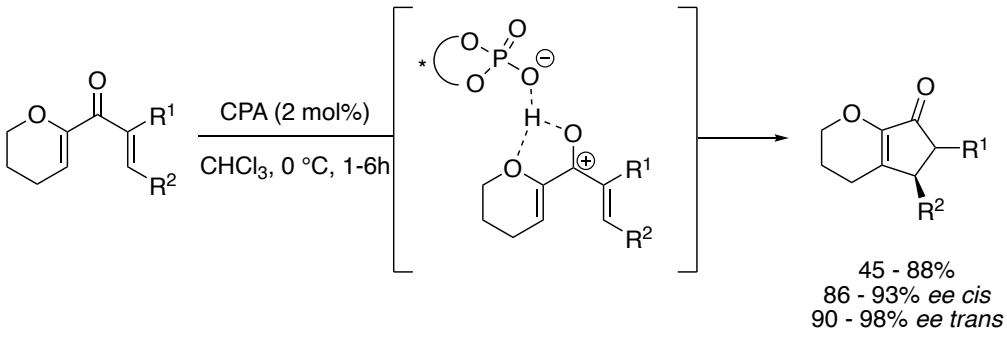
Scheme 1.9 Dual activation through two contacts to the catalyst



HA*: chiral bronsted acid, A* : chiral conjugate base

An example of two contacts to the acidic proton was proposed by Rueping in a Nazarov cyclization (Scheme 1.10).[13] They postulated that the acidic proton of a BINOL- CPA catalyst is involved in a bidentate interaction with the α-alkoxy group and the oxygen of the carbonyl group, which is followed by cyclization and protonation of the enolate species.

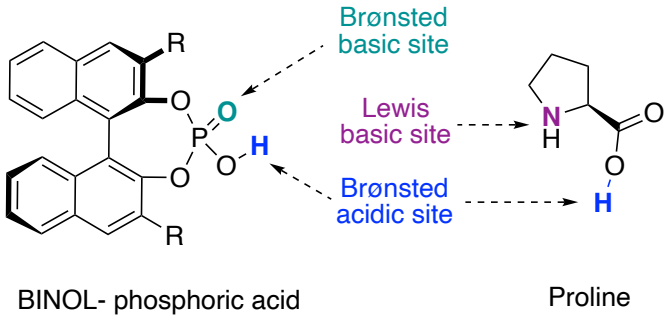
Scheme 1.10 Dual activation in a Nazarov cyclization reported by Rueping[13]



One example of dual activation through an interaction with the acidic proton and the basic site on the catalyst simultaneously, is List's reported Proline catalyst (Scheme 1.6). The

amino group acts as a Lewis base by using its electrons to form a covalent enamine adduct with aldehydes, while the carboxylic acid acts as a Brønsted acid by activating electrophiles through hydrogen bonding and protonation (Scheme 1.11).[8] Similarly, the success of many chiral phosphoric acids (CPAs), such as BINOL-derived CPAs, has been attributed to simultaneous activation of the electrophile and nucleophile, through hydrogen bonding of the Brønsted acidic site and basic site respectively (Scheme 1.11).

Scheme 1.11 Bifunctional activation of BINOL-CPA and L-proline catalyst

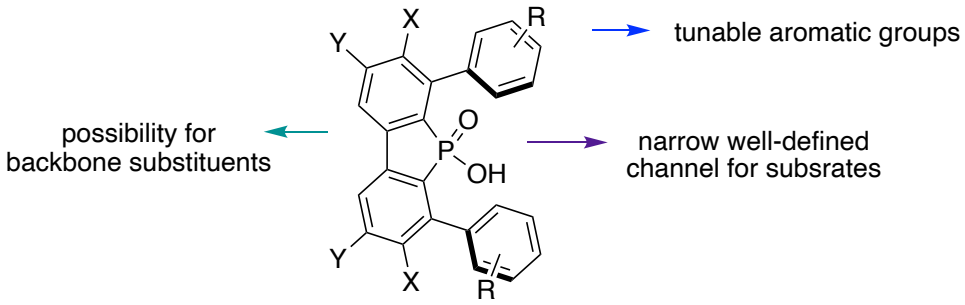


1.4 C_2-Symmetrical Chiral Phosphorus Acids

Sir John Cornforth is most known for his contributions on enzyme-catalyzed reaction, earning him the Nobel prize in Chemistry in 1975,[6] but he is less known for his pioneering work on phosphinic acid catalysts. In 1978, Cornforth investigated 5- membered dibenzo-phosphinic acid derivatives. He found that their rigidity and possibility for attachment of different groups made them ideal catalysts to react with substrates (Scheme 1.12).[14] One could induce a chiral axis on the catalyst with the correct choice of substituents at X and Y and the restricted rotation of the benzene rings. He proposed a potential mechanism for the hydration of olefins and showed that the catalysts performed well, and more efficiently, than other

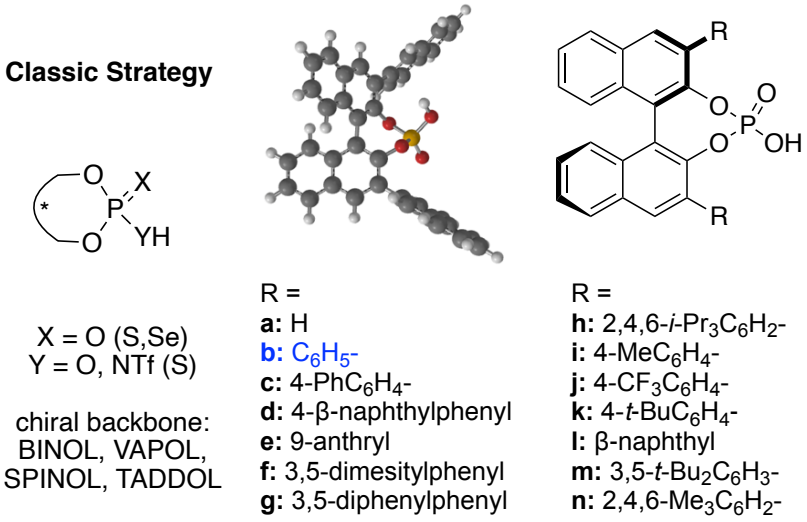
acids.[14] Cornforth's ideas on catalyst design and structure served as the basis for the chiral phosphoric acids that are used today.

Scheme 1.12 Phosphinic acid catalyst design reported by Cornforth



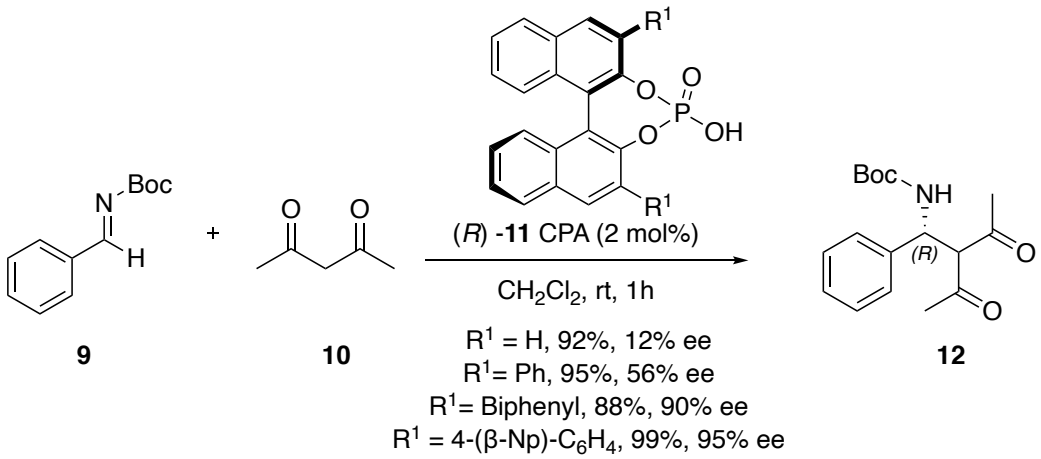
In 2004, Akiyama and Terada both independently launched the field of BINOL-derived chiral phosphoric acids in organocatalysis.[15, 16] Their two papers together have resulted in over 2,000 citations, thus supporting the importance and significance this reserach.[15, 16] The reported C_2-symmetrical CPAs consist of a C_2-symmetrical BINOL backbone and an achiral phosphorus atom (Scheme 1.13). The C_2- symmetry is the sole source of chirality due to the rapid proton exchange between the two equivalent oxygens. Phosphorus acids make good catalysts due to their appropriate acidity.[17] The structure around the phosphorus atom prevents free rotation at the alpha position of the phosphorus center by forming a ring structure, and it can function as a bifunctional catalyst. Substituents can be introduced on the ring system by ortho-functionalization with R groups on each naphthyl ring. This functionalization helps introduce steric bulk and a range of electron densities extending the chirality of the BINOL, creating a chiral pocket or environment for enantioselective transformations within the proximity of the acidic proton and phosphoryl oxygen.

Scheme 1.13 Classic strategy of C_2-symmetrical BINOL-CPA

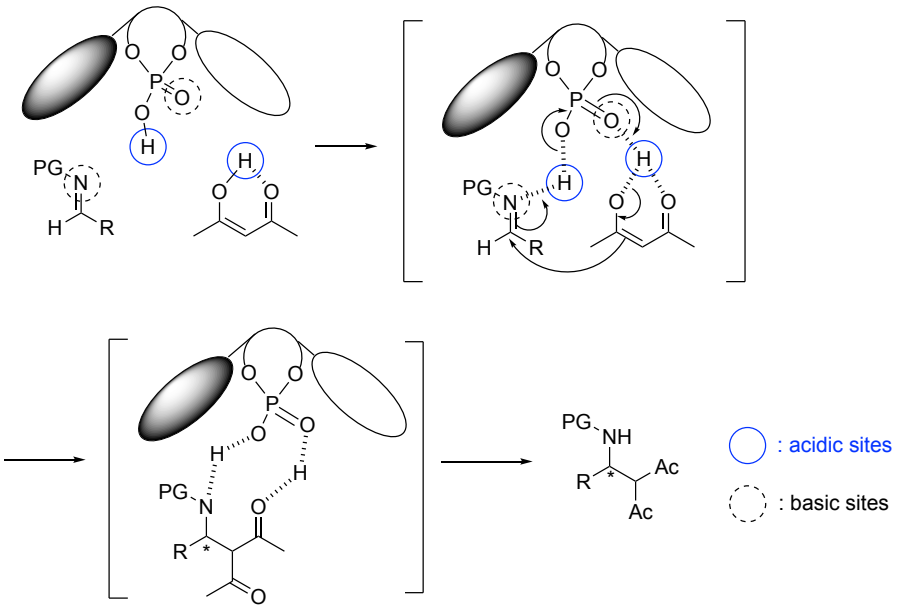


Terada and coworkers reported the enantioselective direct Mannich reaction of an imine with acetylacetone, using 2 mol% of (*R)*-CPA (Scheme 1.14).[16] The phosphoric acid catalyst **11** electrophilically activates the imine **9** through the acidic proton, and the Brønsted basic phosphoryl oxygen interacts with the O-H proton of the enol form of the acetylacetone **10** in a dual activation mode (Scheme 1.15). Subsequent bond recombination results in the formation of the Mannich product **12** and regeneration of the catalyst. The substituents R^1 of the CPA at the 3,3'-position are crucial to the enantioselectivity. When the substituent was a phenyl group, it gave the aminoketone product in 56 % *ee*. In comparison, by increasing the aromatic group to a naphthyl phenyl moiety, it increased the enantioselectivity to 95 % *ee*. This shows the R^1 group needs to be very large because the chiral environment created from the substituents has a heavy influence on the enantioselectivity, and the BINOL framework alone is not enough to have good enantioselectivity.

Scheme 1.14 Enantioselective directed Mannich reaction reported by Terada[16]



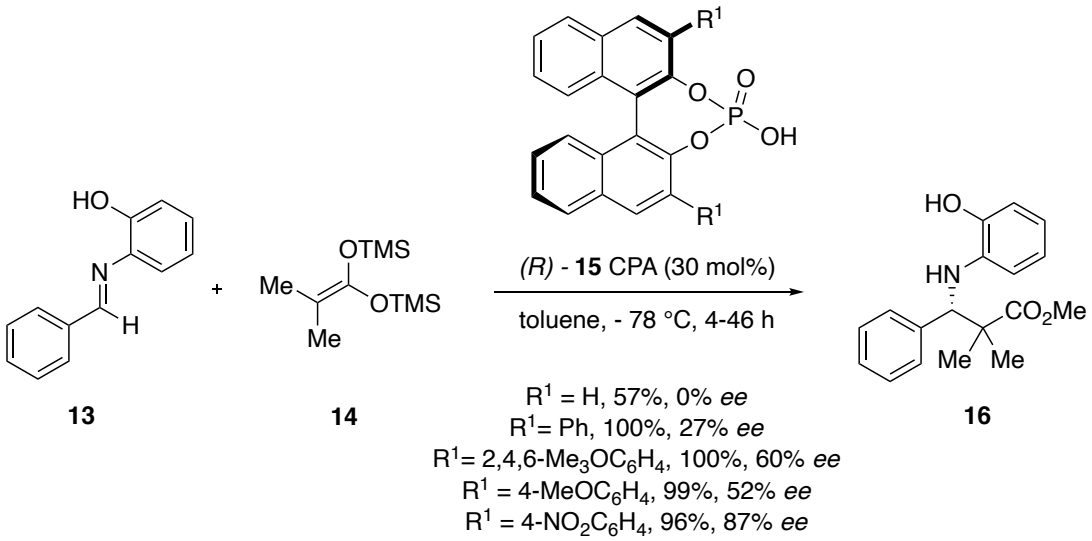
Scheme 1.15 Mechanism of the enantioselective Mannich reaction reported by Terada[16]



This substituent effect of R^1 was also crucial in Akiyama's Mannich-type reaction of aldimines **13** and ketene silyl acetals **14** to form enantioenriched β-aminoesters **16** (Scheme 1.16).[15] Introduction of a 4-nitrophenyl group on CPA **15** improved the enantioselectivity to

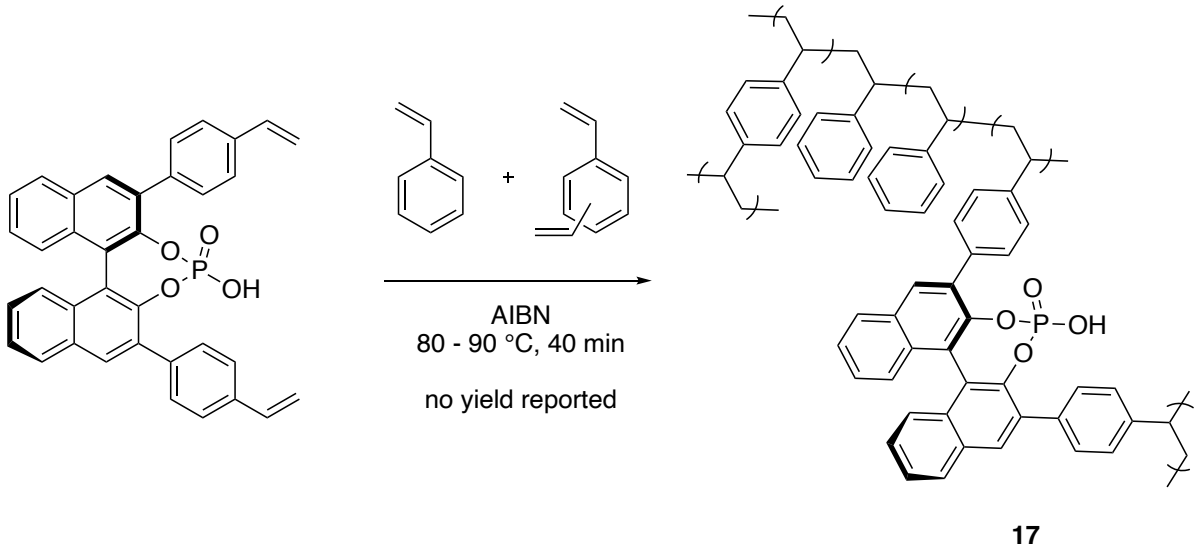
87 % *ee*, compared to a phenyl group which was 27 % *ee*, whilst also accelerating the reaction rate to 4 h from 20 h, respectively.

Scheme 1.16 Enantioselective directed Mannich-type reaction reported by Akiyama[15]

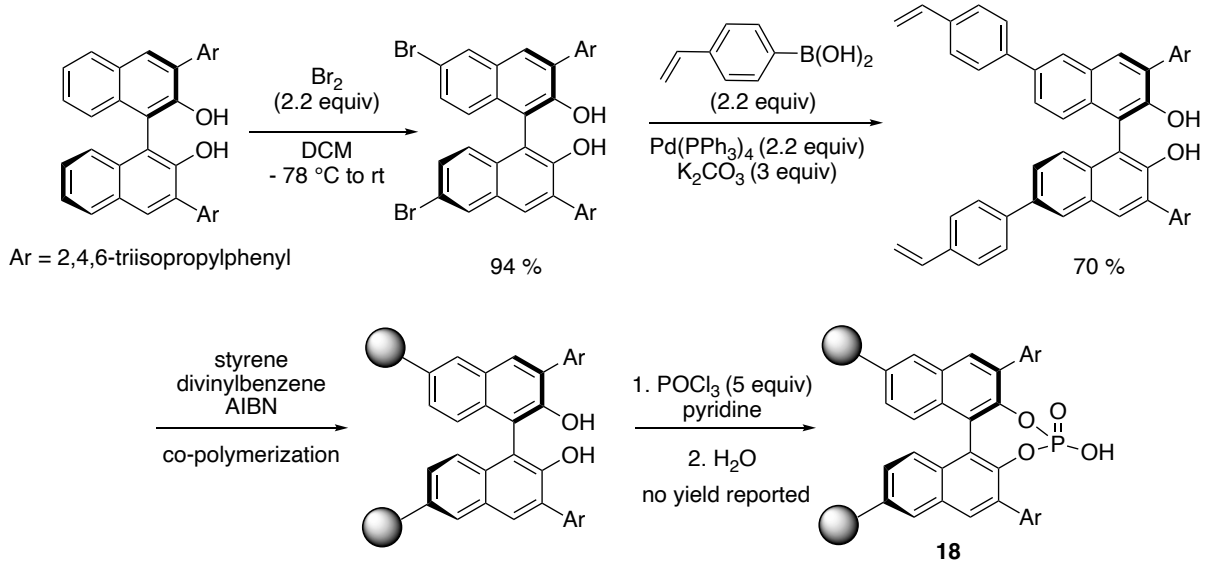


A few examples of polymer immobilized CPAs have been reported. Reuping and Sugiono reported the first example of immobilization of a BINOL-derived CPA **17** synthesized through cross-linking radical polymerization with styrene and divinylbenzene (Scheme 1.17).[18] They found that the catalytic activities are comparable to those of the homogeneous reactions, and the CPA was able to be recycled and reused for 12 cycles without any loss of activity. Later, Pericaș and coworkers described the synthesis of a polystyrene-supported 2,4,6-tris-isopropylphenyl (TRIP)-BINOL catalyst **18** (Scheme 1.18).[19] The resin catalyst has proven to be highly active and enantioselective in the asymmetric allyboration of aldehydes, and reusable for 18 cycles. Since then, a few other studies of heterogeneous CPAs have been or reported.[20, 21, 22]

Scheme 1.17 Polymerization of BINOL catalyst reported by Reuping and Sugiono[18]



Scheme 1.18 Polymerization of TRIP-BINOL catalyst reported by Pericaș and coworkers[19]

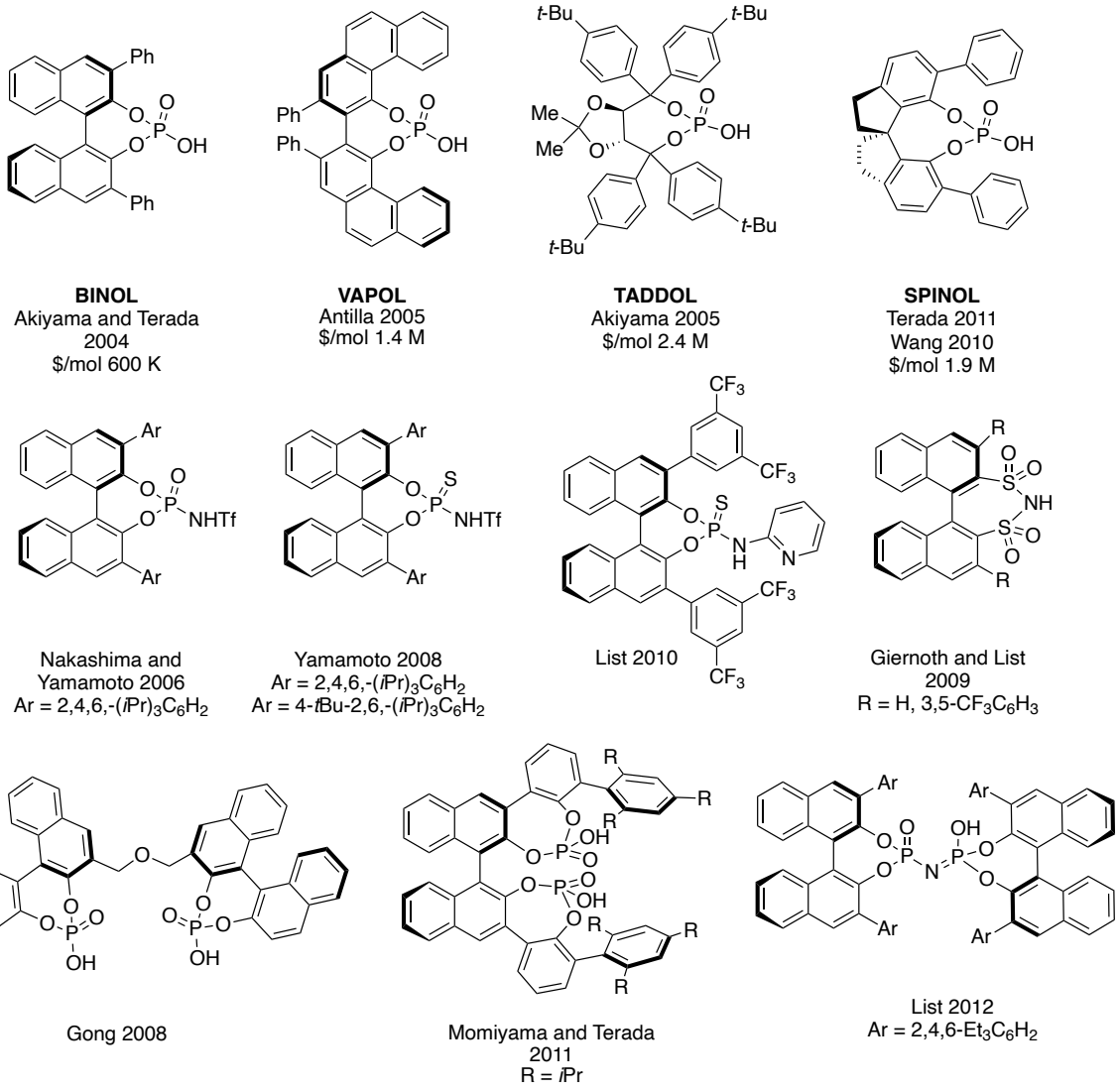


The success of BINOL-derived catalysts prompted the development of new catalysts with alternative backbones, intending to modify the geometrical parameters near the "active site" (Scheme 1.19). Akiyama introduced TADDOL-derived CPAs and evaluated them in a

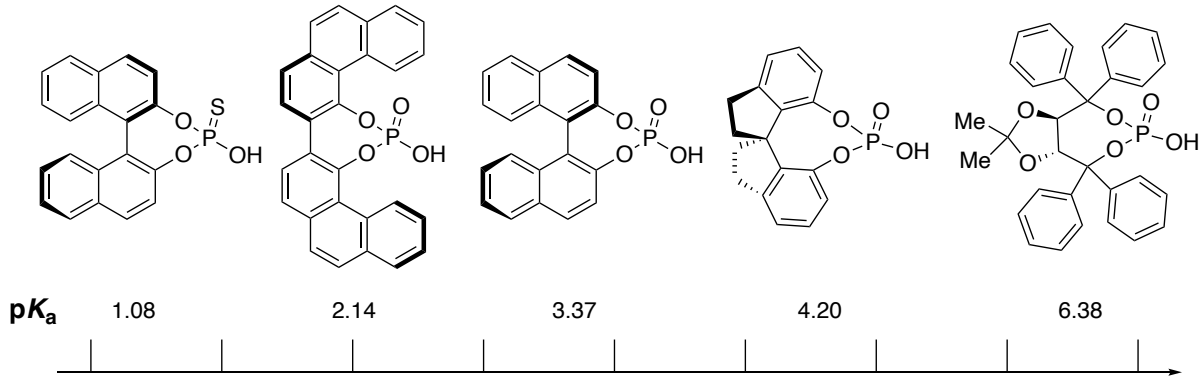
Mannich-type reaction, but they resulted in lower enantioselectivity compared to BINOL.[23] VAPOL-derived CPAs were introduced by Antilla for the synthesis of aminals,[24] and more recently a CPA with a SPINOL backbone was reported.[25] Another example includes a bis-phosphoric acid CPA developed by Gong, Terada, and Mimiyama.[26, 27]

One major development was the discovery of *N*-triflylphosphoramide CPA catalysts**,** as they are less acidic than the parent phosphoric acid catalyst and have been found to activate more difficult substrates through H-bonding.[5] This was reported by Nakashima and Yamamoto, through the use of *N*-triflyl phosphoramides in a highly enantioselective Diels-Alder reaction.[28] By incorporating an triflyl group on the nitrogen as a strong electron-withdrawing group, helps increase the stability of the counter anion and the acidity of the catalyst. For example, the pK_a of *N*-triflyl benzamide and benzoic acid is 11.06 and 20.7 (CH_3CN), respectively.[29] Yamamoto later developed chiral *N*-triflyl thio- and seleno-phosphoramides and evaluated the catalyzed enantioselective protonation of a silyl enol ether.[30] In general, acidity increases as it descends in a column of the periodic table, due to better stabilization of the conjugate base in a larger size atom. For example, the pK_a values of PhOH and PhSH in DMSO are 18.0 and 10.3, respectively.[31] A theoretical pK_a study in DMSO on a range of chiral Brønsted acids was published, and unsurprisingly thiophosphoric acid was found to be considerably more acidic compared to the BINOL-parent compound (Scheme 1.20).[32] More recently, Reuping and coworkers disclosed an acidity study on commonly used Brønsted acids in acetonitrile.[33]

Scheme 1.19 Chiral phosphoric acids and derivatives



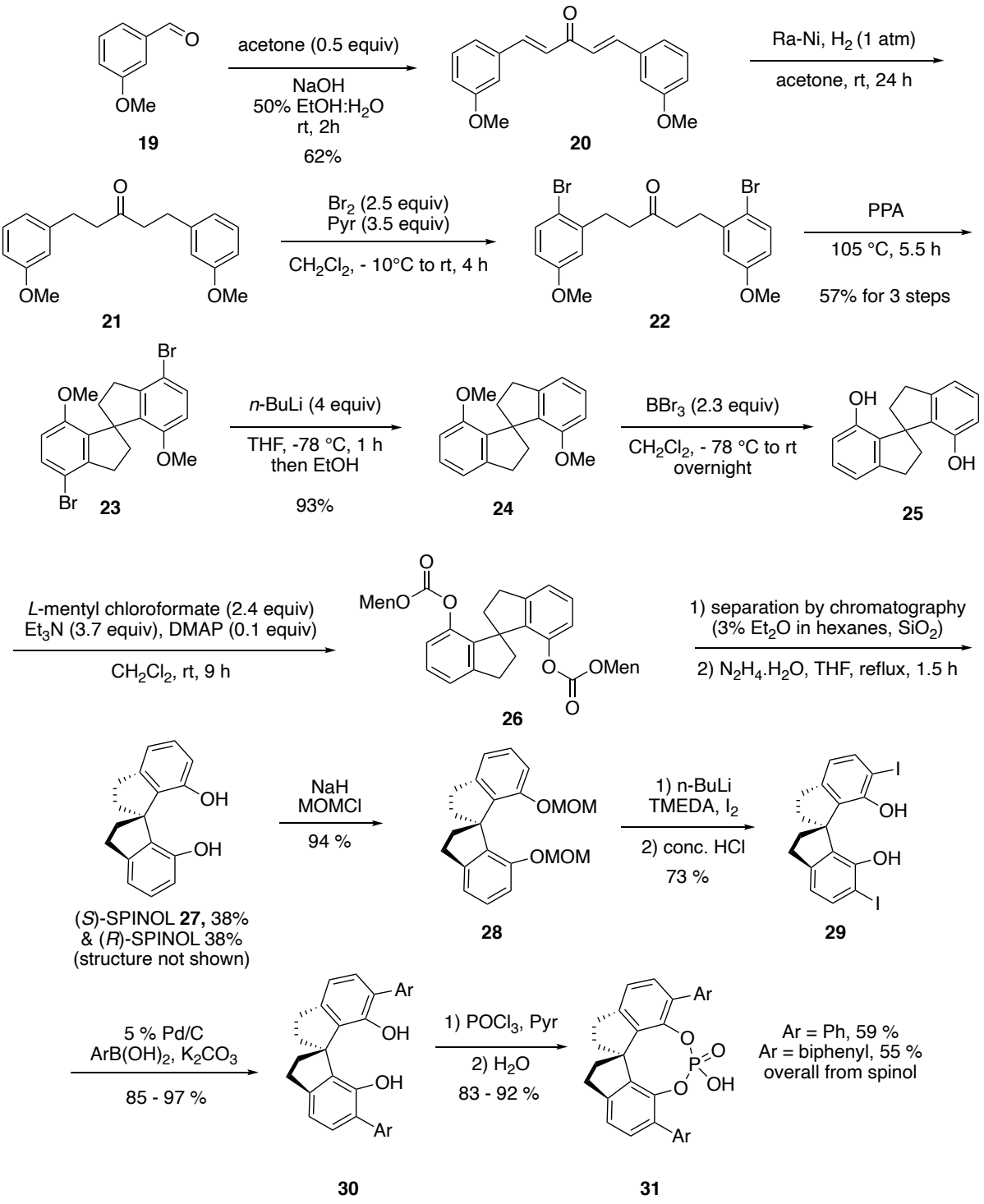
Scheme 1.20 Acidity scale of the unsubstituted phosphoric acids in DMSO



Many CPAs are commercially available, but they are exceedingly expensive. For example, the BINOL CPA is $/mol 600,000 (Strem; R = Ph) and the SPINOL CPA is $/mol 1.9 million (Strem; R = Ph) (Scheme 1.19). As a result of the high cost and need for R- group optimization, most groups synthesize their CPAs starting from the resolved diol.

The synthesis of a SPINOL derived catalyst **30** is a lengthy multistep process, as it first requires synthesis and resolution of the diol precursor (Scheme 1.21).[34] The synthesis starts with a double aldol condensation of 3-anisaldehyde **19** with acetone to afford the intermediate ketone **20**. The ketone is then hydrogenated and brominated at the *para*-position to yield **22**. This step is needed to block that position for the spirocyclization step Friedel-Crafts with polyphosphoric acid (PPA). This forms the spirocyclic product **23** in a 57 % yield over the 3-step sequence. Next is the removal of bromine to give **24**, followed by deprotection of the phenols to generate *rac*-SPINOL **25**. The diol is then resolved by forming menthol carbonates **26** and separation by chromatography to yield (*R)*- and (*S*)- SPINOL **27**. Next is a protection of the hydroxyl groups with MOMCl to form **28**, followed by lithiation-halogenation at the 3 and 3' positions, and deprotection of the phenols to afford the halogenated intermediate **29**. This scaffold can now be used to derivatize with varying substituents through a Pd-catalyzed cross-coupling to form **30**, then phosphorylation to yield the desired catalyst **31**. This generic scheme illustrates the syntheses which are the basis of nearly all the catalysts used in the literature.

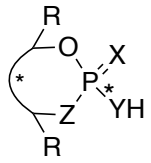
Scheme 1.21 Synthesis and resolution of the SPINOL backbone, and route to SPINOL-derived CPA



A less common approach involves *P*-stereogenic CPAs that also contain a chiral carbon backbone (Scheme 1.22).

Scheme 1.22 *P*-chiral and chiral backbone CPA strategy

Guinchard 2014
Murai 2018
Han 2019

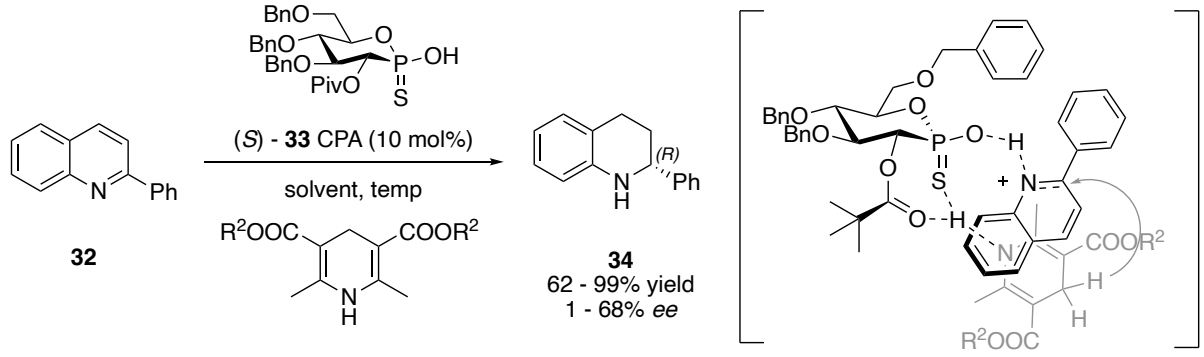


X = S
Y = O, NTf
Z = C, O

P-stereogenic center
+ achiral backbone

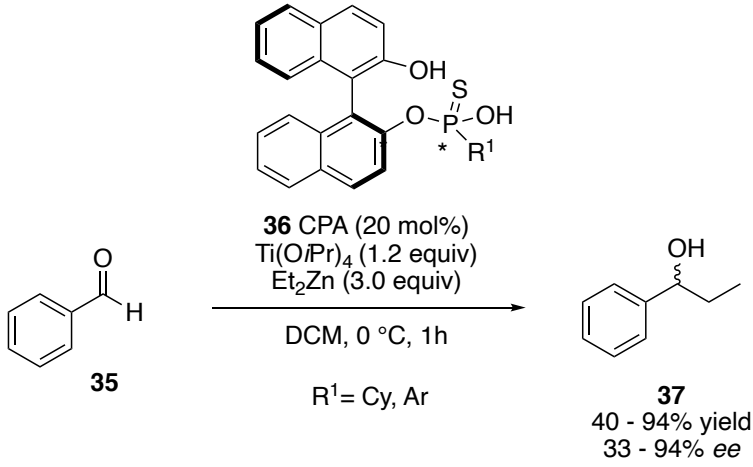
Guinchard and coworkers reported the first CPA **33** that utilized both a chiral backbone and a *P*-stereogenic atom (Scheme 1.23).[35] The backbone was derived from tri-*O*-benzyl-D-glucal and contained a phosphonate or thiophosphonate function. These CPAs were tested in the transfer hydrogenation of 2-phenylquinoline **32** with Hantzsch esters. A transition state was proposed where the P(S) bond and C(O) on the (*S*) CPA are *syn*, and form H-bonding interact with the nitrogen atom on the Hantzsch ester. The approach and positioning of the 2-phenylquinoline would then be directed by the H-bonding between the acidic proton of the CPA and the basic nitrogen atom on the quinoline. This allows an asymmetric hydride transfer by the *Si* face leading to (*R*)-2-phenyltetrahydroquinoline **34**.

Scheme 1.23 Transfer hydrogenation of 2-phenylquinoline and proposed transition state by Guinchard and coworkers



Murai and coworkers later reported the synthesis of *O*-(2'-hydroxy)-binaphthyl phosphonothioic acids **36** from the hydrolysis of BINOL-derived phosphonothioates (Scheme 1.24).[36] The resulting acids were used as optically active ligands for a Ti-mediated asymmetric ethylation of benzaldehyde **35** with Et_2Zn, to give the benzylic alcohol **37**. These ligands possess axial chirality and a central chirality at the phosphorus atom. The enantiomeric excess of the product was optimized by changing the substituents on the phosphorus group and not the BINOL backbone.

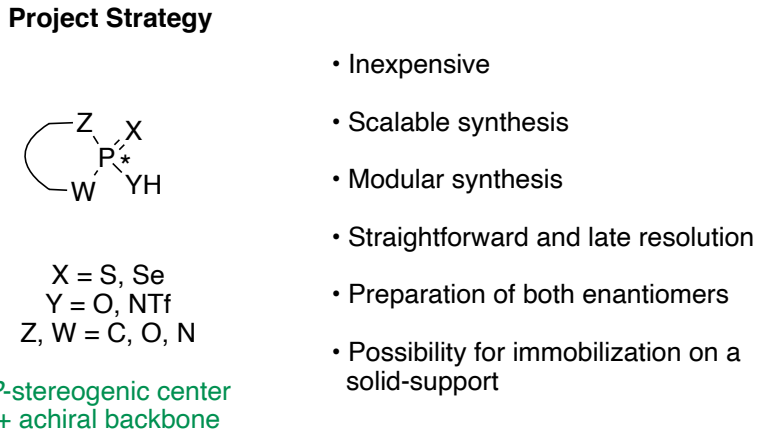
Scheme 1.24 Asymmetric ethylation of benzaldehyde reported by Murai and coworkers



1.5 *P*-Stereogenic Chiral Phosphorus Acids

The objective of this project is to provide general solutions to the problems and limitations of C_2-symmetrical CPAs. C_2-symmetrical CPAs have found frequent application in various asymmetric organic transformations. However, they suffer from serious limitations such as extremely high cost, very high molecular weight, inability to access both enantiomers without a significant and separate synthetic effort, and difficulty in catalyst-immobilization. We propose a different type of scaffold where the backbone is achiral but the phosphorus atom itself is chiral (Scheme 1.25). In addition to delivering high enantioselectivity in a variety of transformations, the *P*-stereogenic phosphorus organocatalysts should be inexpensive, their preparation scalable, have a modular synthesis to optimize asymmetric induction, a straightforward and late-stage resolution, an ability to prepare both enantiomers, and a possibility to immobilize on a polymer-support.

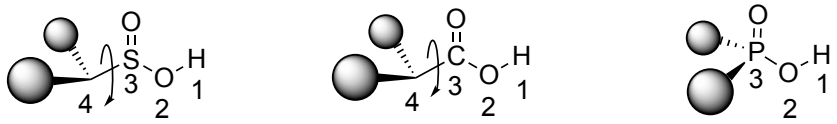
Scheme 1.25 Project strategy of *P*-stereogenic CPAs



When designing a chiral Brønsted acid catalyst, several structural and chemical features are necessary for enantioselective transformations. First, phosphorus acids must have the

appropriate acidity. Second, the chiral backbone should be as close as possible to the acidic functionality. For example, when comparing sulfinic acids, carboxylic acids, and phosphoric acids, phosphoric acids have two substituents directly at the phosphorus atom, so there is more rigidity and less free rotation (Scheme 1.26). Furthermore, the substituents are three atoms away from the acidic proton (compared to four atoms away), which helps bring the chiral environment one atom closer to the reaction site.

Scheme 1.26 Organic acids as a potential chiral Brønsted acid catalyst



Looking at BINOL as our analogy: we designed phosphorus-containing heterocycles **38** – **42** so that the ring structure would prevent free rotation at the phosphorus center (Scheme 1.27). Since BINOL leads to a 7-membered ring system CPA, we designed smaller 5 or 6-membered ring systems that would help bring the aromatic groups closer in proximity to the "active site". Substituents were introduced on the heterocycle scaffold to enhance the chiral environment. For example, the nitrogen can be functionalized with aryl groups, such as an *N*-phenyl or *N*-biphenyl group, which can twist to help block one face of the acidic site, forcing the chiral environment to the other quadrant of the molecule. In the design, the number of bonds away from the aromatic and the phosphorus atom was varied. The *N*-biphenyl group on the DOPO-CPA **42** is one bond-length away from the phosphorus center, the 8-phenyl-DOPO **41** is three bond-lengths away, and the *N*-phenyl on the indole CPA **39** and **40** is two. This allowed us to test what geometrical parameters were optimal for our catalyst. These designs

were accompanied by computational modeling (Figure 1.1; DFT B3LYP-6-31G) to identify the conformer with the lowest energy.

Scheme 1.27 Examples of proposed *P*-stereogenic CPAs

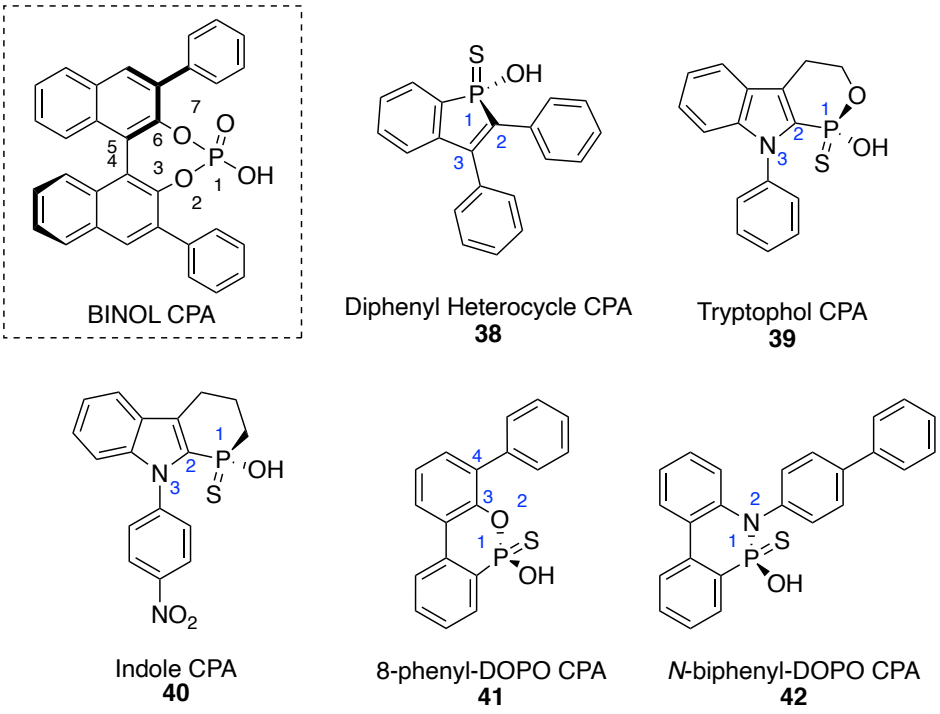
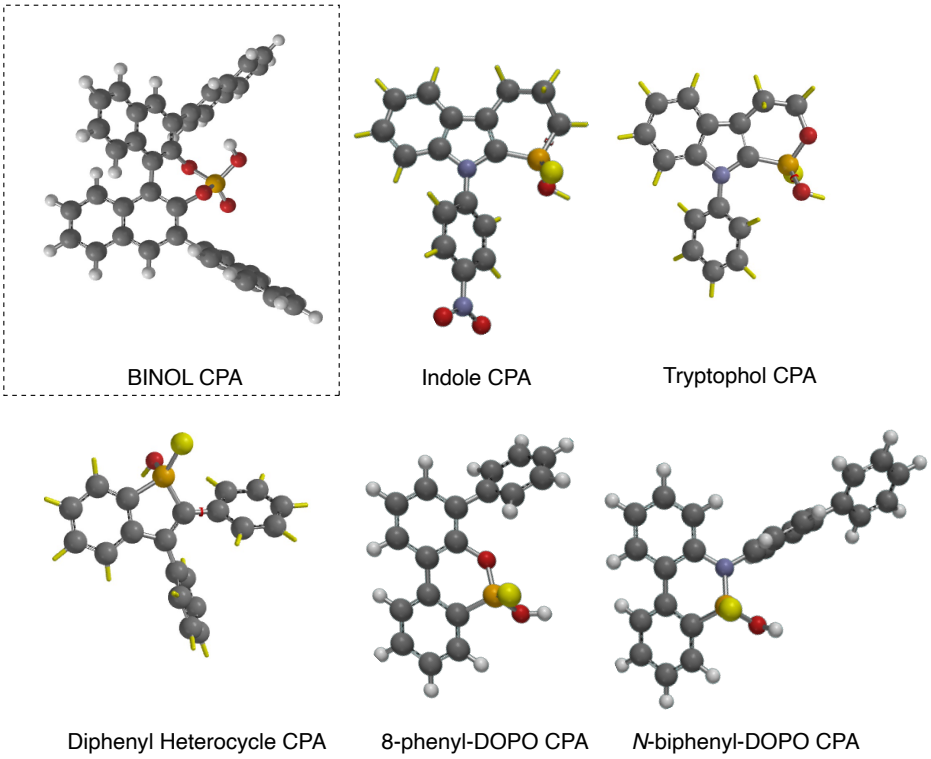


Figure 1.1 Computational modeling of proposed *P*-stereogenic CPAs

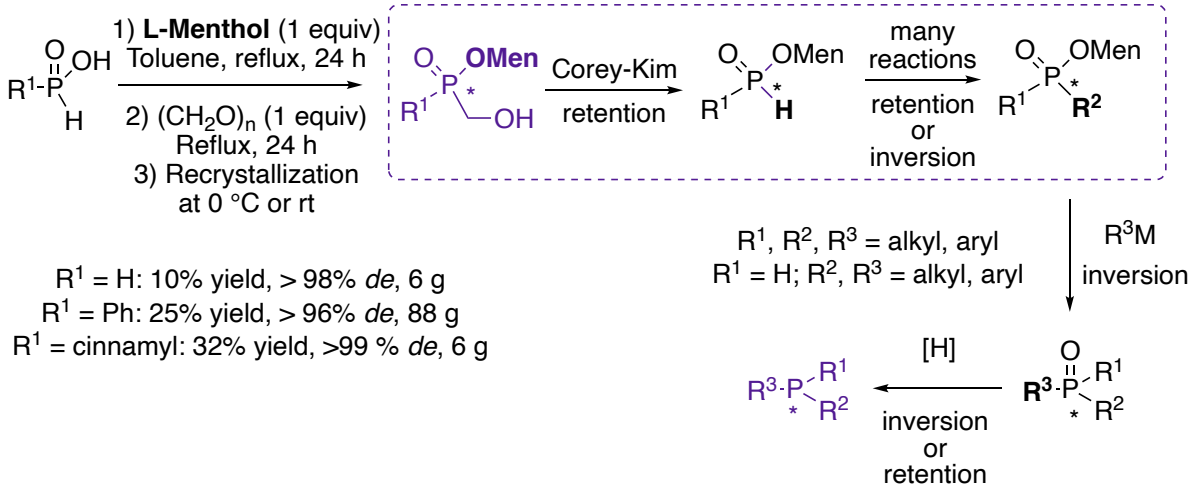


These target CPAs have a *P*-stereogenic center by incorporating a thio-phosphorus bond ($R_1R_2P(S)OH$), rather than an oxo-phosphorus bond (($R_1R_2P(O)OH$), where $R_1 \neq R_2$). The chirality and resolution of these compounds will be through either: 1) a chiral auxiliary covalently bound to the P atom, or 2) enantioseparation of racemates through diastereomeric formation of a salt with a chiral amine.

The use of (-)-menthol as a chiral auxiliary was first described in 1970 by Mislow for the synthesis of diastereomerically pure (-)-menthyl-(phenyl)-*H*-phosphinates from commercially available and inexpensive (-)-menthol.[37] Since then many research groups, including our own, have shown the synthetic potential of this *P*-stereogenic precursor (Scheme 1.28).[4, 38, 39] Key to its success were two discoveries from our laboratory: 1) (hydroxymethyl)

phosphinates crystallize much more easily than *H*-phosphinates, and 2) the hydroxymethyl moiety can be cleaved stereospecifically using the Corey- Kim oxidation.[40, 41] Starting from the resolved menthyl ester for the preparation of our target CPAs, has the advantage that no resolution is required later, and very large quantities can be prepared.

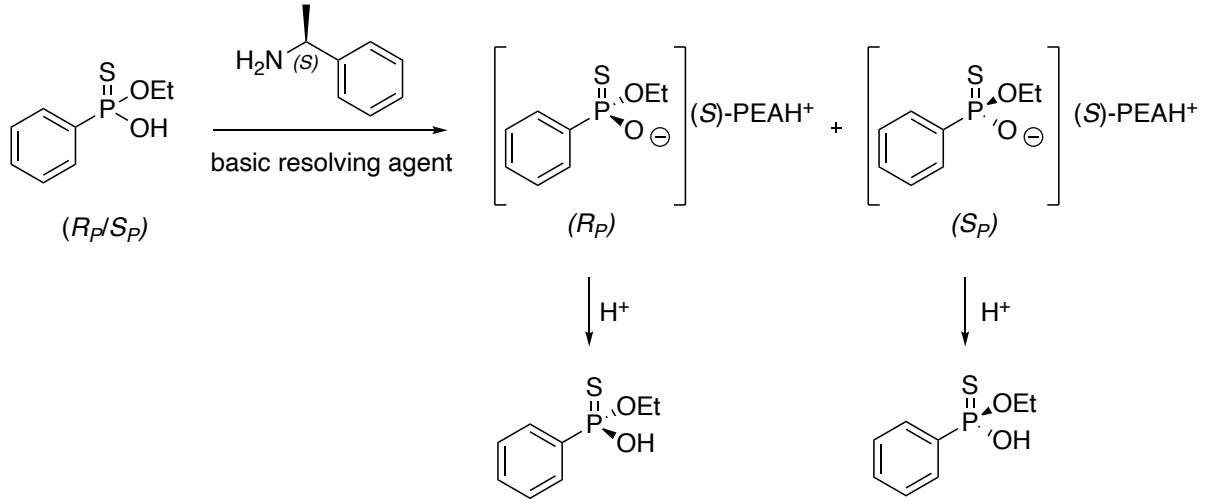
Scheme 1.28 General synthesis of *P*-stereogenic compounds *via* menthyl phosphinates



Use of a chiral amine auxiliary can also be utilized for the stereospecific synthesis of thiophosphorus acids via the Wadsworth−Emmons−Stec reaction, discussed in more detail in Chapter 3. Chiral amines have also been reported to be excellent resolving agents for the enantioseparation of thiophosphorus acids.[3, 42-44] In 1958, the first resolution of an organophosphorus acid was reported for the resolution of *O*-ethyl ethylphosphonothioic acid through quinine or brucine salt formation.[45] Since then, many successful chiral resolutions have been reported, including Saigo's study on the chiral recognition mechanism of *O*-ethyl phenylphosphonothioic acid with chiral amines (Scheme 1.29).[46] Saigo found that the difference in stability between the less- and more-soluble diastereomeric salts is dependent on 1) the hydrogen bonding interaction between the phosphorus anion and ammonium cation, 2)

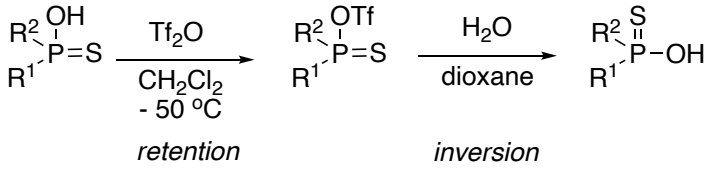
the van der Waals interactions, and 3) CH/π interactions between the phenyl groups. Acidification of the amine salt then gives the optically pure thioic acid **43**.

Scheme 1.29 Synthesis of enantiopure phosphonothioic acid through the resolution with (*S)*-phenylethylamine reported by Saigo



Since resolution generally provides only one enantiomer, in principle the phosphorus stereocenter in the final product could be inverted by forming the P(S)OTf then reacting with H_2O, to obtain the other enantiomer (Scheme 1.30).[47]

Scheme 1.30 Inversion of stereochemistry in a thiophosphorus acid



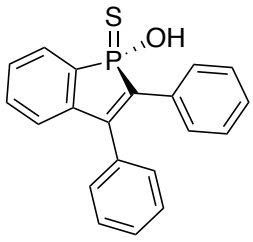
CHAPTER 2

SYNTHESIS OF DIPHENYL HETEROCYCLE AND TRYPTOPHOL CPAs

2.1 Diphenyl Heterocycle *P*-Stereogenic CPA

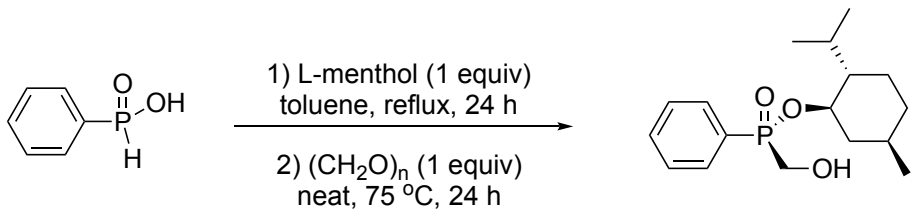
The first target CPA is a diphenyl thiophosphoric acid heterocycle **38**, for which the chirality is to be introduced using L-menthol as a chiral auxiliary (Scheme 2.1). Using our group's methodology, we were able to easily prepare menthyl phosphinates in high diastereoisomeric purity on multigram scale.[40, 41] Heating phenylphosphinic acid **44** with L-menthol in toluene, followed by the addition of paraformaldehyde, affords the crude product (Scheme 2.2). This can be recrystallized at rt in Et_2O to give the pure product **45** in 24 % yield and 96 % de.

Scheme 2.1 Diphenyl heterocycle CPA **38**



38

Scheme 2.2 Synthesis of menthyl(hydroxymethyl)phenyl phosphinate

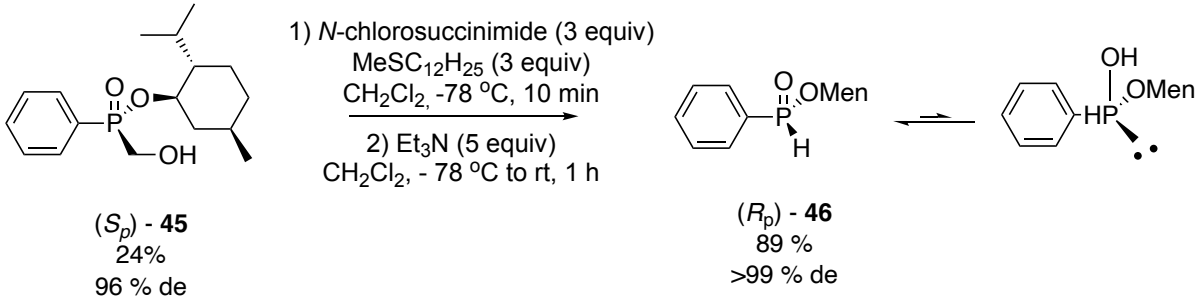


(1 equiv)
44

(S_p) - **45**
24%
96 % de

This was followed by Corey-Kim oxidation using odorless dodecyl methyl sulfide to give the desired *H*-phosphinate **46** in excellent yield (Scheme 2.3).[40, 41] The oxidation proceeds through a chlorosulphonium ion that is generated *in situ* from NCS and dodecyl methyl sulfide. An aqueous workup forms the P(III) intermediate which tautomerizes to the P(V) *H*-phosphinate product **46**.

Scheme 2.3 Corey-Kim oxidative cleavage of the (hydroxymethyl) phosphinate

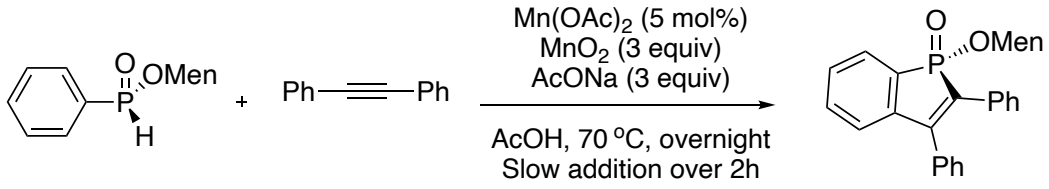


(S_p) - **45**
24%
96 % de

(R_p) - **46**
89 %
>99 % de

An intramolecular radical annulation proceeded with diphenyl acetylene using our Mn(II)/excess Mn(IV) chemistry (Scheme 2.4).[48] $Mn(OAc)_2$ is used as a catalytic radical initiator, and MnO_2 as a mild and inexpensive oxidant. When *P*-stereogenic phosphinates are used, the reaction is stereospecific with retention of configuration, to generate intermediate **47**.

Scheme 2.4 $Mn(OAc)_2$-catalyzed/MnO_2- promoted alkyne-arene annulation



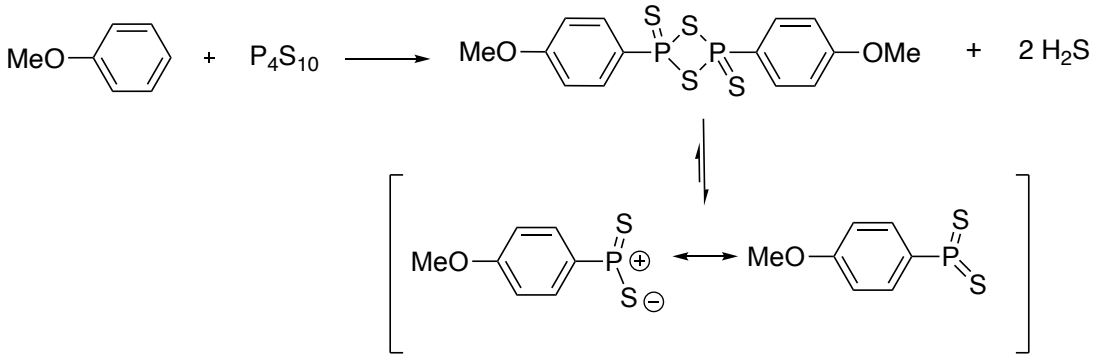
(R_p) - **46**
(1 equiv)
>99 % de

(1 equiv)

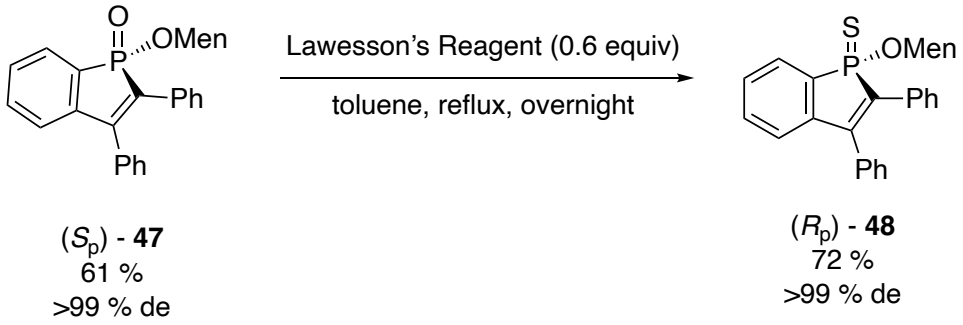
(S_p) - **47**
61 %
>99 % de

In order to introduce the sulfur on the phosphorus, Lawesson's reagent (LR) was first considered as a thionating agent. The concept of thionation has been known since the 1880s. Hydrogen sulfide (H_2S) and tetraphosphorus decasulfide (P_4S_{10}) were both used to synthesize thioamides and thioketones.[49] In 1956, Lecher and co-workers developed a thionating agent by reacting anisole with $P_4S_{10,}$ to yield what is now known as Lawesson's reagent (Scheme 2.5).[50] It has a strong odor of "rotten eggs" due to the hydrogen sulfide that is given off by hydrolysis with atmospheric moisture. It is believed that the active species of LR is formed through an equilibrium (Scheme 2.5). Since this seminal work, Lawesson et al. have published numerous papers discussing the use of LR, and the reagent has since become the most frequently used reagent for thionations, especially for the replacement of the oxo group on phosphorus (P=O) with the thio group (P=S).[51-53] Thionation of the menthyl heterocycle gave the corresponding thiophosphonate in 72 % yield after purification (Scheme 2.6).

Scheme 2.5 Lawesson's reagent synthesis



Scheme 2.6 Thionation of P(O)(OMen) to P(S)(OMen) using LR



(S_p) - **47**
61 %
>99 % de

(R_p) - **48**
72 %
>99 % de

Unfortunately, attempts at cleavage or hydrolysis of the menthyl ester were proven to be unsuccessful. Either the starting material did not react, or complex mixtures were obtained (Table 2.1). This is likely due to the steric hindrance and bulky nature of the menthyl being a secondary ester. For a given ester group in S_N2 reactions, the rate of reactivity decreases the larger the size. For example, the basic hydrolysis relative rate (NaOH in 50 % water/dioxane) of a methyl-ester versus a cyclohexyl-ester is 1000 to 1 respectively.[54]

Table 2.1 Reaction conditions for the cleavage of menthyl ester

(R_p) - **48**
72 %
>99 % de

(R_p) - **38**

Entry	Conditions	NMR
1	4 M NaOH toluene, reflux, 24 h	Mostly SM (minor degradation)
2	4 M NaOH	SM

	dioxane, reflux, 24 h	
3	4 M NaOH, dioxane, reflux, 48 h	SM
4	1) TMSBr (5 equiv), CH_2Cl_2, rt, 24 h 2) MeOH	SM
5	NaI (4 eq), 2-butanone, reflux, 24 h	Mostly SM (minor degradation)
6	TMSCl (4 equiv), NaI (4 equiv), CH_3CN, reflux, 48 h	SM
7	HCl, dioxane, reflux, 19 h	SM
8	1) HBr, rt, 48 h 2) AcOH, rt, 24 h	No visible peaks
9	NaOMe (2 equiv) MeOH, rt, 24 h	Complex Mixture
10	6 M NaOH dioxane, reflux, 24 h	Complex Mixture
11	4 M NaOH dioxane, reflux, 24 h	Most SM (minor degradation)
12	TMSBr (4 equiv), NaI (4 equiv), CH_2Cl_2, rt, 24 h	Most SM (minor degradation)

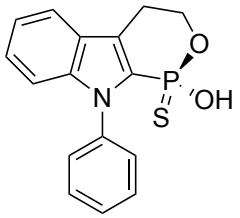
Unable to cleave the menthyl group after numerous attempts, this target molecule was abandoned. It was concluded that instead of introducing the chirality at the beginning as a menthyl ester and carrying the chirality through the reaction sequence, chirality would be introduced at the end of the synthesis by forming thiophosphorus diastereomeric salts with a chiral amine.[45] We also decided to use a methyl ester which should be easier to cleave than the menthyl ester.

2.2 Tryptophol-derived *P*-Stereogenic CPA

The second target CPA is tryptophol-derived thiophosphorus acid **39** (Scheme 2.7). Starting with commercially available tryptophol **49**, an aromatic ring was introduced through

copper-catalyzed Ullmann coupling, producing *N*-phenyl **50** in a 98 % yield (Scheme 2.8).[55] Mono-demethylation of dimethyl phosphite occurs in an excess of *tert*-butylamine at reflux, forming the monomethyl *H*-phosphonate *tert*-butylamine salt ($[(CH_3)_3CNH_3]^+$ $[MeOP(O)HO]^-$) crystals overnight.[56] Pivaloyl chloride formed a mixed ester with the *H*-phosphonate *tert*-butylamine salt, followed by P-O bond formation with the tryptophol, to give diester phosphonate **51** in 89 % yield (Scheme 2.8).

Scheme 2.7 Tryptophol derived CPA **39**



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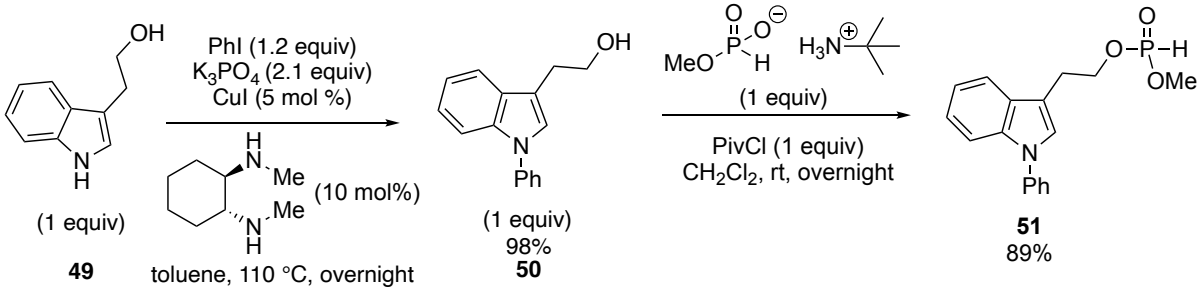
Scheme 2.8 Ullman coupling and phosphonate ester synthesis



Using our manganese-mediated intramolecular arylation methodology, we cyclized the P-H **51** onto the indole moiety (Scheme 2.9).[48] This resulted in a moderate yield of **52**, likely due to oxidation of the *H*-phosphonate and the harsh workup conditions required to quench the

acetic acid. In an attempt at improving the yield, various reaction conditions were tried to perform the arylation catalytically, however none were successful (Table 2.2).[57]

Scheme 2.9 $Mn(OAc)_2$-catalyzed/MnO_2- promoted arylation

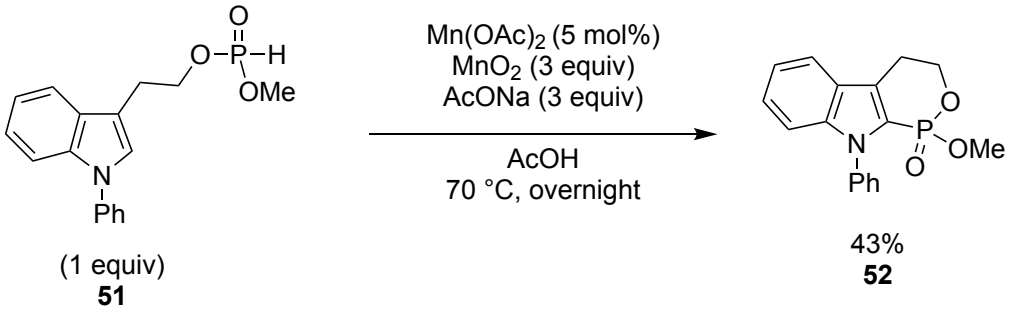
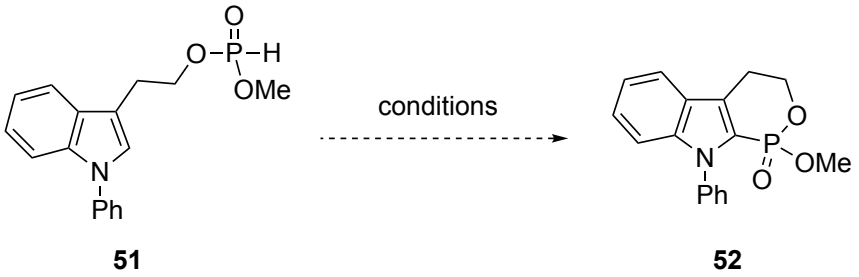


Table 2.2 Reaction conditions for catalytic arylation

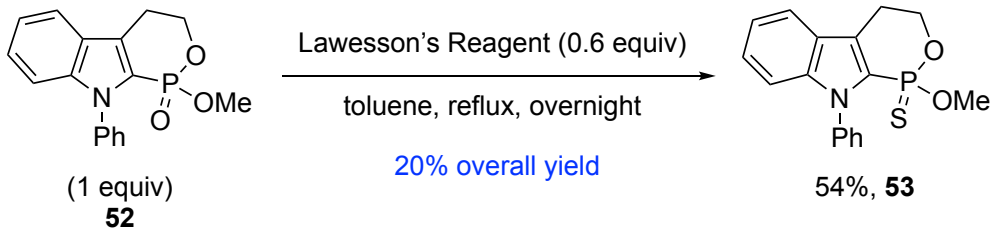


Entry	Conditions	NMR Yield (%)
1	$Mn(OAc)_2$ (5 mol%) DMSO, 100 °C, Air, 20 h	11
2	$Mn(OAc)_2$ (5 mol%) $Co(ethylhexanoate)_2$ (5 mol%) DMSO, 100 °C, Air, 20 h	17
3	$Mn(OAc)_2$ (5 mol%) $Co(ethylhexanoate)_2$ (5 mol%) EtOAc, reflux, O_2 balloon, 24 h	SM
4	AgOAc (3 equiv) Dichloroethane, reflux, 24 h	Complex mixture

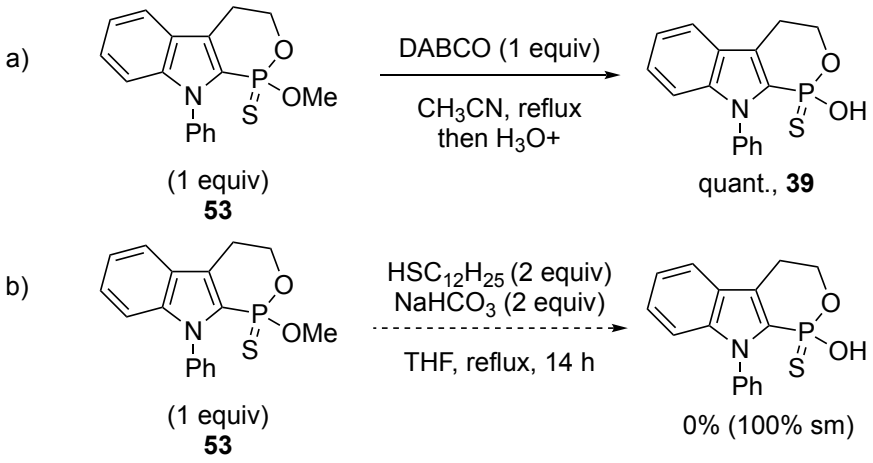
5	$AgNO_3$ (10 mol%), $Na_2S_2O_8$ (2 equiv) CH_3CN:H_2O (1:1), rt, 48 h [58]	SM

The next step involved thionating phosphonate **51** using Lawesson's reagent, which resulted in a low 54 % yield of **53** mainly due to loss of material in the purification step to isolate the product in high enough purity. Due to the apolar nature of the target molecule, the product tends to elute first, along with the LR's byproducts (even when using solvent systems such as 100 % hexanes and dry loading of the column). This gives a 20 % yield overall for the last four steps (Scheme 2.10). Despite the low yield, the cleavage of the methyl ester was possible with DABCO to give racemic thioacid **39** in quantitative yield (Scheme 2.11, entry a). However, nucleophilic substitution with dodecylthiol and base gave unreacted starting material by ^{31}P NMR (Scheme 2.11, entry b).

Scheme 2.10 Thionation of P(O)(OMe) to P(S)(OMe) using LR

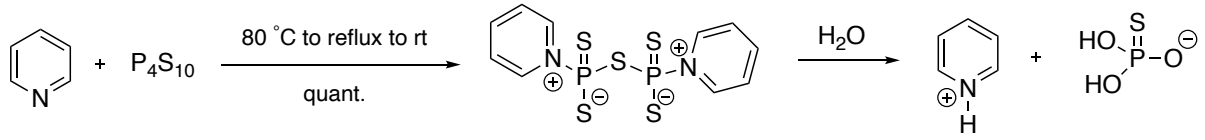


Scheme 2.11 Cleavage of P(S)(OMe) with to P(O)OH



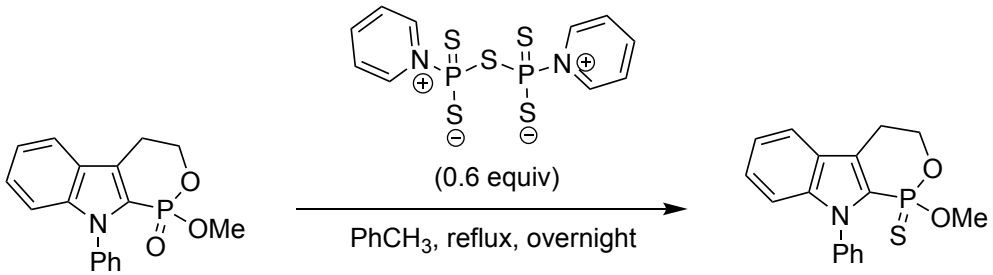
It has been reported that solubility problems are often an issue with LR, plus large scale preparation of LR can be problematic due to the formation of H_2S, therefore alternatives have been developed.[59] One alternative to LR is a pyridine derivative, which is readily formed from P_4S_{10} and pyridine (Scheme 2.12).[60] This reagent has been reported to have a cleaner workup, to be more soluble in organic solvents, and even to not require chromatographic purification in certain cases.[49] This is due to the remaining reagent decomposing to a water soluble salt upon aqueous workup.[60] Use of this reagent has not previously been reported in thiophosphonate synthesis.

Scheme 2.12 Synthesis of pyridine derived thionating reagent



After making the pyridine thionating derivative we tested it on our tryptophol heterocycle. In our hands, we found that the thionation does take place (75 % ^{31}P NMR yield), however, the extractive workup step did not remove the byproducts as hoped, and the product was not sufficiently pure (Scheme 2.13).

Scheme 2.13 Thionation of P(O)(OMe) to P(S)(OMe) using pyridine derived LR



(1 equiv)
52

75% NMR, **53**

In summary, due to the overall low yield from this reaction sequence, we decided to shift our focus to investigating a better methodology to synthesize thiophosphorus acids in order to avoid LR. We also learned through our attempted synthesis of the diphenyl heterocycle CPA, that introducing the chirality in the late-stage, with a possibility to get both enantiomers, is preferable to using the L-menthol chiral auxiliary that we were unable to cleave in this case.

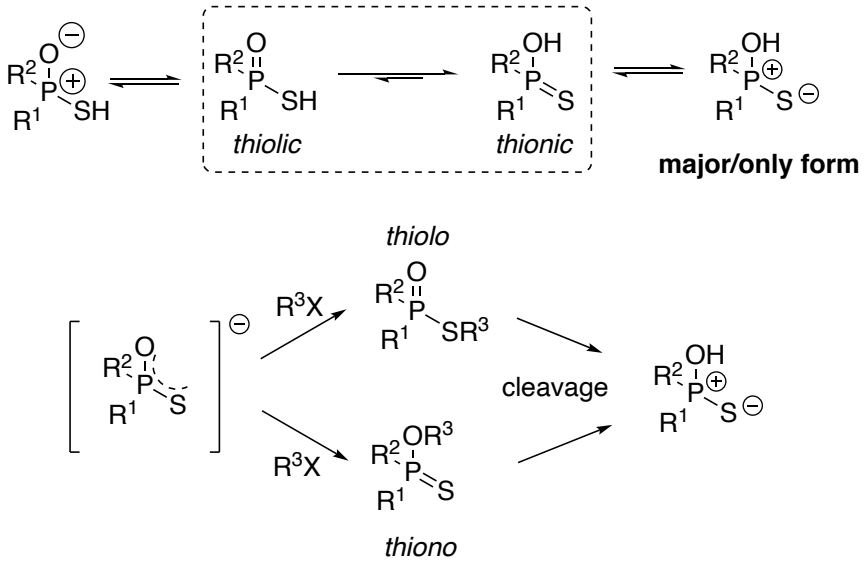
CHAPTER 3

METHODOLOGIES FOR THE SYNTHESIS OF THIOPHOSPHORUS ACIDS

3.1 Introduction to Thiophosphorus Acids

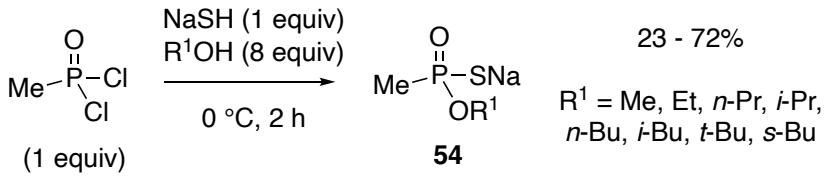
Thiophosphorus acids ($R_1R_2P(S)OH$) constitute an important class of organophosphorus compounds, in which the phosphorus atom is intrinsically chiral if $R_1 \neq R_2$. Thiophosphorus acids exist as a mixture of two tautomers: "thionic" acid and "thiolic" acid (Scheme 3.1). The position of the equilibrium depends on the substituents, but the thionic form is generally major.[61] The thioacids have ambident anions which can react in two ways with electrophiles to form either the thiolo- or thiono- derivative. The reactivity of the anion can be explained through a “hard” and ”soft” acid and base (HSAB) theory.[62] The “hard” basic center of the anion is the more electronegative oxygen atom, which reacts readily with “hard” acid centers. The sulfur atom in the anion of the thioacid is the “soft” base and reacts more readily with “soft” electrophiles.

Scheme 3.1 Prototropic tautomerism in thiophosphorus acids and reactivity



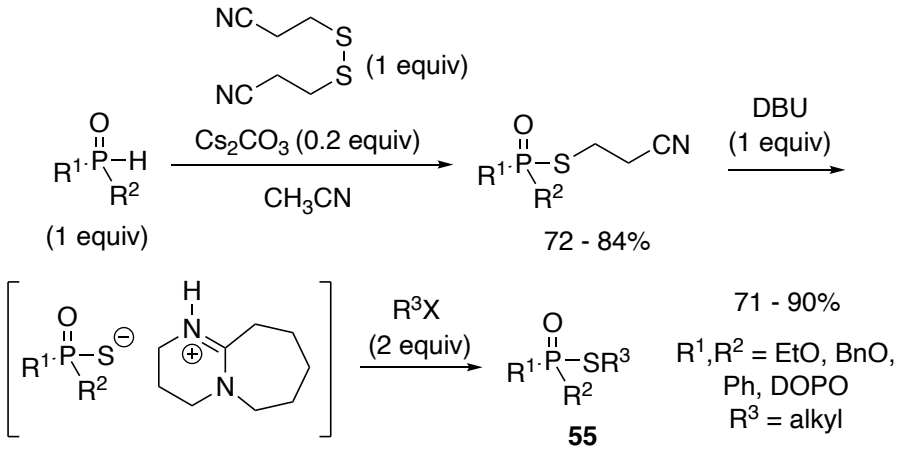
There are many methods used for the preparation of thiophosphorus acids (other than LR as discussed in Chapter 2). The first is the reaction with a metal sulfide, disulfide, or thiol.[63, 64] An early report of this method is Pelchowicz and coworkers' reaction of methyl phosphonic dichloride with sodium hydrogen sulfide, to generate sodium *O*-alkyl methylphosphonothioates **54** (Scheme 3.2).[64]

Scheme 3.2 Synthesis of thiophosphorus salt from MSH and R^1OH



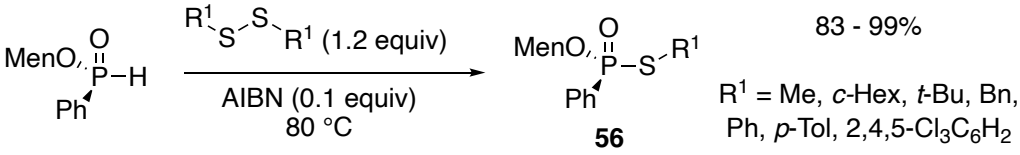
Another method involves O'Sullivan's use of 2-cyanoethyl disulfide to synthesize *S*-alkyl-phosphonothioates **55** from *H*-phosphinates. This thioester then undergoes deprotection with DBU to form the salt, followed by trapping with an alkyl halide (Scheme 3.3).[65]

Scheme 3.3 Synthesis of *S*-alkylphosphates from disulfide



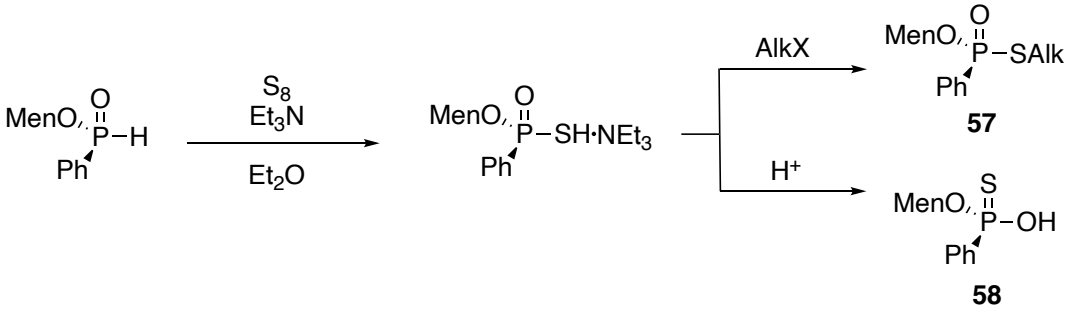
Similarly, Xu and Huang reported a free radical reaction of dialkyl-*H*-phosphites with diaryl disulfide, to give *S*-alkyl phosphonothioates **56**.[66] When this method was applied to a chiral *H*-phosphinate, it proceeded stereospecifically (retention) (Scheme 3.4).

Scheme 3.4 Synthesis of *S*-alkylphosphates from disulfides and a radical initiator



Phosphonothioates can also be prepared by reacting *H*-phosphinates with elemental sulfur in the presence of base to give a phosphonothioate salt (Scheme 3.5). This can either be reacted further with an or alkyl halide to give the thioester **57**, or directly protonated to give the acid **58**.[39, 66]

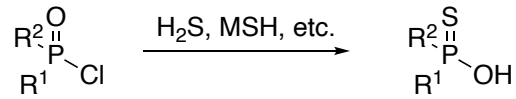
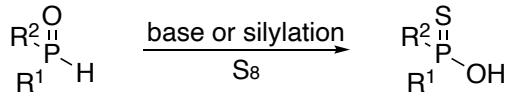
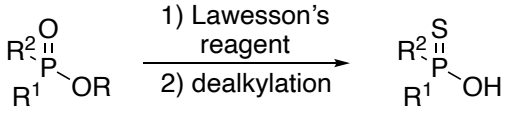
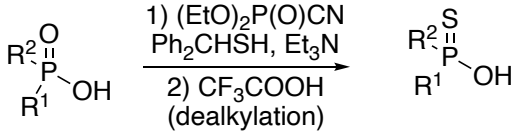
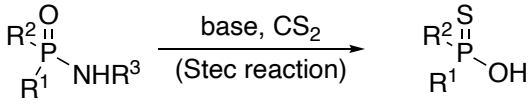
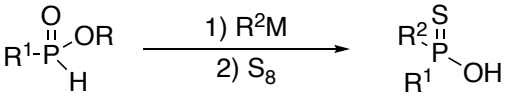
Scheme 3.5 Synthesis of a thiophosphorus salt with elemental sulfur and base, followed by alkylation to give the thioester or protonation to give the thioacid



Confronted with the problems experienced with LR (see Chapter 2, Scheme 2.10), finding a general method to synthesize thiophosphorus compounds that would have facile isolation and purification of the product became necessary. Additionally alleviating the need

for malodorous reagents would be desirable. It should be noted that all the above methods employ extremely malodorous reagents, except for that in Scheme 3.5. A summary of the methodologies for the synthesis of thiophosphorus acids is listed in Table 3.1 and the results are presented below.

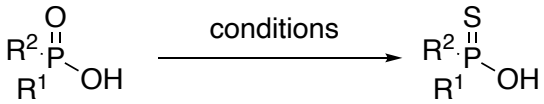
Table 3.1 Summary of methodologies for the preparation of thiophosphinic acids and related compounds

Entry	Reaction	Comments
1)		Commonly used method stench, toxic
2)		commonly used method odorless S, Se, BH_3 derivatives
3)		commonly used method stench often problems during purification
4)		only one literature report stench
5)		general reaction, *stereospecific* odorless
6)		odorless S, Se, BH_3 derivatives

3.2 Synthesis of Thiophosphorus Acids

We first investigated converting a phosphorus acid $R_1R_2P(O)OH$ directly into the desired thiophosphorus acid, *via* activation and reaction with metal sulfides (Table 3.2, entry 2). The reaction with Na_2S gave moderate yields at high temperatures (Table 3.2, entries 4-7), however, we found this NMR yield to be inconsistent between reactions (Table 3.2, entry 3 vs entry 6), likely due to the salts' lack of solubility (Table 3.2). To increase solubility *n*Bu_4NI was tried as a phase transfer agent, and various solvents other than DMF (DMSO, 1-methyl-2-pyrrolidone, diglyme, water:toluene, ethylene glycol:toluene, CH_3CN) were tried, however, none increased solubility nor the yield.

Table 3.2 Summary of conditions for the conversion of P(O)OH to P(S)OH using M_2S



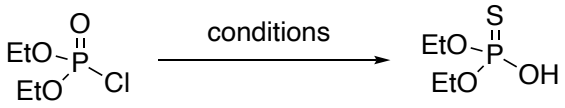
Entry[b]	R^1	R^2	M_2S	Coupling Agent	Solvent	Temp., Time	Yield (%)[c]
1	Ph	Me	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv)	DMF	0 °C to rt, 3 h	0[a]
2	Ph	Tr	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv)	DMF	0 °C to rt, 3 h	0[a]
3	Ph	Me	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv), *n*-Bu_4NI (10 mol%)	DMF	120 °C, 14 h	0[a]
4	Ph	Tr	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv), *n*-Bu_4NI (10 mol%)	DMF	120 °C, 14 h	75
5	Ph	Me	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv)	DMF	120 °C, 14 h	69
6	Ph	Me	$Na_2S·9H_2O$ (3 equiv)	EDC (1.1 equiv), *n*-Bu_4NI (10 mol%)	DMF	120 °C, 14 h	67

7	Ph	Me	$Na_2S \cdot 9H_2O$ (3 equiv)	DCC (1.5 equiv)	DMF	120 °C, 14 h	74
8	Ph	Me	$Na_2S \cdot 9H_2O$ (2 equiv)	T3P (1.1 equiv, 50 wt% in EtOAc)	DMF	120 °C, 14 h	0
9	Ph	Me	Li_2S (1.5 equiv, 0.5M in THF)	EDC (1.1 equiv)	DMF	100 °C, 14 h	0

[a] Reaction shows 100% sm by ^{31}P-NMR; [b] 1 equiv of P(O)OH sm unless otherwise noted; [c] Determined by ^{31}P-NMR.

Instead of the mixed anhydride, we then explored acid chloride conversion to the thiophosphorus acid (Table 3.3). We quickly ran into the same solubility problem, as well as competing hydrolysis of the chloride (even when using anhydrous sodium sulfide (Table 3.3, entries 5-6) with the formation of large amounts of acid $R^1R^2P(O)OH$, anhydride $[R^1R^2P(O)(OH)]_2O$, and a trace of mixed anhydride $R^1R^2P(S)OP(O)\text{-}R^1R^2$. Moreover, sodium sulfide and lithium sulfide have a rotten egg-like stench from the hydrogen sulfide gas that occurs during hydrolysis.

Table 3.3 Summary of conditions for the conversion of P(O)Cl to P(S)OH using M_2S

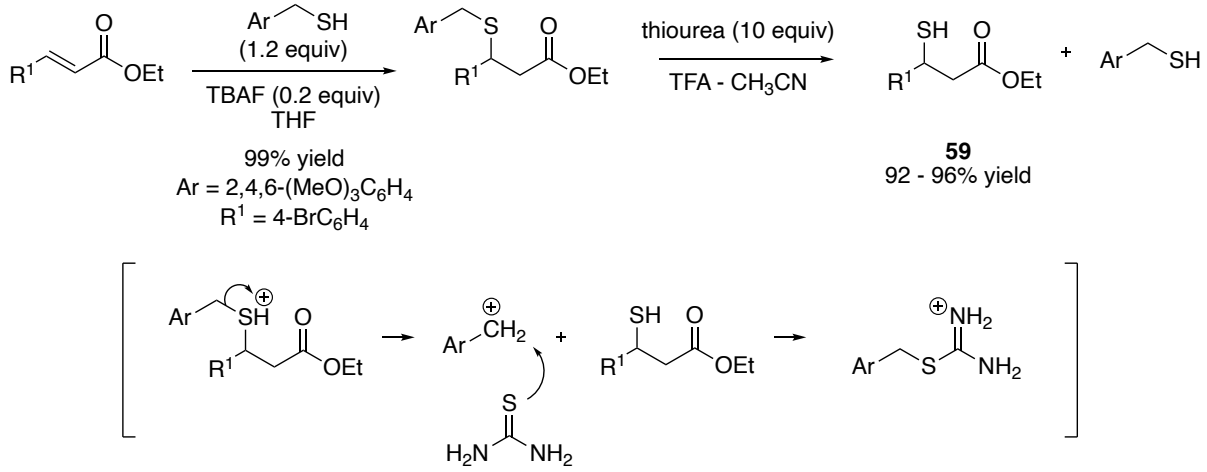


Entry[b]	M_2S	Reagent	Solvent, Temp., Time	Yield (%)[c]
1	$Na_2S·9H_2O$ (3 equiv)	*n*-Bu_4NCl (5 mol%)	DCM:H_2O reflux, 16 h	0
2	$Na_2S·9H_2O$ (3 equiv)	*n*-Bu_4NCl (10 mol%)	DCM reflux, 16 h	0
3	$Na_2S·9H_2O$ (1 equiv)	*n*-Bu_4NCl (5 mol%)	DMF, reflux, 16 h	3
4	$Na_2S·9H_2O$ (3 equiv)	Bu_4NCl (5 mol%)	DCM:H_2O reflux, 16 h	0
5	Na_2S (4.5 equiv)	$(Me)_3SiCl$ (1.5 equiv)	DCM, reflux, 24 h	9
6	Na_2S (4.5 equiv)	(*i*-Pr)$_3$SiCl (1.5 equiv)	DCM, reflux, 24 h	6

[a] Reaction shows 100% sm by ^{31}P-NMR; [b] 1 equiv of P(O)Cl sm unless otherwise noted; [c] Determined by ^{31}P-NMR.

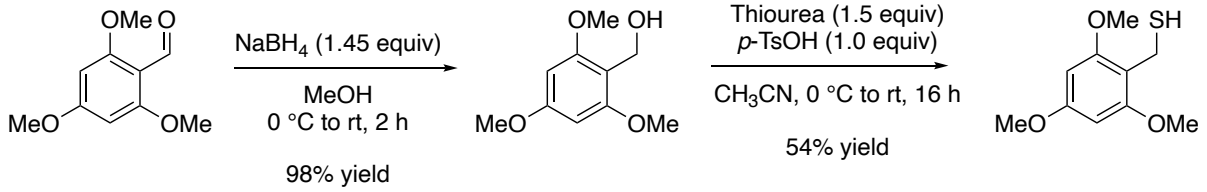
Recently, Node and coworkers reported the use of 2,4,6-trimethoxybenzyl thiol (TmobSH) as an odorless substitute of hydrogen sulfide, as demonstrated through a Michael addition to form alkanethiols (Scheme 3.6).[67, 68] Debenzylation of the Michael adducts with thiourea, should regenerate the starting benzylic mercaptan and deliver the thiol product **59**. To the best of our knowledge, use of this odorless mercaptan has not been used previously in phosphonothioate synthesis.

Scheme 3.6 Node and coworkers use of TmobSH in Michael addition and a proposed recycle pathway mechanism to regenerate the TmobSH

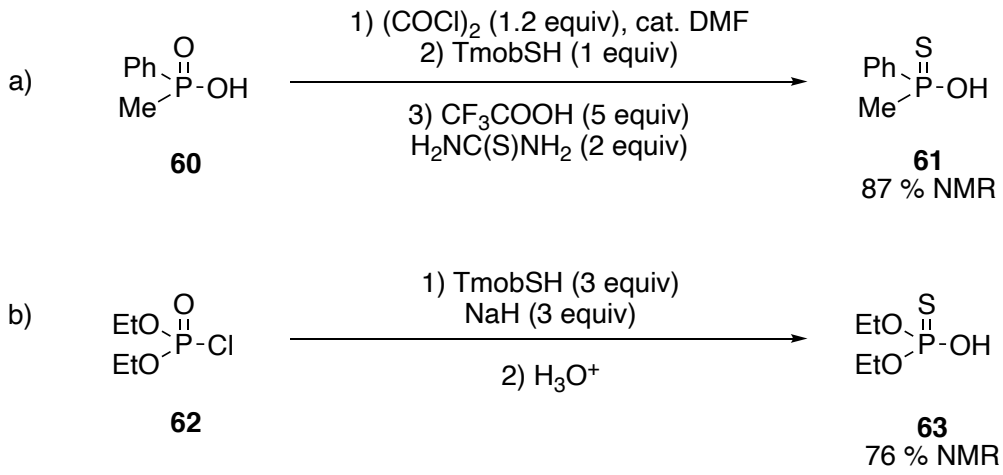


TmobSH is easily synthesized in two steps from the commercially available aldehyde (Scheme 3.7).[68] When TmobSH was reacted with PhMeP(O)OH **60**, via the chloride as an intermediate, it resulted in the desired thioacid **61** in an 87 % NMR yield (Scheme 3.8, entry a). However, in our hands, the recycling of TmobSH was unsuccessful. After thiourea was added for the benzyl cleavage step, the thiol could not be isolated or reused. We also tried this transformation with an excess of TmobSH, in the hope that the excess deprotonated thiol would cleave the benzylic position of the phosphinothioester. This proved to be successful in a 76 % NMR yield of the product **63** (Scheme 3.8, entry b). Despite this sequence giving the desired product and being odorless, the fact that TmobSH could not be recycled seemed wasteful and a significant drawback, thus the approach was not pursued further.

Scheme 3.7 Synthesis of TmobSH

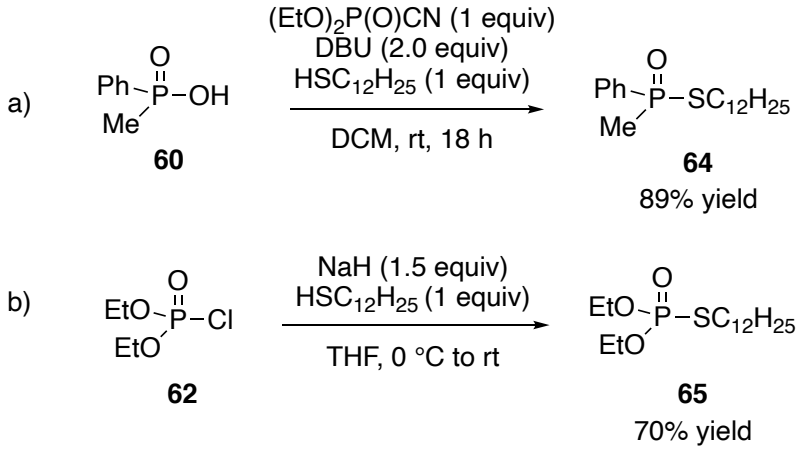


Scheme 3.8 Synthesis of thiophosphorus acids via TmobSH



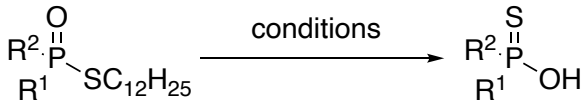
Next, we explored the synthesis of thiophosphorus acids via cleavage of a thioester (Table 3.1, entry 3). To address the solubility and odor issues, we looked at replacing the sulfur nucleophile with *n*-dodecyl thiol as an alternative, because it is organic-soluble, odorless, and inexpensive ($/mol 6). The synthesis of the thioester precursors was done either through the phosphorus acid or the chloride. For example, starting with the acid **60** and using diethylcyanophosphonate as the coupling agent, resulting in the mixed anhydride intermediate, which was then esterified with the dodecylthiol, to give the thioester **64** in good yield (Scheme 3.9, entry a).[69] Starting from the acid chloride **62**, followed by nucleophilic substitution with the deprotonated dodecylthiol, also formed the desired thioester **65** in good yield (Scheme 3.9, entry b).

Scheme 3.9 Synthesis of phosphinothioesters through a) diethylcyanophosphonate or b) substitution



Cleavage of $R^1R^2P(O)SC_{12}H_{25}$ via S_N2 with various nucleophiles (DABCO, $NaS_2CN(C_2H_5)_2$, NaN_3, TFA/thiourea) was unsuccessful (Table 3.4, entries 1-3). On the other hand, Na_2S (2 equiv)/DMF 100 °C gave a 77 % NMR yield with >15 % unreacted starting material (Table 3.4, entry 4) of the desired salt, however, these conditions are obviously not odorless and were not pursued at this point.

Table 3.4 Summary of conditions for the cleavage of $R^1R^2P(O)SC_{12}H_{25}$ to $R^1R^2P(S)OH$



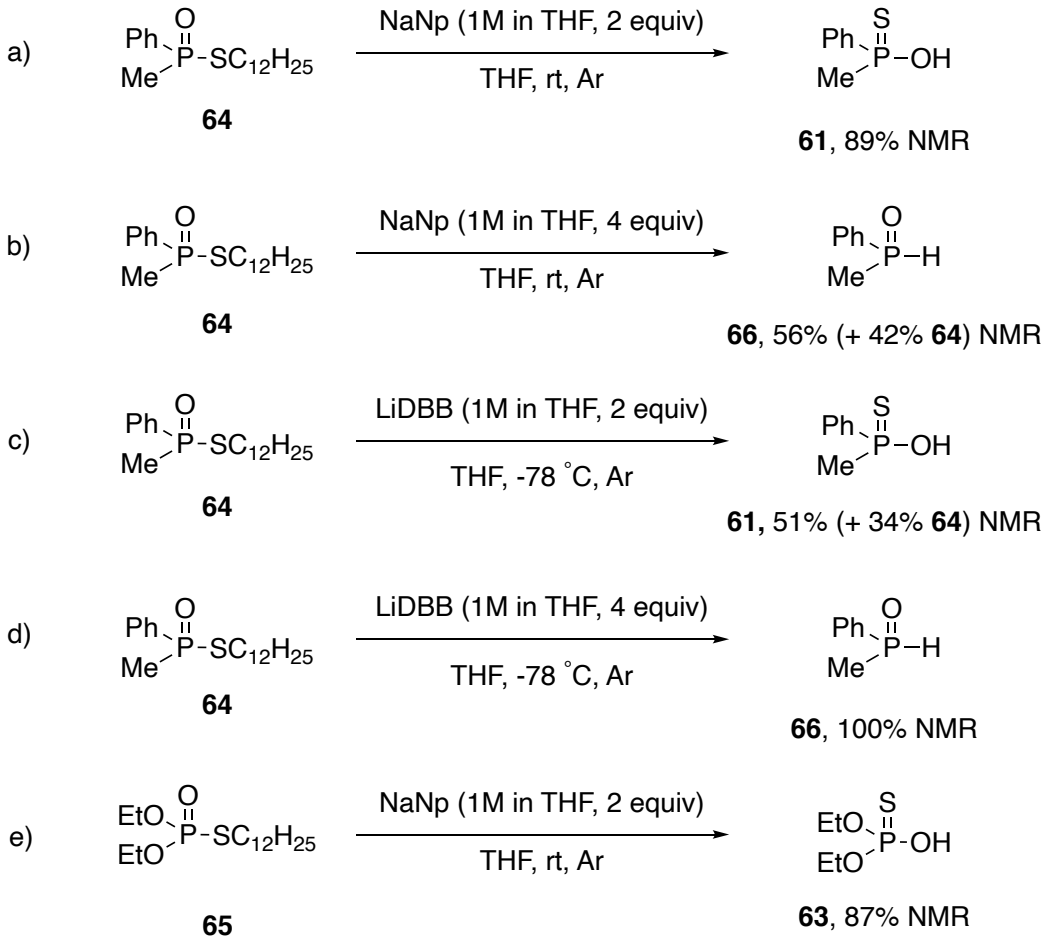
Entry[b]	R^1	R^2	Reagent(s)	Solvent, Temp., Time	Yield (%)[d]
1	Ph	Me	Thiourea (2 equiv), TFA (2.3 M)	toluene, rt, 16 h	0[a]
2	Ph	Me	DABCO (1 equiv)	CH_3CN, reflux, 16 h	0[a]
3	Ph	Me	$NaS_2CN(C_2H_5)_2$ (1 equiv)	CH_3CN, reflux, 16 h	0[a]
4	Ph	Me	$Na_2S{\cdot}9H_2O$ (2 equiv)	DMF, 100 °C, 14 h	77[c]

5	Ph	Me	$Na_2S \cdot 9H_2O$ (5 equiv)	DMF, 100 °C, 14 h	38
6	EtO	EtO	TMSBr (1 equiv)	1) DCM, rt, 4 h 2) MeOH, 16 h	0
7	Ph	Ph	NaN_3 (1.1 equiv)	CH_3CN, reflux, 16 h	0

[a] Reaction shows 100% sm by ^{31}P-NMR; [b] 1 equiv of P(O)Cl sm unless otherwise noted; [c] 15% sm remained by ^{31}P-NMR; [d] Determined by ^{31}P-NMR.

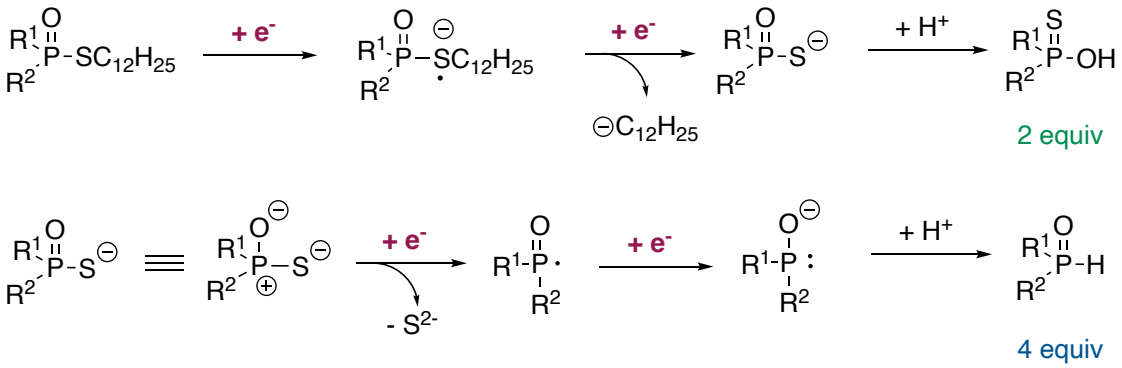
The reduction of $R^1R^2P(O)SC_{12}H_{25}$ into $R^1R^2P(O)H$ was considered next, since P(O)H is easily converted into P(S)OH with elemental sulfur (Table 3.1, entry 4), and is also a key intermediate in numerous other transformations. Because the transformation P(O)SR to P(O)H was unknown, this reduction was examined through the use of two alkali metals: sodium naphthalene (NaNp) and lithium di-*t*-butyl-biphenylide (LiDBB), as they had been shown to reduce phosphorus-halogen bonds.[70, 71] Interestingly, depending on the stoichiometry of the reducing agent, either the thiophosphorus acid P(S)OH or the phosphinylidene P(O)H (Scheme 3.10) could be obtained. It appears that 2 equiv give the thiophosphorous acids as the major products (Scheme 3.10, entry a, c, e), whereas 4 equiv produced the more fully reduced phosphinylidene P(O)H (Scheme 3.10, entry b, d), and the nature of the reducing agent (NaNp vs LiDBB) is not as important as the stoichiometry.

Scheme 3.10 Summary of $R^1R^2P(O)SC_{12}H_{25}$ thioester reduction methods



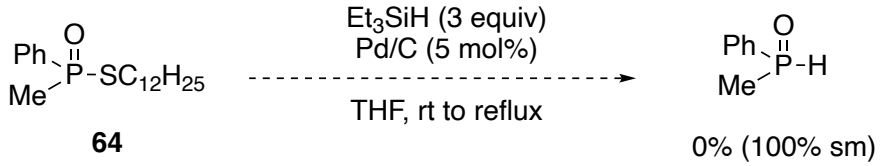
Mechanistically, the $P(O)SC_{12}H_{25}$ can accept an electron to generate a sulfur-centered radical (Scheme 3.11). The sulfur radical undergoes another reduction to give the carbanion and sulfur anion, and upon protonation will generate the P(S)OH. The sulfur anion may accept another electron to form the phosphorus-centered radical and S^{2-}. The phosphorus radical would be reduced to form the P(III), and upon protonation give the phosphinyldiene P(O)H. Alkylation of the P(III) anion was not attempted but could be tried to see if the phosphate product forms.

Scheme 3.11 Proposed mechanism for the reduction of thioester with alkali metals



Seki and coworkers reported on the reduction of thioesters into aldehydes using Et_3SiH in the presence of a Pd/C catalyst.[72] The reaction takes place under mild reaction conditions and tolerates substrates with various functional groups. However, this reduction did not proceed with a thiophosphonate, and gave unreacted starting material (Scheme 3.12). Moreover, the direct conversion of P(O)Cl into P(O)H had been reported previously,[70, 71] and might be a more efficient approach than through the thioester.

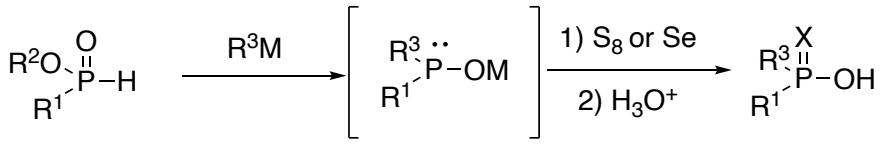
Scheme 3.12 Reduction with Et_3SiH and Pd/C

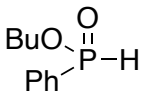
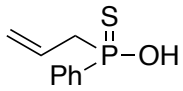
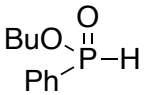
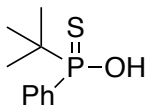
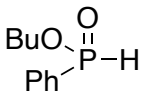
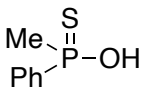
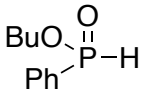
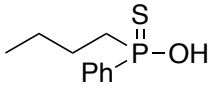


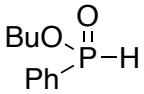
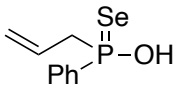
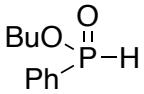
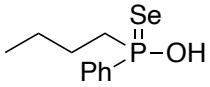
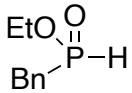
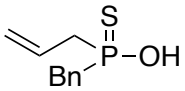
Since our group has experience in the preparation of *H*-phosphinates, another approach to synthesize thiophosphorus acids was examined that involved the displacement of *H*-phosphinates followed by trapping with elemental sulfur (Table 3.1, entry 5). The displacement of *H*-phosphinates with organometallics (RLi, RMgX) is well-known to deliver the corresponding secondary phosphine oxide.[39] By using at least 2 equivalents of the

organometallic, the first is used for deprotonation of the H-phosphinate to form the P(III) from the P(V) then the second equivalent is used to displace the ester. Because the nucleophilic substitution of an *H*-phosphinate should form R^1R^2POM as the intermediate, quenching with elemental sulfur (or selenium) would deliver the thiophosphorus acid (or selenophosphorus acid) directly, in a one-pot transformation. Indeed, this transformation does occur and the results are summarized in Table 3.5.

Table 3.5 Substrate scope for the synthesis of thiophosphinic acids via nucleophilic substitution of *H*-phosphinates with organometallics, followed by trapping with elemental sulfur or selenium



Entry	Substrate	Organometallics	Trapping	Product	Yield (%)[a]
1a 1b		H_2C=$CHCH_2MgBr$ (2.4 equiv) H_2C=$CHCH_2MgBr$ (3.5 equiv)	S_8 (3/8) S_8 (5/8)		100 (57) 83 (67)
2		*t*-BuMgCl (5 equiv)	S_8 (5/8)		37 (-)[b]
3		MeLi (2.5 equiv)	S_8 (3/8)		100 (91)
4		*n*-BuLi (2.5 equiv)	S_8 (3/8)		100 (80)

5		$H_2C{=}CHCH_2MgBr$ (3.5 equiv)	Se (5)		94 (65)
6		*n*-BuLi (2.5 equiv)	Se (5)		100 (72)
7		$H_2C{=}CHCH_2MgBr$ (3.5 equiv)	S_8 (5/8)		97 (62)

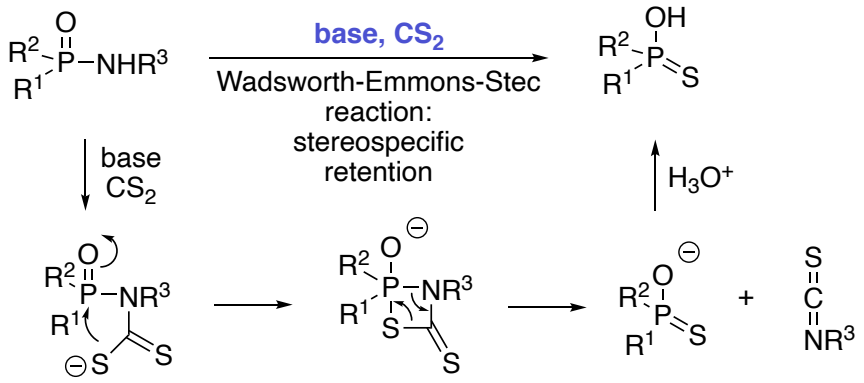
[a] Determined by ^{31}P-NMR. In parentheses: yield of product (>95% purity) after extractive workup; [b] Complex mixture of products; not isolated.

In most instances, the product can be obtained in good purity (>95 %) by a simple extractive workup. However, with *t*-BuMgCl (Table 3.5, entry 2), a significant amount of unreacted *H*-phosphinate is converted into the thiophosphonic acid $R^1P(S)(OR)OH$, which prevents purification. In this case, a two-step process via the secondary phosphine oxide would be better (Table 3.1, entry 4). As expected, the more reactive organolithium organometallics are superior to the Grignard reagents (Table 3.5, entries 3-4 versus entries 1-2). Trapping of the phosphinite anion with elemental selenium was also successful (Table 3.5, entries 5-6). Ethyl benzyl-*H*-phosphinate and butyl phenyl-*H*-phosphinate worked equally well (Table 3.5, entry 7). Because phosphinates $R^1R^2P(O)(OR)$ are typically derived from *H*-phosphinates $R^1P(O)(OR)H$, this transformation could well be the most efficient approach to thiophosphinic acids $R^1R^2P(S)(OH)$. One drawback is that the racemic thiophosphinic acid would need to be resolved via a diastereoisomeric salt.

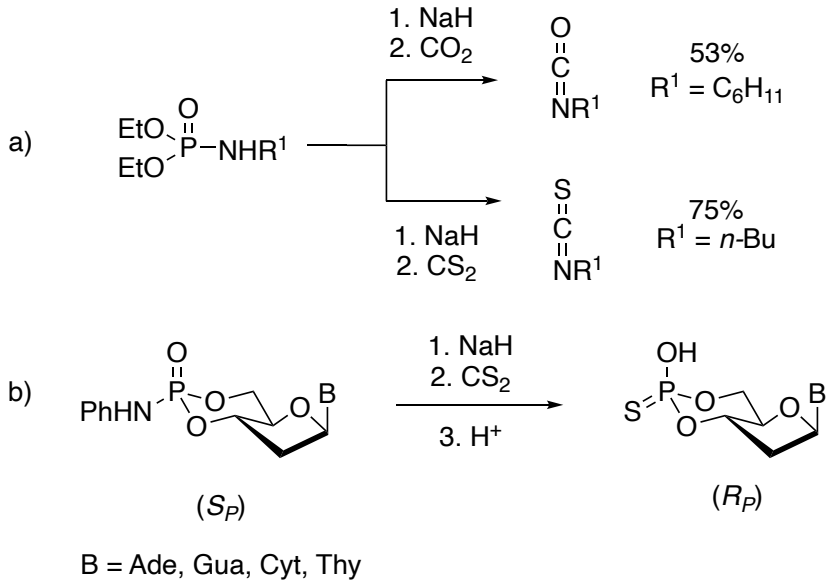
Our next investigation focused on the synthesis of thiophosphorus acids via phosphonamides and the Wadsworth−Emmons− Stec reaction (Table 3.1, entry 6).[73-75] The Stec reaction converts a phosphorus amide P(O)NHR, using a base and carbon disulfide, into

the thiophosphorus acid, stereospecifically, and isothiocyanate (Scheme 3.13). Wadsworth and Emmons made the initial discovery in 1962, where they focused on the isothiocyanate product generated by reacting a phosphoramidate anion with carbon disulfide (Scheme 3.1, entry a).[75] In 1983, Stec revisited this transformation and was the first to realize the reaction's usefulness in organophosphorus chemistry through the synthesis of nucleoside phosphorothioates (Scheme 3.14, entry b), and confirmed the reaction's stereospecificity and proceeds with retention of configuration at the phosphorus atom.[73] Pure carbon disulfide is a clear, colorless liquid that has a sweet odor,[76] thus making this transformation a good alternative to the previously reported methods.

Scheme 3.13 Mechanism of the Wadsworth−Emmons−Stec reaction

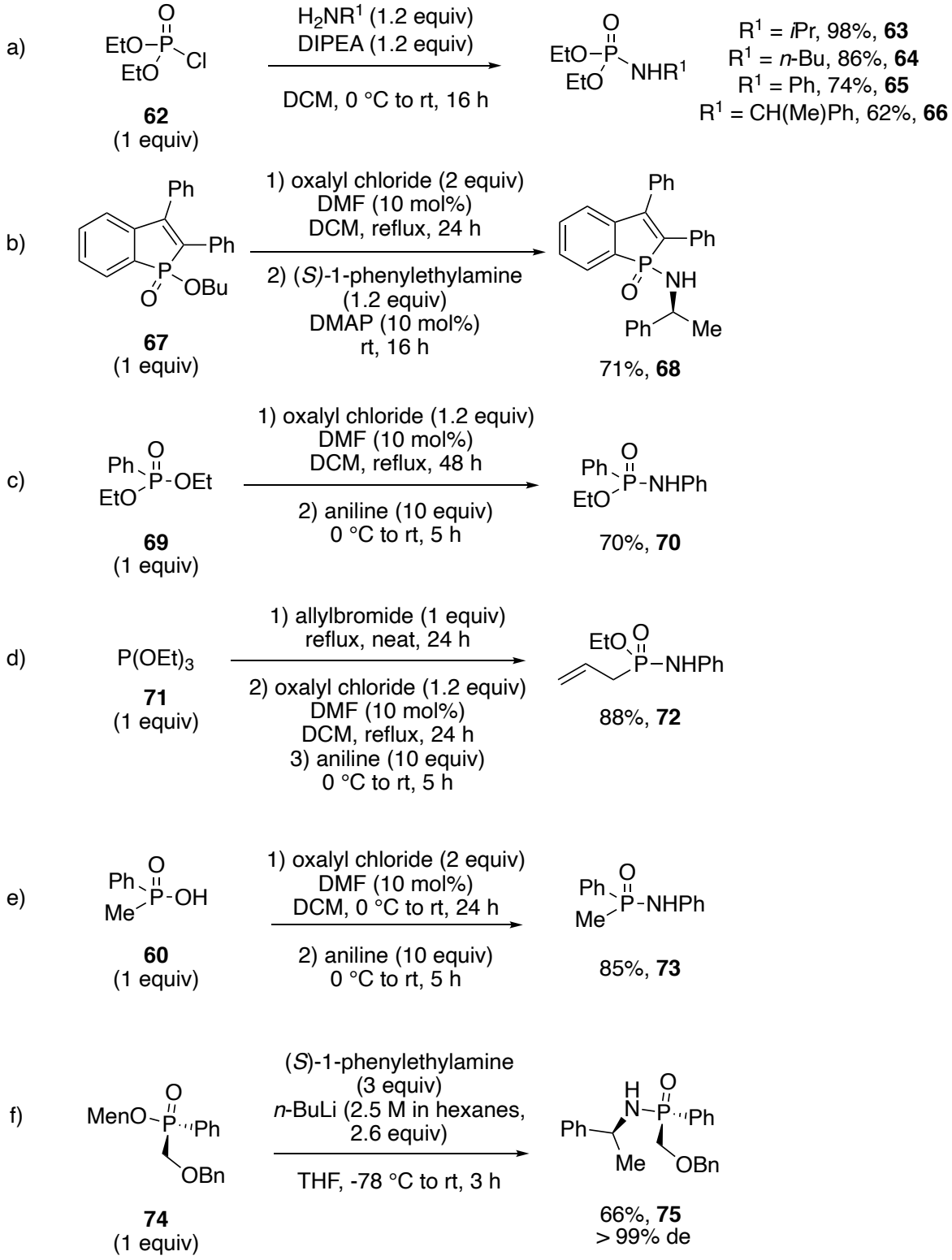


Scheme 3.14 Preparation of a) isothiocyanates and carbodiimides reported by Wadsworth and Emmons; b) nucleoside phosphorothioates by Stec



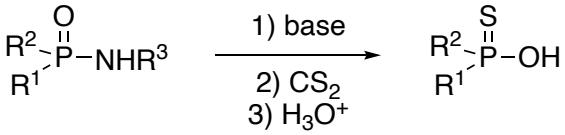
Since there was no comprehensive study of the scope of this transformation reported in the literature, we decided to investigate.[73] We began our study by synthesizing various phosphonamides, by reacting the acid chloride P(O)Cl (either from a commercial reagent or formed in situ from the reaction of P(O)(OR) (R = Alk, H)), with a primary amine (isopropylamine, *n*-butylamine, aniline and chiral (*S*)-1-phenylethylamine). All substrates gave good yields of the corresponding amide P(O)NHR (Scheme 3.15).

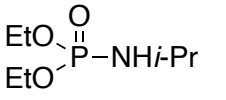
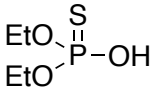
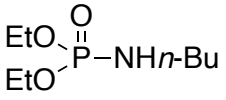
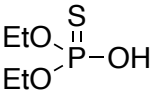
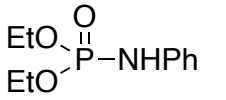
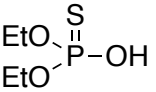
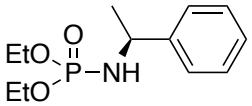
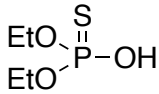
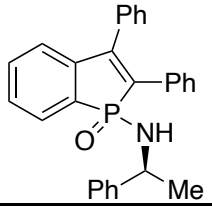
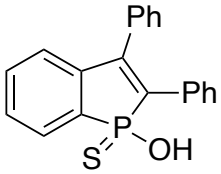
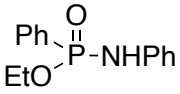
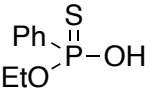
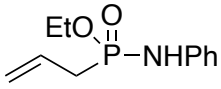
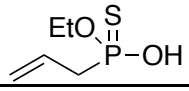
Scheme 3.15 Synthesis of phosphonamide substrates

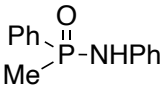
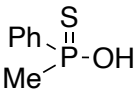
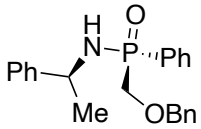
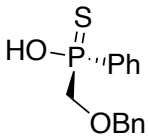


The results from our Wadsworth−Emmons−Stec investigation are summarized in Table 3.6. This transformation was equally successful with different bases, such as NaH, LiHMDS, and *n*-BuLi, and reacting with CS_2 resulted in the P(S)OH product. As before, we found that we were able to isolate the thiophosphorus acids in over 95% purity through an extractive workup.

Table 3.6 Substrate scope for the synthesis of thiophosphinic acids via the Wadsworth−Emmons−Stec reaction



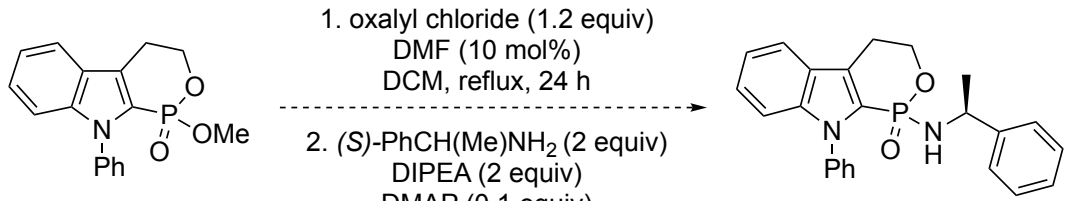
Entry	Substrate	Conditions[a]	Product	Yield (%)[b]
1a		A		90 (88)
1b		B		88
1c		C		77
2a		A		91
2b		B		97 (95)
2c		C		91
3a		A		96
3b		B		100 (99)[c]
3c		C		95[c]
4a		A		45
4b		B		81 (75)[c]
4c		C		44
5		B		96 (85)
6		B		100 (79)
7		D		90 (76)

8a 8b		B D		79 94 (85)[c]
9	 > 99% de	E	 > 99% de	88 (72)

[a] Conditions A: NaH (3 equiv), THF, 0 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions B: *n*-BuLi (2 equiv), THF, −78 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions C: LiHMDS (1.5 equiv), THF, 0 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions D: LiHMDS (1.25 equiv), THF, 0 °C to rt, 2 h; then CS_2 (5 equiv), overnight. Conditions E: NaH (2.0 equiv), THF, 0 °C to rt, then CS_2 (5 equiv), overnight. [b] Determined by ^{31}P-NMR. In parentheses: yield of product (>95% purity) after extractive workup. [C] The reaction with CS_2 was conducted overnight instead of 2 h.

Once the optimized Wadsworth-Emmons-Stec reaction conditions were found, we then set out to apply this transformation on our tryptophol-derived CPA **39** (Section 2.2). First, the chlorination of **52** with oxalyl chloride to form the P(O)-Cl *in-situ,* followed by the addition of the chiral (*S*)-phenylethylamine to generate **76** was tried. This resulted in unreacted starting material, as the P-Cl never formed by ^{31}P- NMR, and this is likely due to the steric hindrance from the *N*-phenyl group (Scheme 3.16).

Scheme 3.16 Synthesis of phosphonamide *via* P-Cl generation by oxalyl chloride

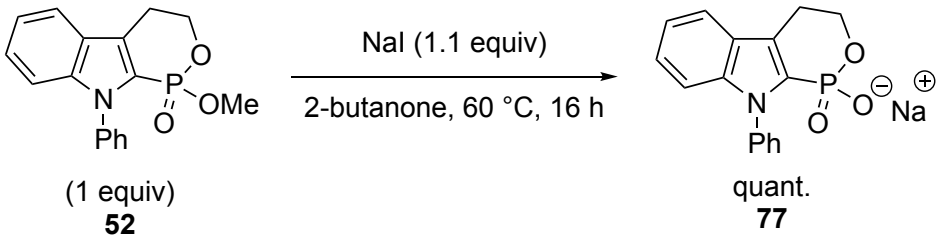


(1 equiv)
52

0% (100% SM)
76

We then attempted to introduce the chiral amine through the acid P(O)-OH. Cleavage of the methoxy ester with NaI in 2-butanone resulted in the phosphorus acid sodium salt **77** in a quantitative yield (Scheme 3.17). Next, various conditions were tried to form the phosphonamide product **76**. Oxalyl chloride resulted in a complex mixture of P(O)OH, ring-opened starting material, and some P(O)-O-P(O) anhydride (Scheme 3.18, entry a). Coupling with EDC in DMF resulted in a 61 % NMR yield (Scheme 3.18, entry b), and no product was formed with DCC (Scheme 3.18, entry c). Pivaloyl chloride also failed and only reformed the acid P(O)OH (Scheme 3.18, entry d).

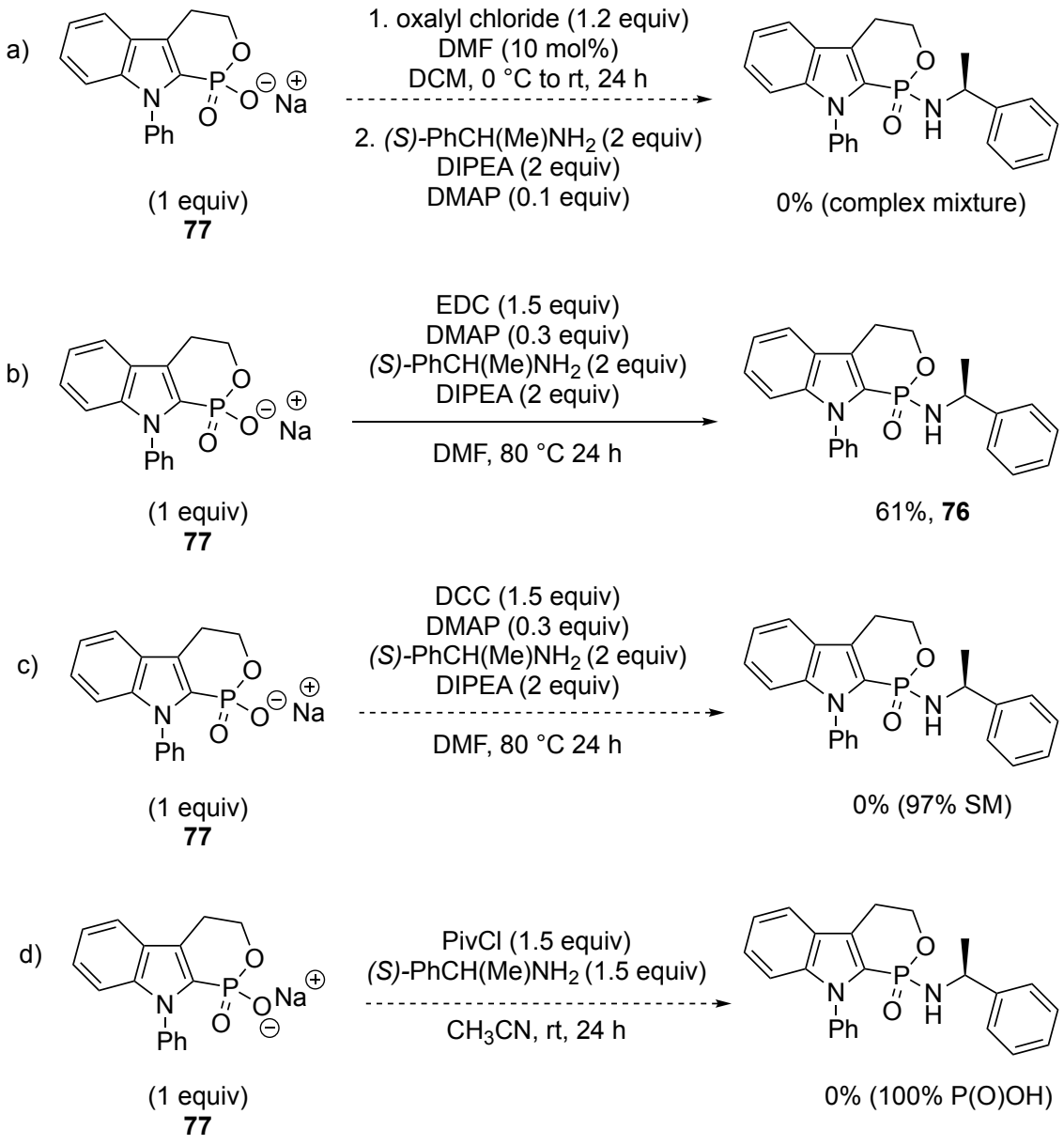
Scheme 3.17 Synthesis of phosphorus acid sodium salt



(1 equiv)
52

quant.
77

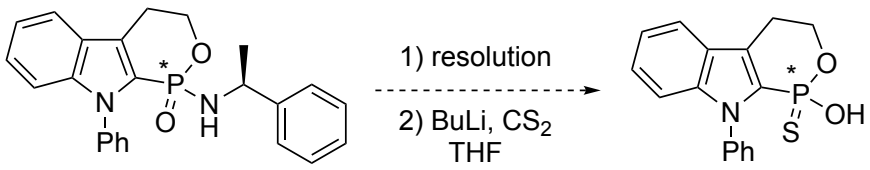
Scheme 3.18 Synthesis of phosphonamide from P(O)ONa



At the time of this writing, the phosphonamide tryptophol diastereoisomers have not yet been resolved. They could not be separated by column chromatography (elutes together), therefore the resolution through crystallization may be an alternative for future research. The last step would be the Wadsworth-Emmons-Stec reaction using CS_2 to generate the thiophosphorus acid

39, this was not tried on the diastereomeric mixture of phosphonamide **76** as we desired the enantiopure chiral phosphorus acid product (Scheme 3.19).

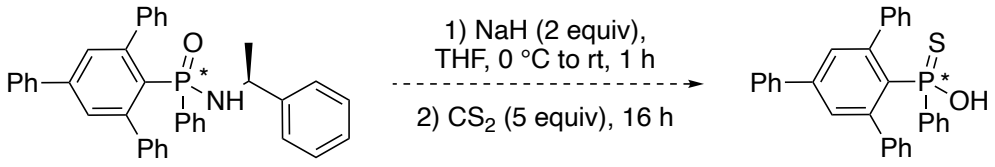
Scheme 3.19 Proposed completion of CPA **39**



76 (S_p) or (R_p) - **39**

During our investigation, there were some cases when the Wadsworth-Emmons-Stec reaction failed to react completely. For example, the 2,4,6-triphenyl(phenyl)phosphonamide **78** remained completely unreacted after performing the reaction under standard conditions (Scheme 3.20). As there was no change in the ^{31}P NMR, this implies that the amine anion is too hindered to undergo a nucleophilic attack on the CS_2 molecule. This example represents another CPA scaffold as well as some limitations of the Wadsworth-Emmons-Stec transformation.

Scheme 3.20 Synthesis of 2,4,6-triphenyl(phenyl) thiophosphinic acid *via* Wadsworth-Emmons-Stec reaction

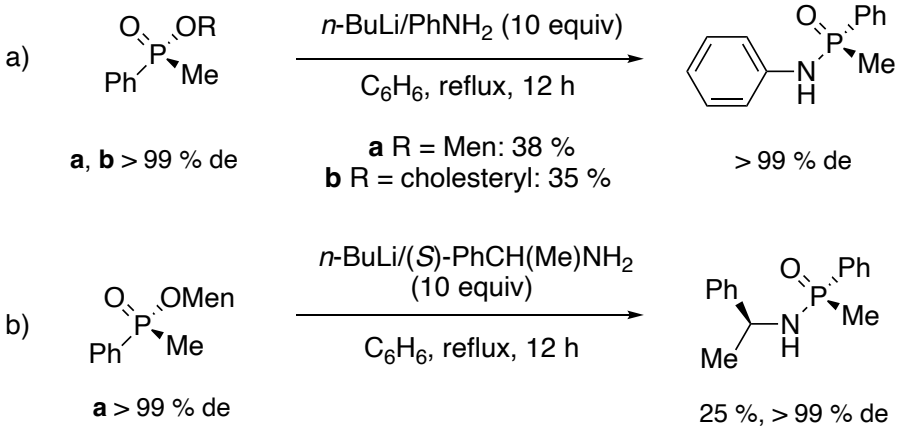


(1 equiv)
> 99 % de
78

(S_p) or (R_p) - **79**
0 % (100 % SM)

With the goal of making the Wadsworth−Emmons−Stec reaction a one-step process (as opposed to synthesizing P(O)NHR through the P(O)Cl), the direct transamidation of P(O)OR to P(O)NHR was investigated. In 1968, Cram and Nudelman reported the substitution reactions of chiral menthyl and cholesteryl phosphinate esters with lithium amides derived from aniline and (*S*)-1-phenylethylamine (Scheme 3.21).[77, 78] These reactions proceed stereospecifically with the formation of the phosphinic amides, although the yields were low and the reactions required a large excess (10 equiv) of reagent. In our case, the reaction of PhP(O)(OMen)CH_2OBn **74** with (*S*)-1-phenylethylamine and *n*-BuLi, also proved to take place stereospecifically, and in satisfactory yield to deliver the phosphinic amide **75** (Scheme 3.22, entry a). Unfortunately, a similar transamidation approach was not successful on phosphonate diesters (Table 3.7). In principle, the intermediate phosphorus amide could be deprotonated *in situ* with an excess of base and then reacted with CS_2. This one-pot method was successful in the case of butyl phosphinate **80** (Scheme 3.22, entry b); however, it failed on the menthyl phosphinate **74**, although it was successful in a stepwise fashion (Table 3.6, entry 9).

Scheme 3.21 The transamidation of menthyl and cholesteryl esters reported by Cram and Nudelman



Scheme 3.22 The direct transamidation of a) menthyl ester with (*S*)-1-phenylethylamine and b) butyl ester with aniline

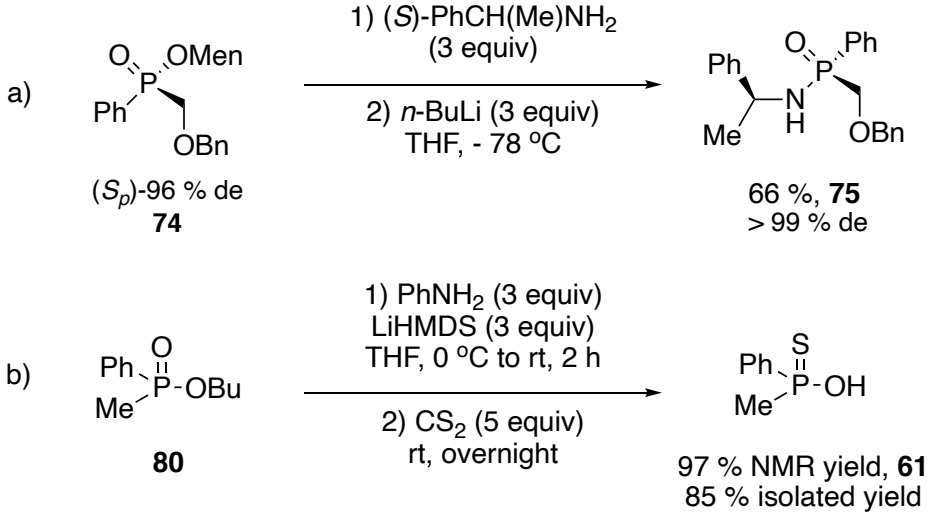
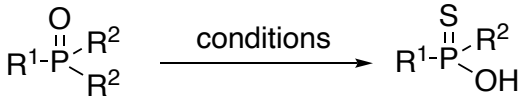


Table 3.7 Summary of substrates and conditions tried for a one-pot transamidation/CS_2 reaction



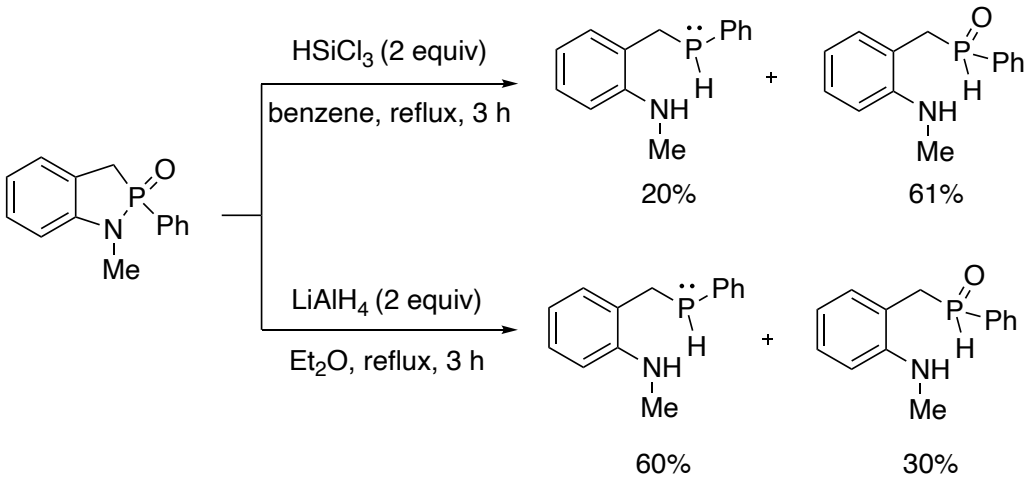
Entry	R^1	R^2	Conditions[b]	Yield (%)[c]
1	Bn	EtO	1) *n*-BuLi (3 equiv, 2.5 M in hexanes), *n*-$BuNH_2$ (1.2 equiv), THF, -78 °C to rt, 1 h 2) CS_2 (3 equiv) rt to reflux, 3 h	0
2	Me	MeO	1) *n*-BuLi (3 equiv, 2.5 M in hexanes), *n*-$BuNH_2$ (1.2 equiv), THF, -78 °C to rt, 1 h 2) CS_2 (3 equiv) rt to reflux, 3 h	0
3	Me	*i*-PrO	1) *n*-BuLi (3 equiv, 2.5 M in hexanes), *n*-$BuNH_2$ (1.2 equiv), THF, -78 °C to rt, 1 h 2) CS_2 (3 equiv) rt to reflux, 3 h	0[a]
4	Ph	EtO	1) LiHMDS (3 equiv, 1 M in toluene), $PhNH_2$ (3 equiv), THF, 0 °C to rt, 1 h 2) CS_2 (5 equiv) rt, 24 h	11
5	Ph	EtO	1) *n*-BuLi (2.5 equiv, 2.5 M in hexanes), $PhNH_2$ (1.5 equiv), THF, -78 °C to rt, 1 h 2) CS_2 (3 equiv) rt to reflux, 3 h	0

6	MeO	MeO	1) *n*-BuLi (3 equiv, 2.5 M in hexanes), *n*-$BuNH_2$ (1.2 equiv), THF, -78 °C to rt, 1 h 2) CS_2 (3 equiv) rt to reflux, 3 h	0

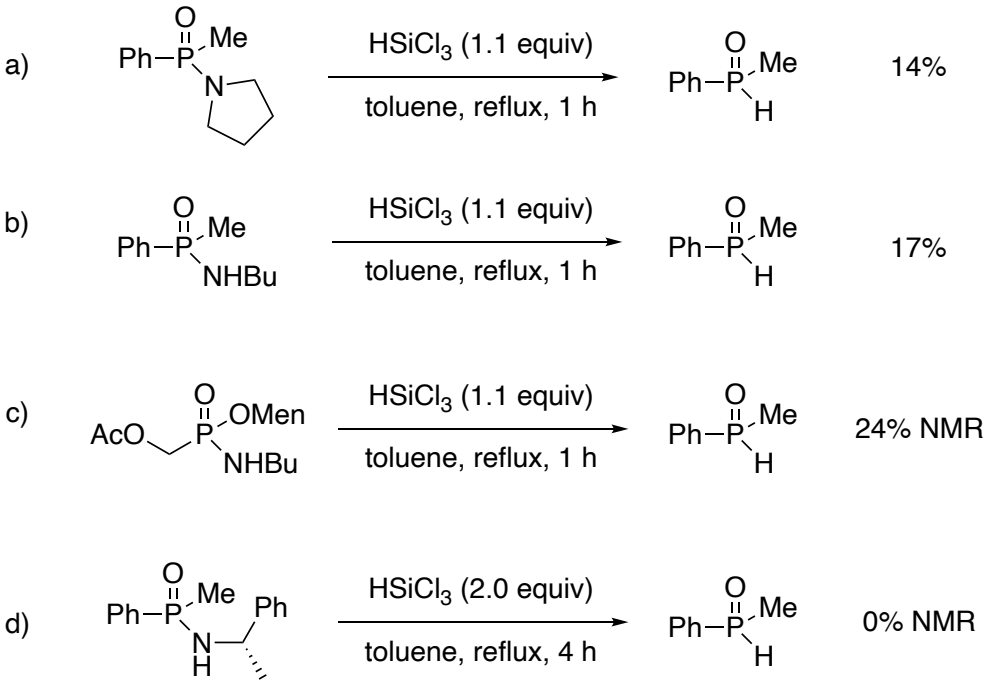
[a] Reaction shows 100% sm by ^{31}P-NMR; [b] 1 equiv of $R^1P(O)(R^2)_2$ unless otherwise noted; [c] Determined by ^{31}P-NMR.

We were also interested in the reduction of $R^1R^2P(O)NHR$ to $R^1R^2P(O)H$, as there is limited precedent for the reduction of phosphinamides using chlorosilane,[79-82] which would allow for P(O)H to be converted to P(S)OH with elemental sulfur. This transformation would also be useful if the reduction of a chiral amide proceeded stereospecifically, to give enantiopure *H*-phosphinates. An initial report of this reaction was Swan, Drygala, and Collins' reduction of a cyclic phosphoramidate (Scheme 3.23) with trichlorosilane, which gave 61 % of the ring-opened aminophosphine oxide and 20 % of the phosphine.[83] However, when using lithium aluminum hydride as the reducing agent, they obtained 60 % of the phosphine and 30 % of the phosphine oxide; which assumes that the reductive ring cleavage first generates the aminophosphine oxide, that is then further reduced to the P(III). In our hands, the reduction of P(O)NR was either low yielding with amides derived from *n*-$BuNH_2$ or pyrrolidine (Scheme 3.24, entries a-c), or there was no reaction observed (Scheme 3.24, entry d). At present, the low yield obviously limits the usefulness of this reaction, and a more thorough investigation would be needed.

Scheme 3.23 Reduction of 2,3-dihydro-1*H*-1,2-benzazaphosphole 2-oxides reported by Swan and coworkers[83]



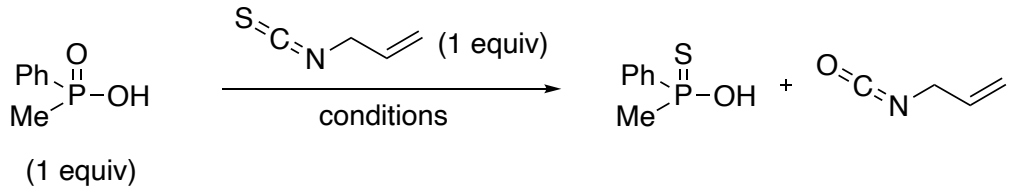
Scheme 3.24 Reduction of phosphonamides with trichlorosilane



Lastly, we investigated going directly from the acid $R^1R^2P(O)OH$ to the $R^1R^2P(S)OH$ using commercially available allyl isothiocyanate. In principle, the acid could attack the isothiocyanate (to form a similar pentacovalent intermediate as shown in Scheme 3.13), which

would undergo synchronous cleavage of the P-O and C-S bonds resulting in the thiophosphorus acid and isocyanate. Different bases (Et_3N, DIPEA, K_2CO_3, NaH), solvents (toluene, mesitylene, THF), and temperatures were tried, but none formed the thiophosphorus acid product (Table 3.8). This transformation resulted in either 100 % unreacted starting material (entries 1-3, 5-6), or some intermediate in certain conditions (Scheme 3.25; Table 3.8, entry 4), but this intermediate never fully rearranged to form the acid product.

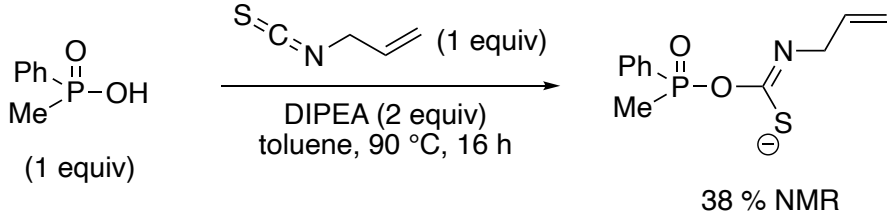
Table 3.8 Conversion of $R^1R^2P(O)OH$ to $R^1R^2P(S)OH$ via isothiocyanate rearrangement



Entry	Base	Solvent	Temp., Time	Yield (%)[a]
1	Et_3N (1 equiv)	toluene	reflux, 16 h	0
2	K_2CO_3 (3 equiv)	toluene	reflux, 16 h	0
3	DIPEA (2 equiv)	toluene	reflux, 16 h	0
4	DIPEA (2 equiv)	toluene	90 °C, 16 h	38[b]
5	DBU (2 equiv)	mesitylene	120 °C, 16 h	0
6	NaH (3 equiv, 60 wt% in mineral oil)	THF	0 °C to reflux, 16 h	0

[a] Determined by ^{31}P-NMR; [b] intermediate NMR yield

Scheme 3.25 Intermediate from $R^1R^2P(O)OH$ to $R^1R^2P(S)OH$ via isothiocyanate rearrangement



In summary, the odorless preparation of thiophosphinic acids and derivatives was investigated and two successful solutions were developed. The Wadsworth-Emmons-Stec reaction of phosphorus amides P(O)NHR was identified as an odorless solution to foul-smelling conditions (Lawesson's reagent and related). We also found an alternative based on the displacement of *H*-phosphinate esters with organometallics, followed by trapping of the intermediate with elemental sulfur or selenium. Therefore, these two methods were subsequently used in the synthesis of our target chiral phosphorus acid compounds.

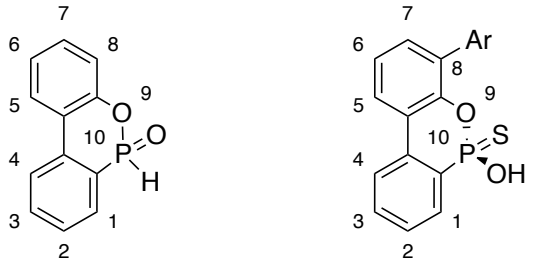
CHAPTER 4

SYNTHESIS OF DOPO DERIVED CPAS

4.1 *O*-DOPO *P*-Stereogenic CPA

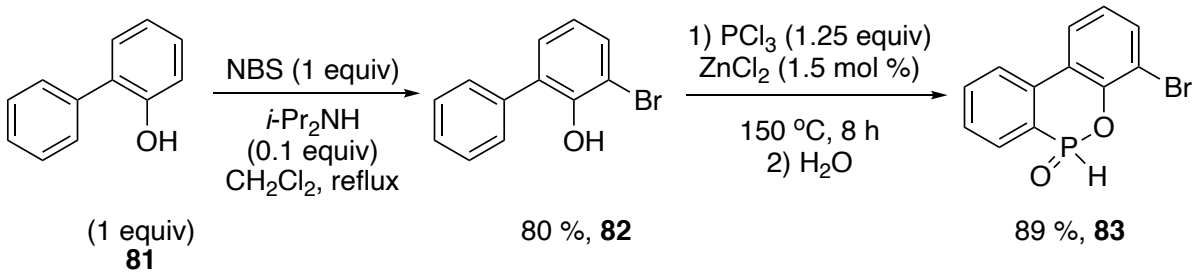
BINOL CPAs can be mimicked through derivatives of 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO; Scheme 4.1). DOPO is an industrial flame retardant manufactured in over 10,000 tons/year.[84, 85] We desired a precursor that would allow for functionalization on the DOPO scaffold with various aromatic groups. Bromination of 2-phenylphenol, resulted in the formation of *ortho*-bromo-2-hydroxybiphenyl **82** in 80 % yield (Scheme 4.2).[86] This reaction proceeded by first generating the *N*-bromoamine through NBS and a catalytic amount of amine. Then the strong hydrogen bonding between the bromoamine with the phenol causes bromination at one *ortho*-position of the phenol and regenerates the amine.[87] Next was an electrophilic aromatic substitution with $ZnCl_2$ and PCl_3, followed by hydrolysis of the P(III)-Cl intermediate with water, to generate the 8-bromo-DOPO **83** in excellent yield (Scheme 4.2).[88]

Scheme 4.1 Structure of DOPO and DOPO CPA target



DOPO 8-Ar-DOPO CPA

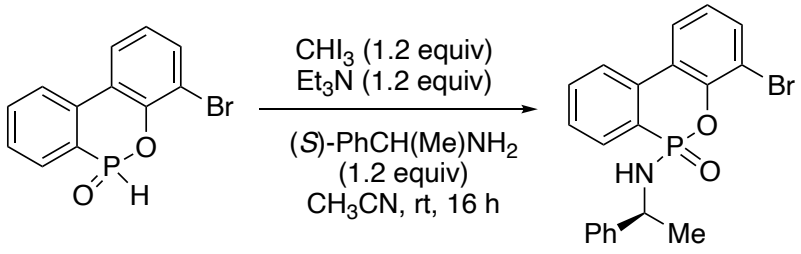
Scheme 4.2 Bromination followed by EAS with PCl_3 to give 8-bromo-DOPO



(1 equiv) **81** | 80 %, **82** | 89 %, **83**

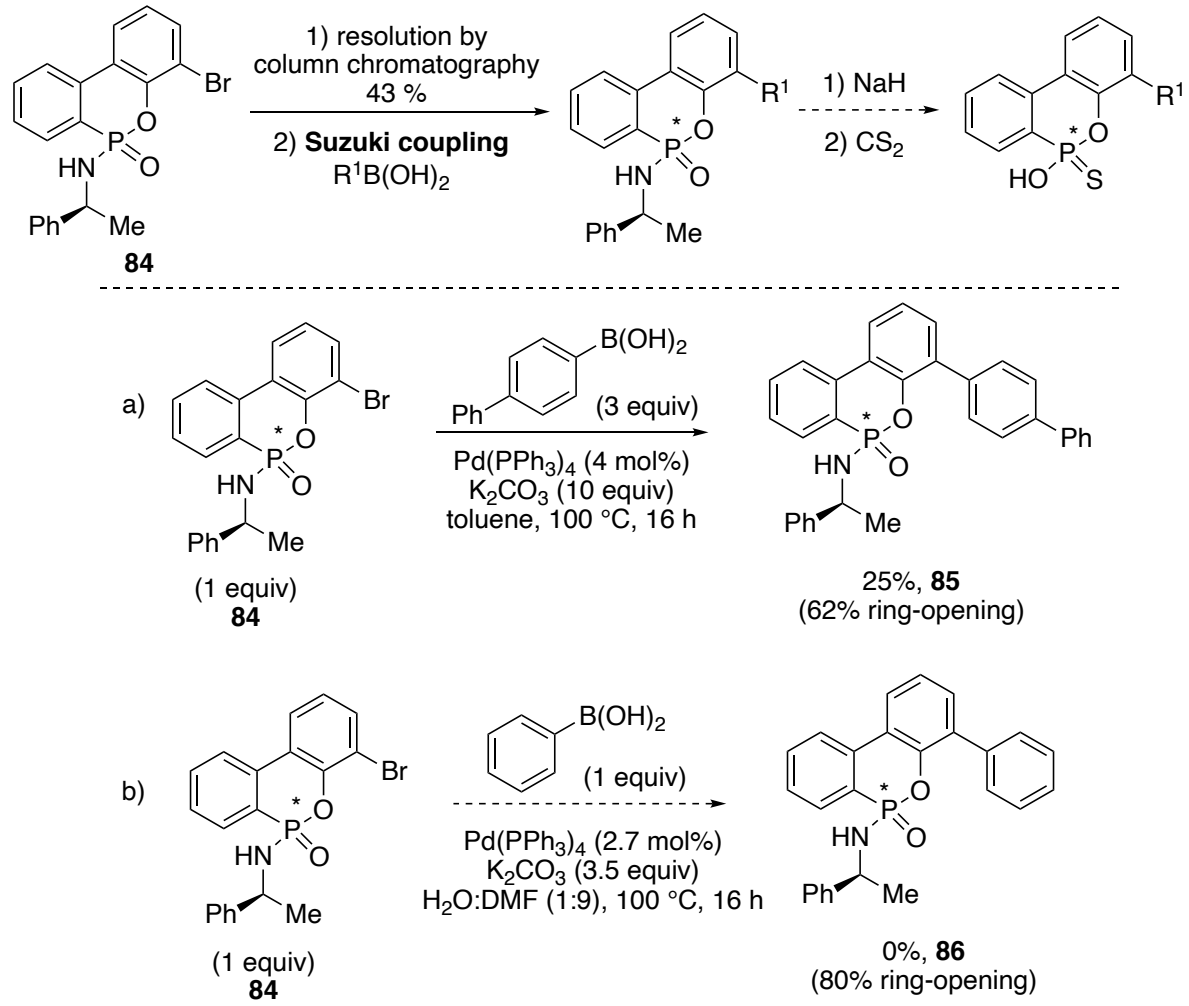
An Atherton-Todd[89] reaction with a chiral amine resulted in the phosphonamide **84** as a mixture of diastereoisomers in 60 % yield (Scheme 4.3). The diastereoisomers could be separated by column chromatography in 43 % yield (hexanes:ethyl acetate 70:30). In principle, the bromo C-8 position would allow for Suzuki couplings with various aromatic groups to functionalize the C-8 position. When attempting this with a biphenylboronic acid, we obtained the desired product **85** in a disappointing 25 % yield with the major product being the ring-opened racemic phosphorus acid (Scheme 4.4, entry a). Similarly, using phenylboronic acid provided only ring-opened product, which demonstrates how labile the P-O bond is with phenol as a good leaving group (Scheme 4.4, entry b).

Scheme 4.3 Atherton-Todd reaction with (*S)*-phenylethylamine



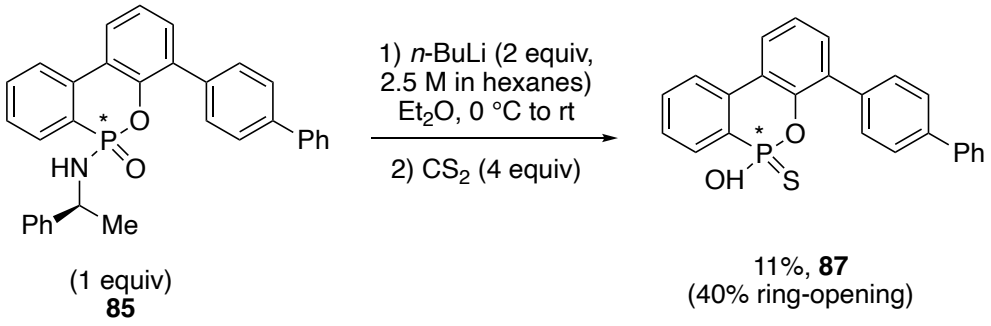
(1 equiv) **83** | 60 %, **84** (43 % resolved yield)

Scheme 4.4 Functionalization of DOPO at the C-8 position *via* Suzuki coupling



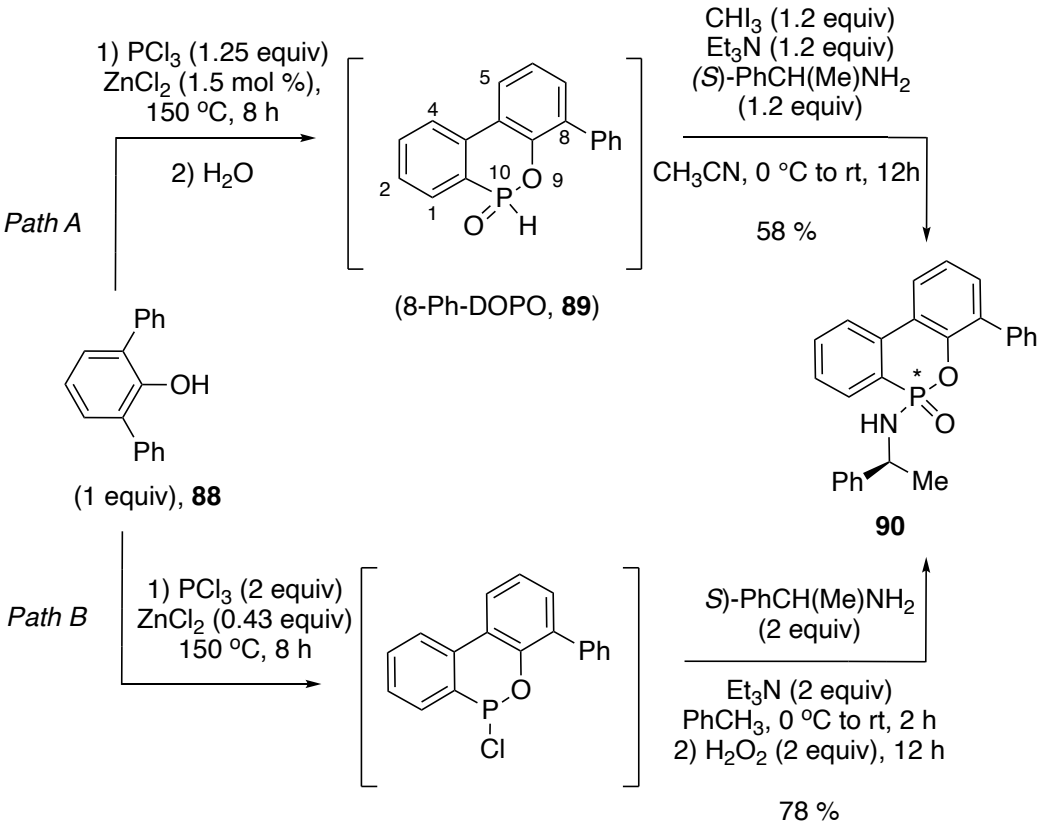
We then proceeded with the Wadsworth-Emmons-Stec reaction on the 8-biphenyl-DOPO **85** (Scheme 4.5). However, this gave ring-opening as the major product with a poor yield of thiophosphorus acid **87**.

Scheme 4.5 Synthesis of 8-biphenyl DOPO *via* the Wadsworth-Emmons-Stec reaction



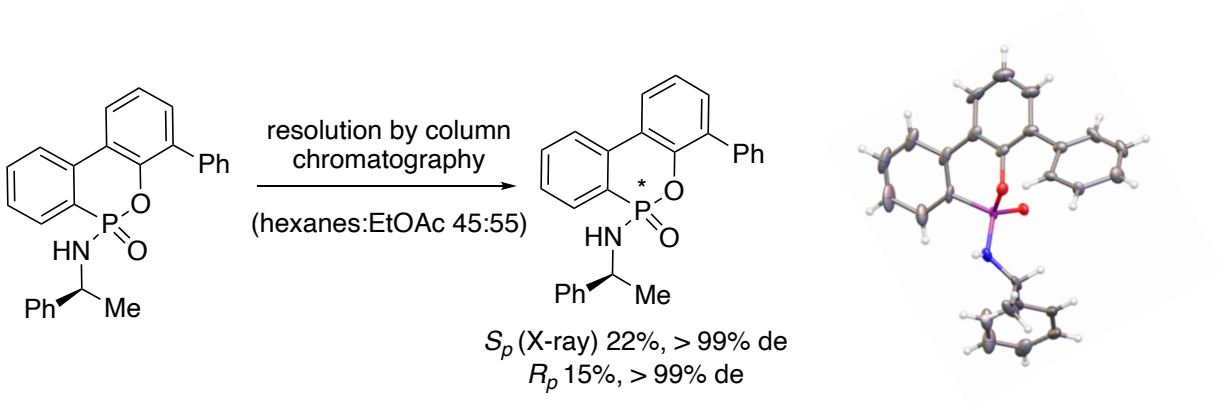
Due to the low yield, we looked for an alternative to 8-bromo DOPO and decided to start directly from commercially available 2,6-biphenylphenol **88**. 8-Phenyl DOPO CPA **41** was synthesized *via* 2 different pathways (Scheme 4.6). Pathway A starts with an electrophilic aromatic substitution with PCl_3, to form the cyclized P(III)-Cl intermediate, which is then hydrolyzed with water leading to the 8-phenyl-DOPO-*H*-phosphinate **89**. This *H*-phosphinate can then react through an Atherton-Todd reaction with iodoform and (*S*)-1-phenylethylamine, to provide the phosphonamide intermediate **90** in an overall 58 % yield. Pathway B begins with an electrophilic aromatic substitution, to form the cyclized P(III)-Cl that is directly substituted with the chiral amine. This P(III)NHR is then oxidized with hydrogen peroxide to form the same phosphonamide intermediate **90** in a 78 % yield after 2 steps, making pathway B the better route.

Scheme 4.6 Synthesis of 8-phenyl DOPO phosphonamide *via* path A or path B



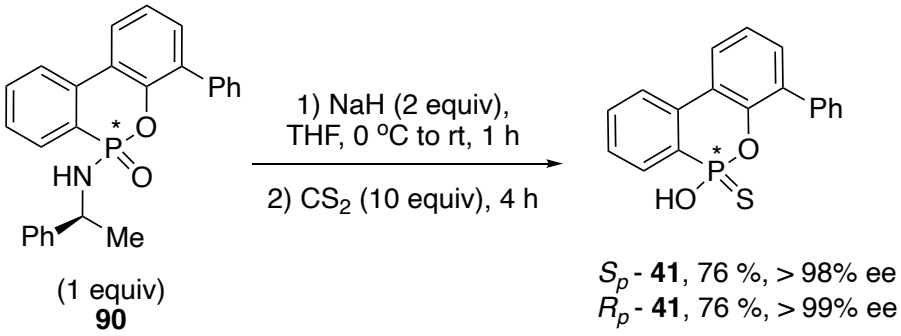
The diastereomers were separated by column chromatography (hexanes:ethyl acetate 45:55), albeit in a low yield, into the enantiopure phosphonamides (Scheme 4.7). The absolute configuration at phosphorus was determined by X-ray crystallography.

Scheme 4.7 Resolution of 8-phenyl DOPO phosphonamide and X-ray structure



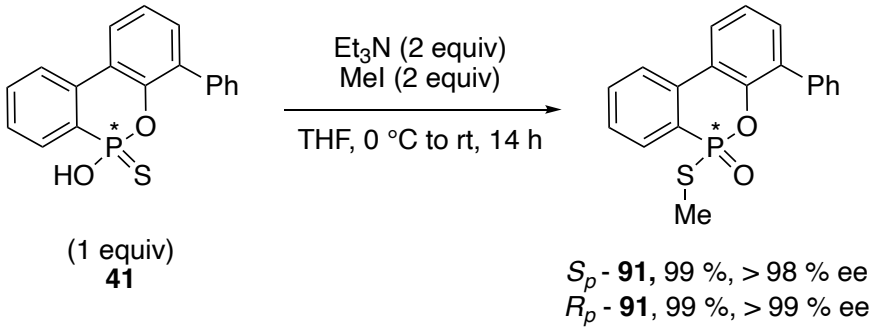
Lastly, the Wadsworth-Emmons-Stec reaction led to the desired thiophosphorus acid **41** (Scheme 4.8). We found that for this scaffold, sodium hydride was the best base to use, to limit the amount of ring-opened product.

Scheme 4.8 Synthesis of 8-phenyl DOPO thiophosphorus acid *via* the Wadsworth-Emmons-Stec reaction



The enantiomeric excess after the Wadsworth-Emmons-Stec reaction was determined via chiral HPLC, by comparing the enantiopure (S_p) and (R_p) thioesters P(O)(SMe) to the racemic P(O)(SMe). Thioester **91** was formed through reacting the thioacid with iodomethane in the presence of Et_3N (Scheme 4.9).

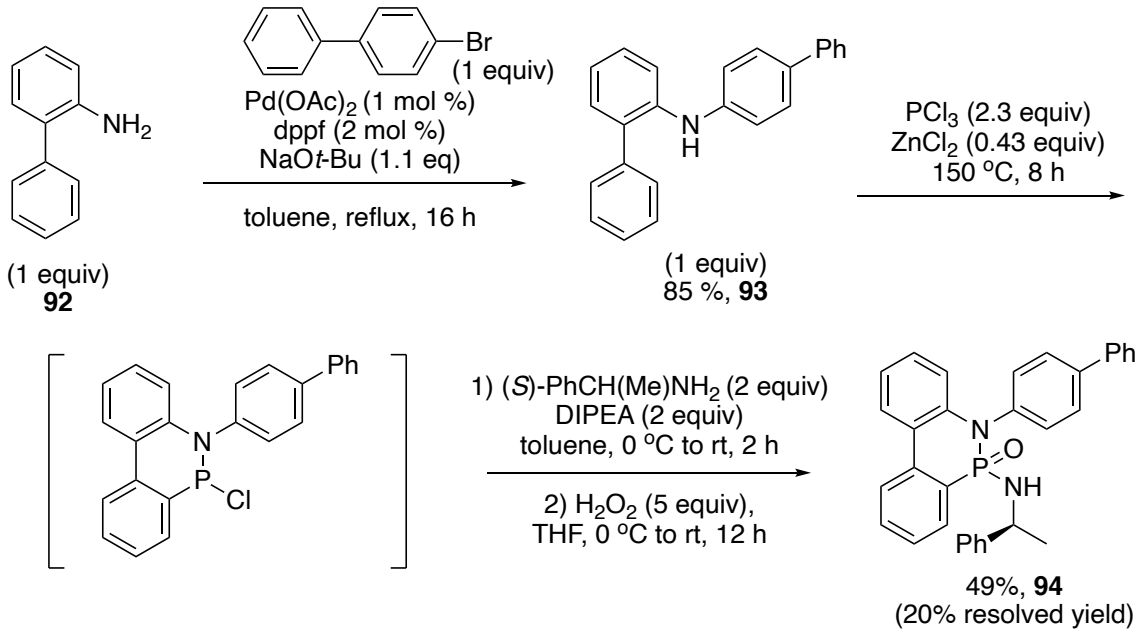
Scheme 4.9 Synthesis of the methyl-thioester from the thioacid for chiral HPLC analysis



4.2 *N*-biphenyl-DOPO *P*-Stereogenic CPA

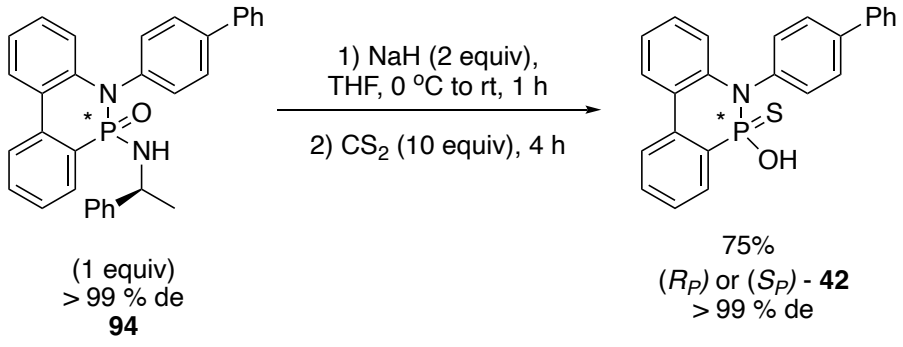
An *N*-DOPO thiophosphorus acid derivative was also synthesized through a similar sequence as the *O*-DOPO to see the influence of the aryl moiety being closer to the chiral center (Scheme 4.10). First, a palladium-catalyzed Buchwald-Hartwig reaction between 2-aminobiphenyl and 4-bromobiphenyl resulted in amine **93** in good yield. This then underwent the same Zn- catalyzed electrophilic aromatic substitution to give the P(III)-Cl, followed by displacement with the chiral amine, and then oxidation of the P(III) to give the P(V) phosphonamide **94** in a moderate yield.

Scheme 4.10 Buchwald-Hartwig coupling followed by EAS and displacement with a chiral amine



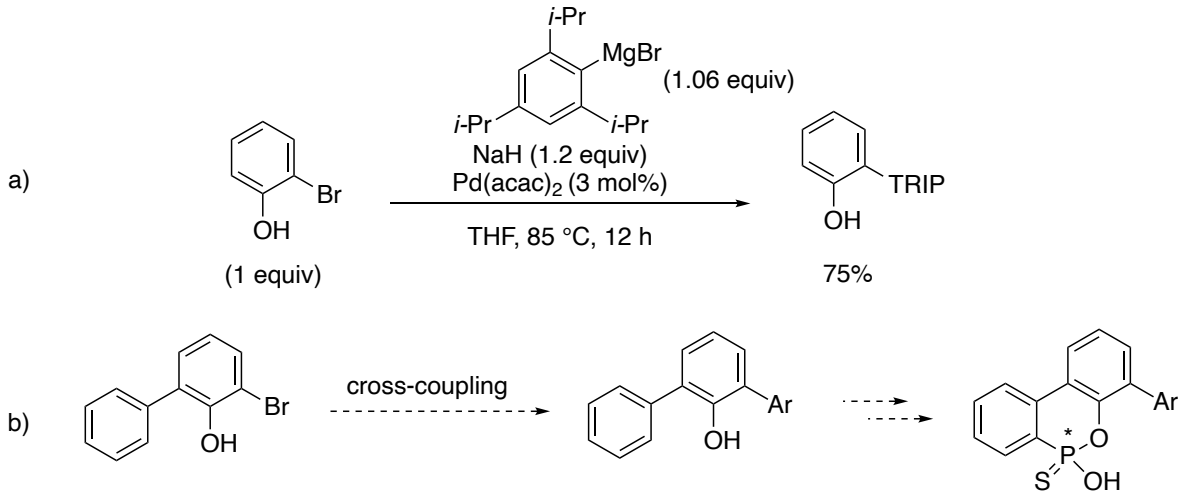
The diastereomers were separated by crystallization (hexanes:ethyl acetate, 0 °C, overnight) to give a 20 % yield of a resolved diastereoisomer, its absolute configuration at phosphorus has not been determined. Lastly, the Wadsworth-Emmons-Stec reaction was employed to give the *N*-biphenyl-DOPO thiophosphorus acid **42** in good yield (Scheme 4.11).

Scheme 4.11 Synthesis of *N*-biphenyl DOPO thiophosphorus acid *via* the Wadsworth-Emmons-Stec reaction



Although some of the yields for the DOPO-derivative CPAs are low, the reactions are unoptimized and the resolution is straightforward. The issues of cost and yield are addressed as the reactions can be done on large scale and in very short sequences. The failed Suzuki coupling may be solved by performing the cross-coupling before introducing the phosphorus. Bae and coworkers reported the synthesis of TRIP-phenol through a palladium-catalyzed Kumada coupling reaction (Scheme 4.12, entry a).[90] This intermediate would be expected to undergo our previously mentioned conditions to introduce the phosphorus, and form the resulting TRIP-DOPO CPA (Scheme 4.12, entry b).

Scheme 4.12 Alternative cross-couplings to the Suzuki coupling to form DOPO derivatives



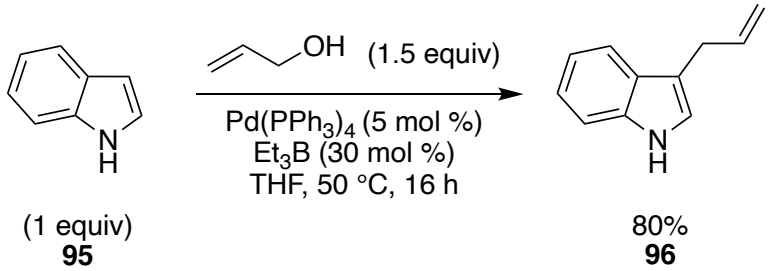
CHAPTER 5

SYNTHESIS OF INDOLE DERIVED CPA

5.1 Indole-derived *P*-Stereogenic CPA

An indole-derived *P*-stereogenic CPA consisting of an all-carbon framework will thus avoid the P-O bond in tryptophol that is sensitive to cleavage (see Chapter 2.2). The synthesis started with a palladium-catalyzed allylation, to give the known allyl indole **96** in good yield (Scheme 5.1).[91] This is followed by a palladium-catalyzed hydrophosphinylation, forming the *H*-phosphinate **97** in moderate 63 % yield (Scheme 5.2).[92, 93] Other conditions, such as Ni-catalyzed[94] or radical initiated hydrophosphinylation[95] were tried but resulted in a lower yield (Scheme 5.3, entries a-d).

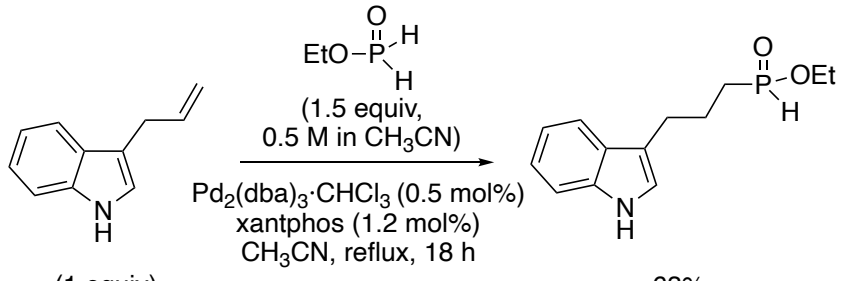
Scheme 5.1 Pd-catalyzed allyl indole synthesis



(1 equiv)
95

80%
96

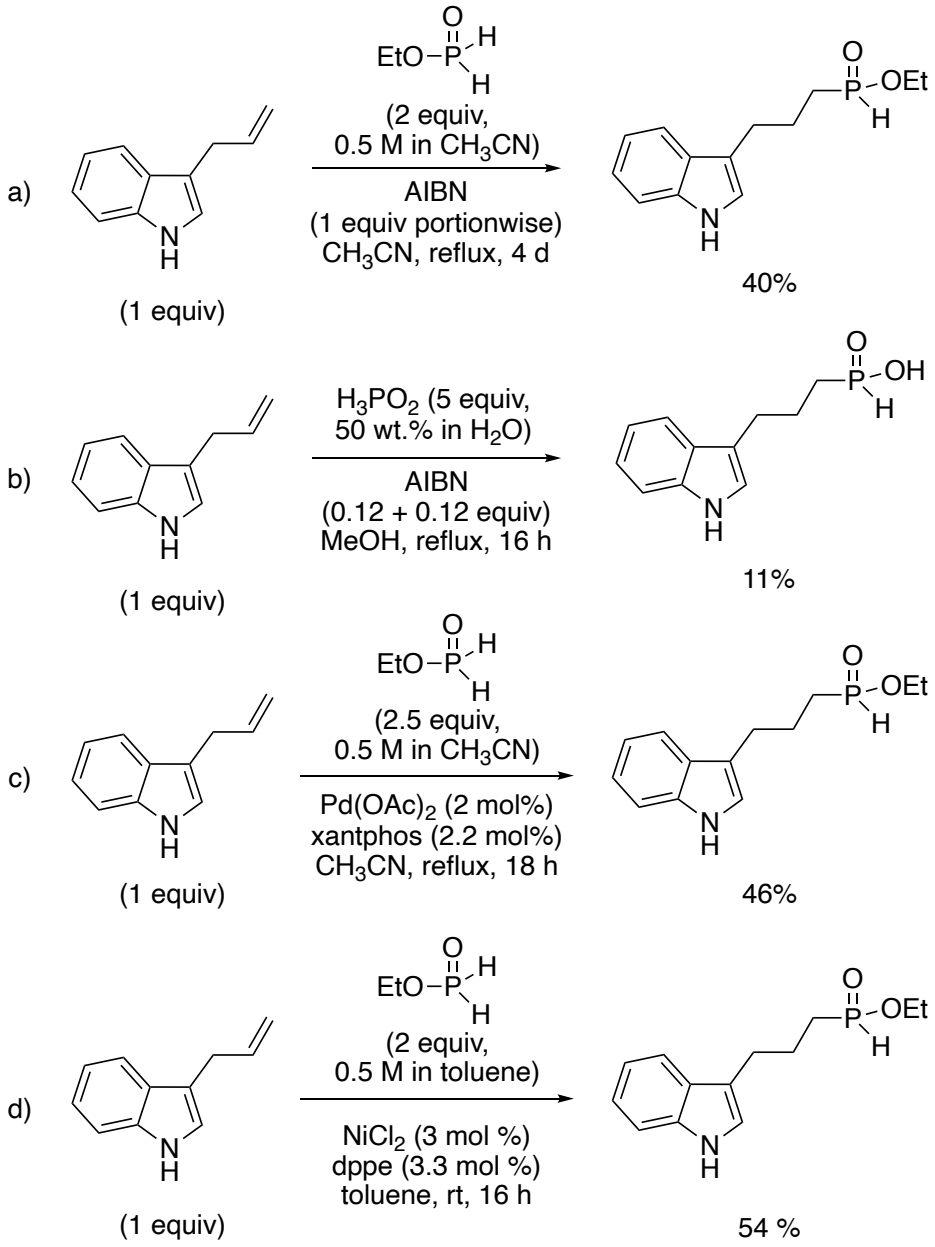
Scheme 5.2 Pd-catalyzed hydrophosphinylation



(1 equiv)
96

63%
97

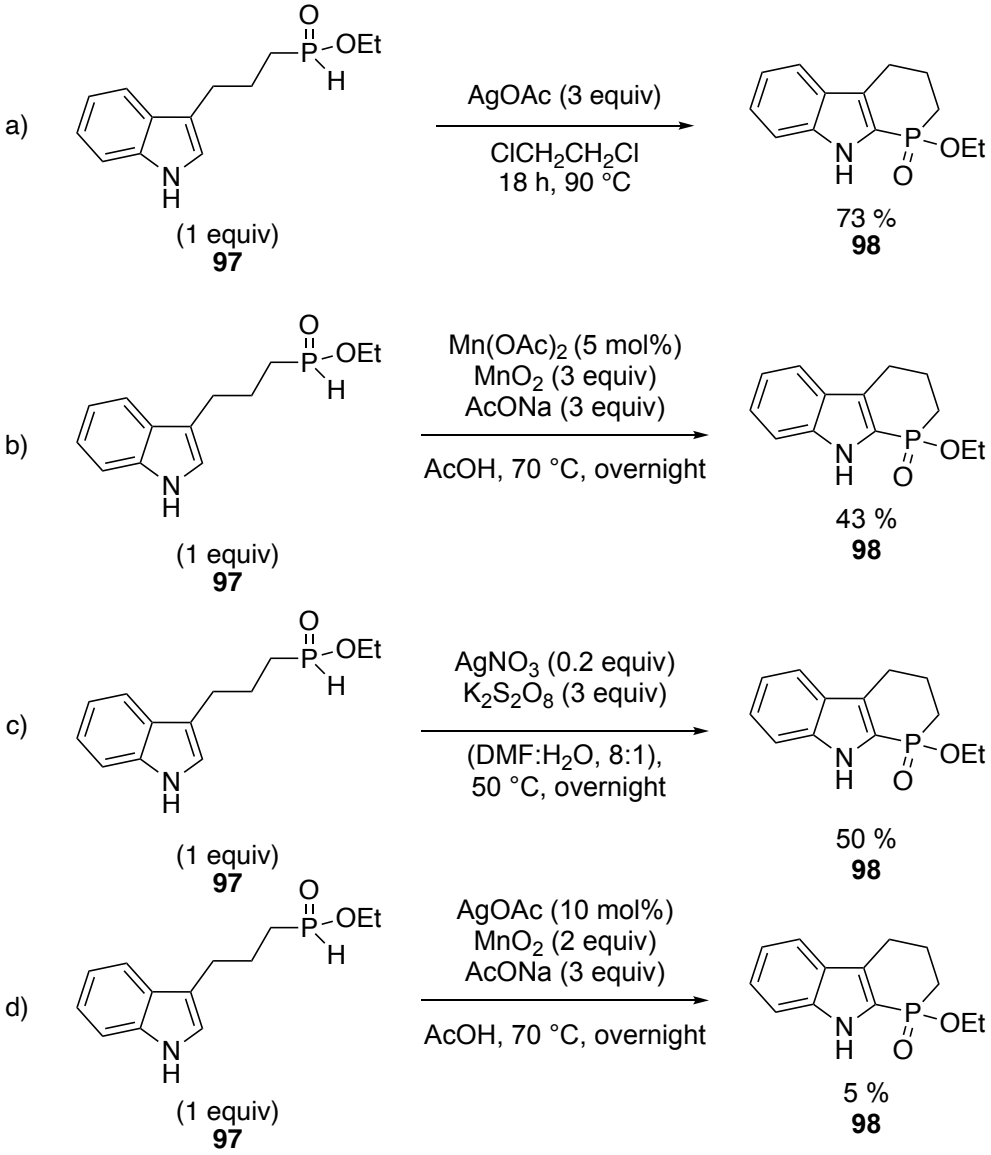
Scheme 5.3 Hydrophosphinylation conditions tested



Next, various free radical homolytic arylation methods were tried. Wan and coworkers reported the direct oxidative C-P bond formation of indoles mediated by silver (I) acetate.[96] We utilized this method on our scaffold which gave the cyclized product **98** in a 73 % yield (Scheme 5.4, entry a)**.** Other oxidation conditions were also tested; however, silver acetate

remained the superior method. The manganese-mediated arylation[48] gave a 43 % yield of cyclized product, silver nitrate[97] resulted in a 50 % yield, and a dual silver acetate/manganese system gave little product (Scheme 5.4, entries b-d).

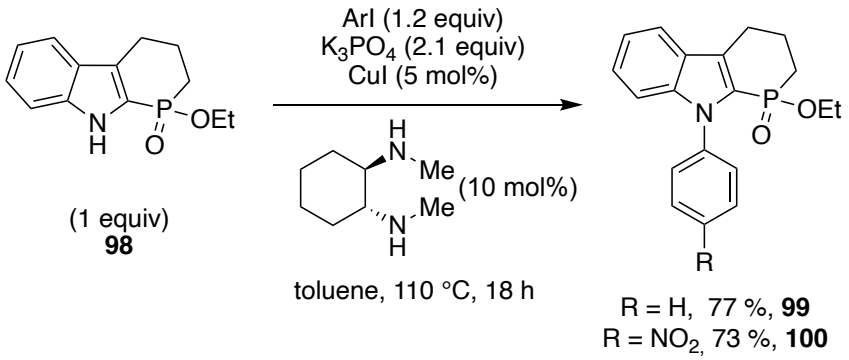
Scheme 5.4 Arylation conditions tested



The aromatic group was introduced through a copper catalyzed Ullman coupling[55] with either iodobenzene or *p*-iodonitrobenzene, to give the *N*-aryl intermediates **99** and **100**

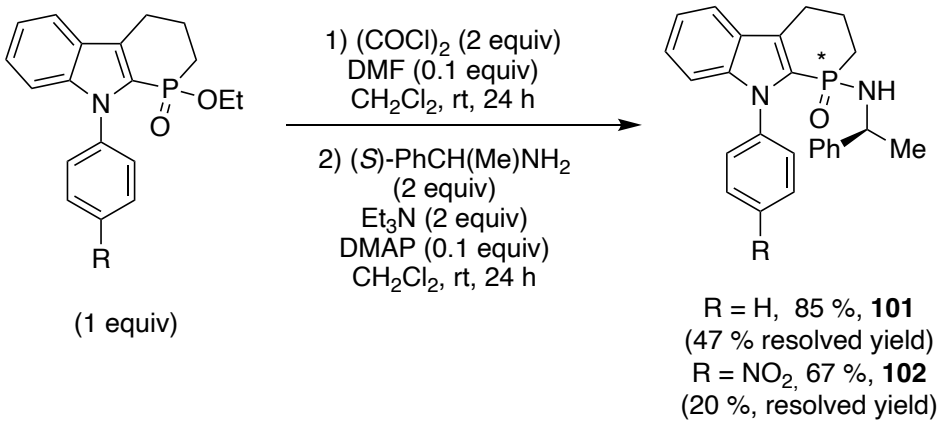
(Scheme 5.5). This reaction was the reason for using an indole scaffold since C-N bonds are easier to form than C-C.

Scheme 5.5 Cu-catalyzed Ullman coupling with iodobenzene or *p*-iodonitrobenzene



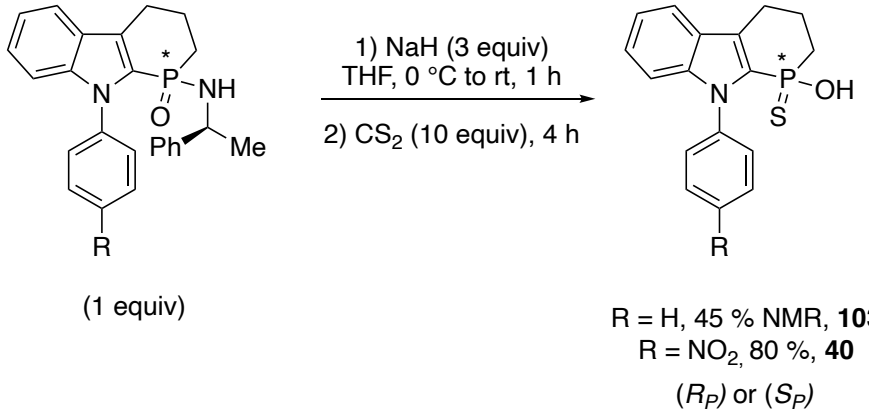
Next, the diastereomeric phosphonamide was formed as usual by reacting (*S)*-phenylethyl amine and P-Cl generated *in situ* from oxalyl chloride, to give the phosphonamide mixture in good yield (R = H, 85 %; R = NO_2, 67 %). The diastereoisomers were separated by column chromatography (hexanes:ethyl acetate 50:50 to 10:90) in a 47 % or 20 % resolved yield, for R = H or NO_2 respectively.

Scheme 5.6 Synthesis of phosphonamide through forming the P(O)Cl



Finally, the Wadsworth-Emmons-Stec reaction was utilized to synthesize the thiophosphorus acid (Scheme 5.7). When R = NO_2, the reaction proceeds to form the *N*-(*p*-nitrophenyl) thiophosphoric acid **40** in good yield. This was not the case when R = H and resulted in the thiophosphoric acid **103** in a low yield (45 % by ^{31}P NMR). Moreover, the product was not acceptably pure after an extractive workup, and crystallization would be needed to remove the impurities.

Scheme 5.7 Synthesis of indole thiophosphorus acid *via* the Wadsworth-Emmons-Stec reaction

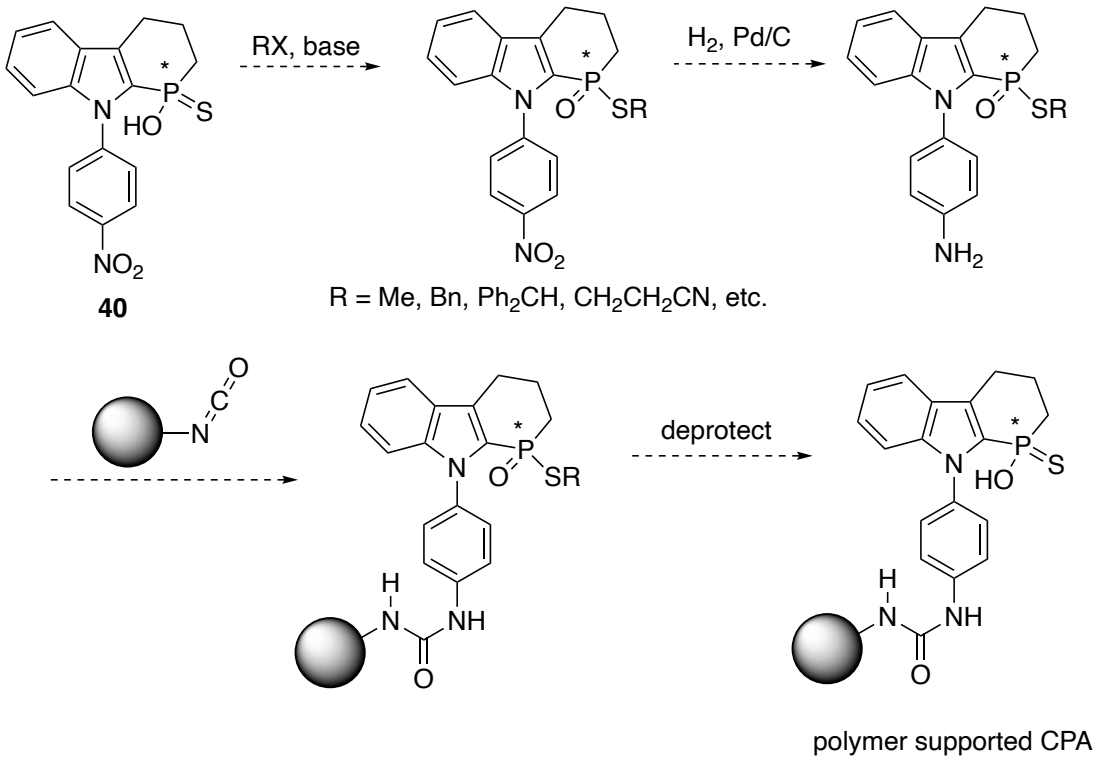


(1 equiv)

R = H, 45 % NMR, **103**
R = NO_2, 80 %, **40**
(R_P) or (S_P)

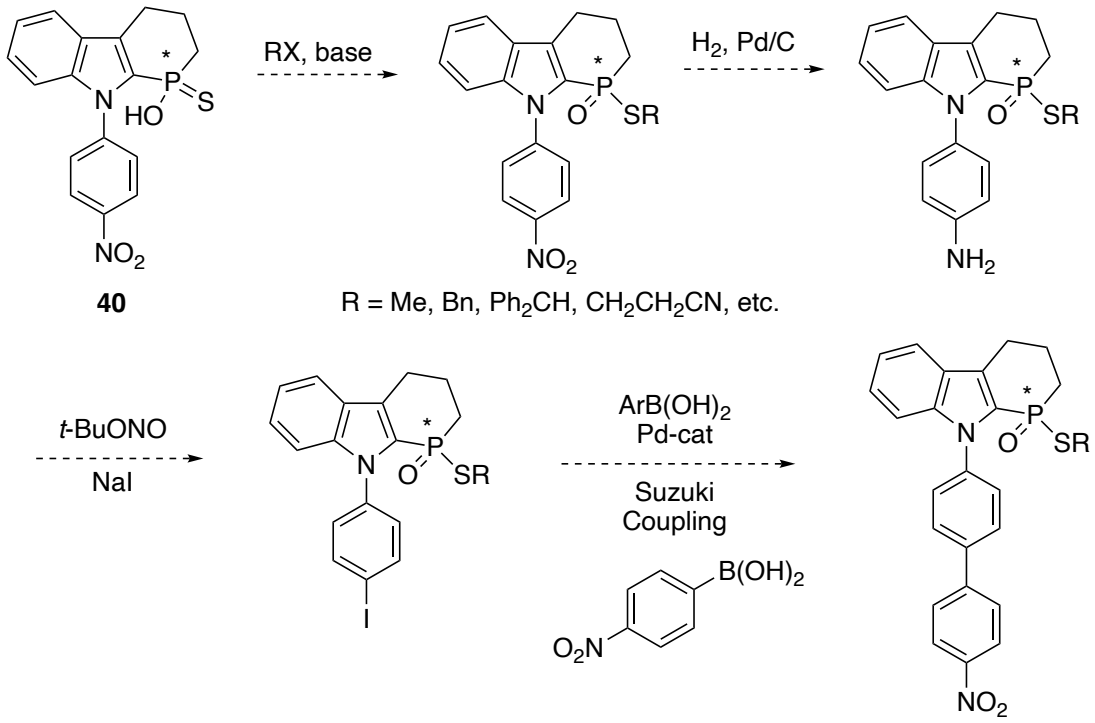
One of our CPA requirements presented in Chapter 1.5 was to have a possibility for immobilization on solid support. The NO_2- group on the catalyst scaffold can be used as a handle for polymer support. This can be done using our indole catalyst by first protecting the acid functionality, then reducing the nitro group to the amine, which can then be attached to an isocyanate polymer for example (Scheme 5.8). Thereby making scalability, recycling and catalyst loadings less of an issue.

Scheme 5.8 Proposed attachment to a polymer support



The nitro group also allows for the potential to derivatize and extend the aryl group on the nitrogen. For example, the indole CPA could undergo a Sandmeyer reaction[98] to form the iodobenzene, which is a precursor for a Suzuki coupling with various aryl boronic acids (Scheme 5.9).

Scheme 5.9 Proposed extension of aryl group via Suzuki coupling



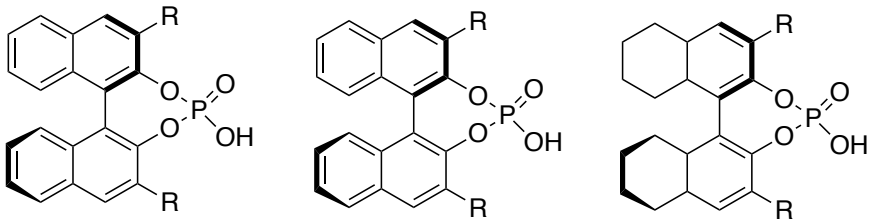
CHAPTER 6

EVALUATION OF *P*-STEREOGENIC CHIRAL PHOSPHORUS ACIDS

6.1 Allylation of Aldehydes

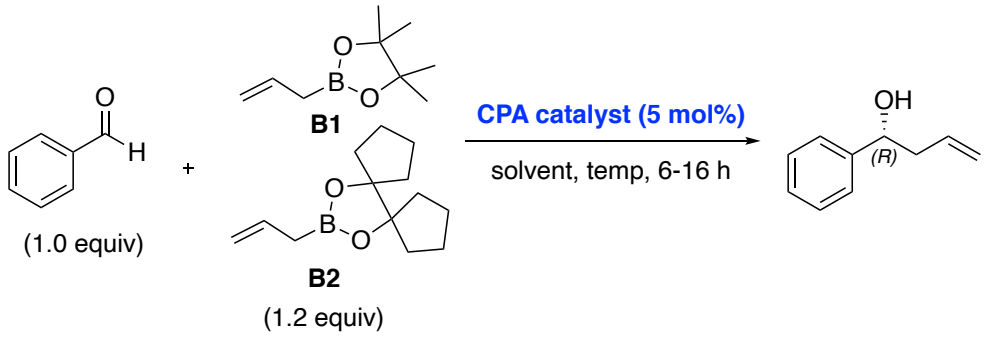
Antilla and coworkers recently reported a CPA-catalyzed allylation reaction of benzaldehyde, to generate enantioenriched homoallylic alcohols (Table 6.1).[99] We chose this reaction for two main reasons: 1) chiral alcohols are useful products and 2) Antilla reports a wide scope of CPAs tested (Scheme 6.1), that resulted in a wide range of *ee's*, thus emphasizing how the various R groups on the BINOL framework have a heavy influence on this selectivity. For example, when R = 4-(β-Naphthyl) there is no selectivity; but when R = $(2,4,6\text{-iPr})_3\text{-}C_6H_2$, they were able to achieve a high selectivity up to >99 % *ee* in toluene or cyclohexane (Table 6.1, entry 2, 15-16). The allylation presumably occurs through a heterotrimer between the catalyst, nucleophile, and electrophile (Scheme 6.2). There is an H-bonding effect between the aldehyde and the acidic hydrogen on the CPA, as well as a Lewis base/Lewis acid interaction of the phosphoryl oxygen with the boronate. Antilla and coworkers also state the importance of the steric interactions of the boronate backbone and the CPA, as the *ee*'s decrease when changing the boronate from a larger to smaller boronate ester group (B2 vs B1, Table 6.1 entry 9 vs 12).

Scheme 6.1 BINOL- catalysts tested by Antilla and coworkers[99]



a R = $SiPh_3$
b R = 4-(β-Naphthyl)
c R = 9-anthryl
d R = 4-(α-Napthyl)
e R = (2,4,6-*i*Pr)$_3$-C_6H_2
f R = (2,5-CF_3)$_2$-C_6H_2
g R = (2,4,6-*i*Pr)$_3$-C_6H_2
h R = (2,4,6-*i*Pr)$_3$$C_6H_2$
i R = (2,4,6-cyclohexyl)$_3$-C_6H_2

Table 6.1 CPA-catalyzed allylation of aldehydes with boronates reported by Antilla and coworkers[99]

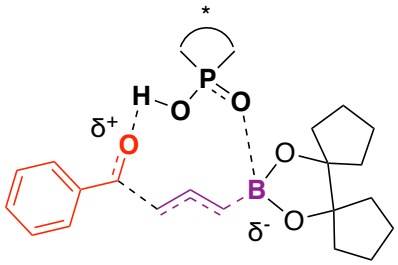


Entry	Catalyst	Boronate	Solvent/temp	% Yield	ee %[a]
1	**a**	B1	toluene, rt, 16h	100	11
2	**b**	B1	toluene, rt, 16h	100	0
3	**c**	B1	toluene, rt, 16h	100	70
4	**d**	B1	toluene, rt, 16h	100	36
5	**e**	B1	toluene, rt, 16h	100	94
6	**f**	B1	toluene, rt, 16h	100	8
7	**g**	B1	toluene, rt, 16h	100	80

8	**h**	B1	toluene, rt, 16h	100	88
9	**e**	B1	cyclohexane, rt, 6h	100	93
10	**i**	B1	cyclohexane, rt, 6h	100	93
11	**i**	B2	cyclohexane, rt, 6h	100	94
12	**e**	B2	cyclohexane, rt, 6h	100	99
13	**i**	B2	cyclohexane, rt, 6h	100	94
14	**h**	B2	cyclohexane, rt, 6h	100	77
15	**e**	**B2**	**cyclohexane, rt, 6h**	**100**	**>99**
16	**e**	**B2**	**toluene, - 30 °C, 6h**	**100**	**>99**

[a] Enantiomeric excess was determined by HPLC with a Chiracel OD-H column (hexane/iPrOH = 99/1, 0.7 min/mL)

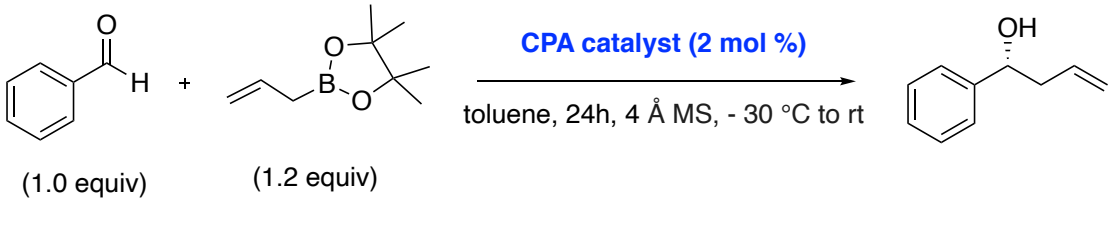
Scheme 6.2 Our proposed CPA bifunctional activation of benzaldehyde and allylboronate

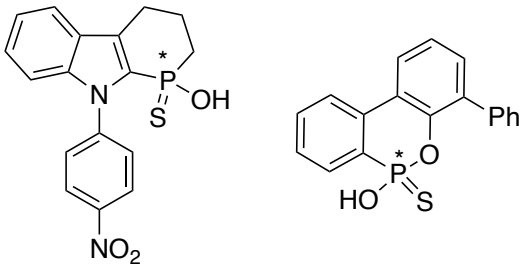


After running the allylation with the *P*-stereogenic CPAs **40 - 42**, and running the chiral HPLC assay, poor enantioselectivity was observed (Table 6.2). We hypothesized that the reason why the enantioselectivity was poor, was because the heterotrimer between the catalyst, nucleophile, and electrophile, could not form in this case. Since the sulfur is not a good Lewis base, there was no, or little, interaction between the sulfur and boronate, due to sulfur being less electronegative than oxygen (2.4 and 3.5, respectively). The reaction time was also slower

in our case, taking 24 hours for full conversion, as opposed to Antilla's 6-hour reaction time. This points toward activation of only the carbonyl through hydrogen bonding of the acid. Therefore, we concluded that a bidentate mode or bifunctional activation mode is needed in this particular reaction. We also found that the reaction proceeds in the absence of a catalyst, over a longer reaction time (Table 6.2, entry 4). This may mean our catalysts had little to no interaction with the substrates.

Table 6.2 Chiral assay results of *P*-stereogenic CPA-catalyzed allylation of aldehydes





40 **41** **42**

Entry	Catalyst	% Yield	ee %[a]
1	**40**	90	8
2	**41**	95	4
3	**42**	95	4
4	-	90[b]	-

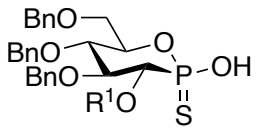
[a] Enantiomeric excess was determined by HPLC with a Chiracel OD-H column (hexane/iPrOH = 99/1, 0.7 min/mL); [b] reaction time was 6 d at rt

6.2 Hydrogen Transfer of Quinolines

Guinchard reported thiophosphonic acid catalysts possessing both a chiral backbone and a chiral phosphorus functionality, as described previously in Section 1.4 (Scheme 6.3).[35] The influence of *P*-stereogenic CPAs was evaluated in the hydrogen transfer hydrogenation of 2-phenylquinoline with Hantzch esters (Table 6.3). This test reaction was chosen because Guinchard used thiophosphorus acid catalysts.

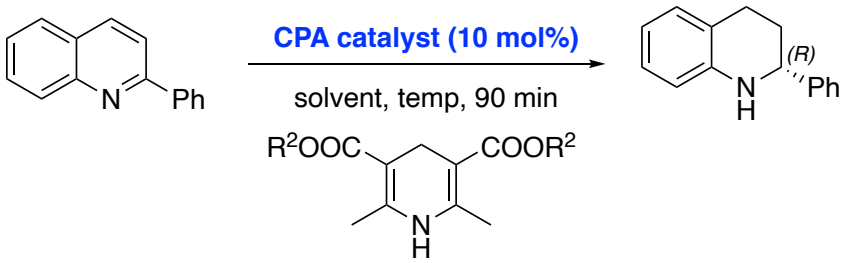
Guinchard found that the reduction when R^1 = H gave the highest yield, but with no enantioselectivity (Table 6.3, entry 2). However, when R^1 is an acetate, 3-methylbutanoate, xanthate, or a carbamate group, the *ee*'s improved slightly (Table 6.3, entries 3-5). Overall, the pivaloyl group resulted in the highest *ee* of 52 % (Table 6.3, entry 6). The influence of the ester group on the Hantzch reductant was also evaluated (Table 6.3, entry 6-8), with *tert*-butyl esters giving the best enantioselectivity. Cyclopentyl methyl ether (CPME) as the solvent, was also found to be the best when at room temperature (Table 6.3, entry 14). Under optimal conditions the best *ee* was 68 %. The stereochemistry of the final product was attributed to the transition state described in Scheme 1.21.

Scheme 6.3 *P*-stereogenic catalysts tested by Guinchard et. al.[35]



a R_1 = H
b R_1 = Ac
c R^1 = C(O)*i*Bu
d R^1 = C(S)SMe
e R^1 = C(O)NH*t*Bu
f R^1= Piv

Table 6.3 CPA-catalyzed transfer hydrogenation of 2-phenylquinoline reported by Guinchard

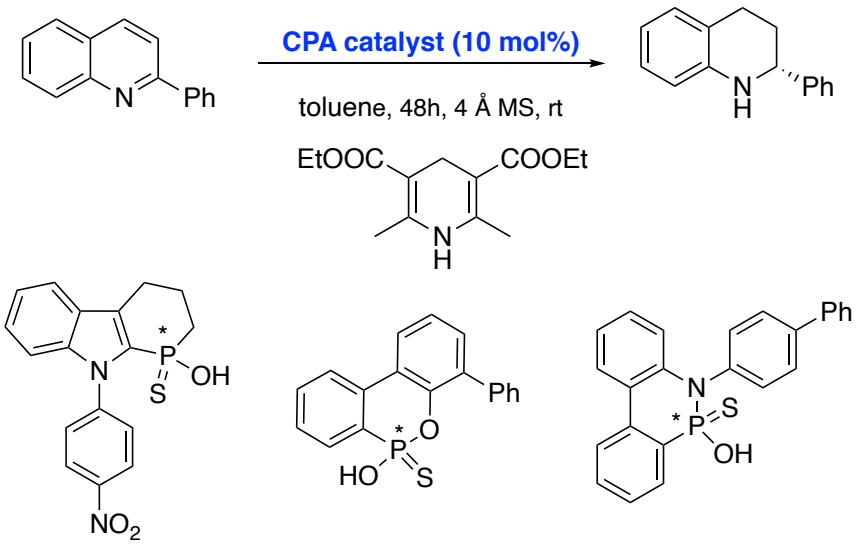


Entry	Catalyst	R^2	Solvent/temp	% Yield	ee %[a]
1	**a**	Et	toluene, 60 °C	83	1
2	**b**	Et	toluene, 60 °C	80	40
3	**c**	Et	toluene, 60 °C	62	38
4	**d**	Et	toluene, 60 °C	73	40
5	**e**	Et	toluene, 60 °C	67	41
6	**f**	Et	toluene, 60 °C	86	52
7	**f**	Me	toluene, 60 °C	90	45
8	**f**	*t*Bu	toluene, 60 °C	89	59
9	**f**	*t*Bu	cyclohexane, 60 °C	89	65
10	**f**	*t*Bu	Et_2O, 22 °C	99	66
11	**f**	*t*Bu	CPME, 60 °C	97	55
12	**f**	*t*Bu	CPME, 22 °C	97	67
13	**f**	*t*Bu	CPME, -4 °C	80	62
14	**f**	***t*Bu**	**CPME, 22 °C**	**82**	**68**
15	**f**	*t*Bu	CPME, 22 °C	98	5

[a] Enantiomeric excess was determined by HPLC with a Chiralpak IB column (hexane/iPrOH = 95/5, 1 min/mL, 30 °C)

In our chiral assay, catalyst **41** gave an enantioselectivity of 30% *ee*, whilst CPA **40** and **42** showed marginal results (Table 6.4). Since the DOPO catalyst gave the best enantioselectivity, it can be reasoned a phenyl group further away from the acidic site (3 bond lengths away from the phosphorus atom instead of 2 for **40**, and 1 for **41**) might be needed for better selectivity. From these two tests, we concluded that overall, the versatile nature of the catalysts is not solely due to their Brønsted acidity, and more often, additional modes of activation are needed.

Table 6.4 *P*-stereogenic CPAs in the hydrogen transfer of quinolines



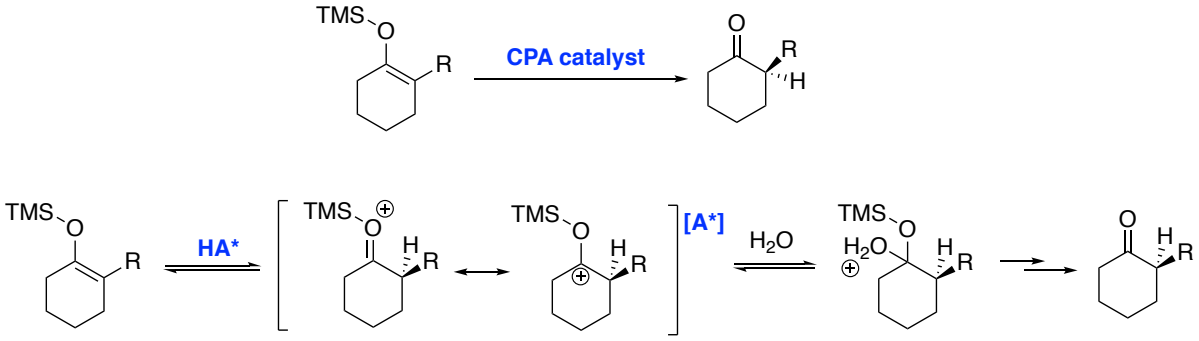
40 **41** **42**

Entry	Catalyst	% Yield	ee %[a]
1	**40**	90	10
2	**41**	95	30
3	**42**	95	2

[a] Enantiomeric excess was determined by HPLC with a Chiracel OD-H column (hexane/iPrOH = 95/5, 1 min/mL)

Perhaps using a test reaction that does not require dual activation from the catalyst could provide better results with our CPAs. For example, Yamamoto and coworkers reported the first enantioselective BINOL-catalyzed protonation reaction of silyl enol ethers.[30] In principle, this would not require a Brønsted basic site, as this mechanism likely proceeds through protonation of the α-carbon, which then tautomerizes from the enol to the ketone product (Scheme 6.4).

Scheme 6.4 Protonation of silyl enol ether with CPA catalyst

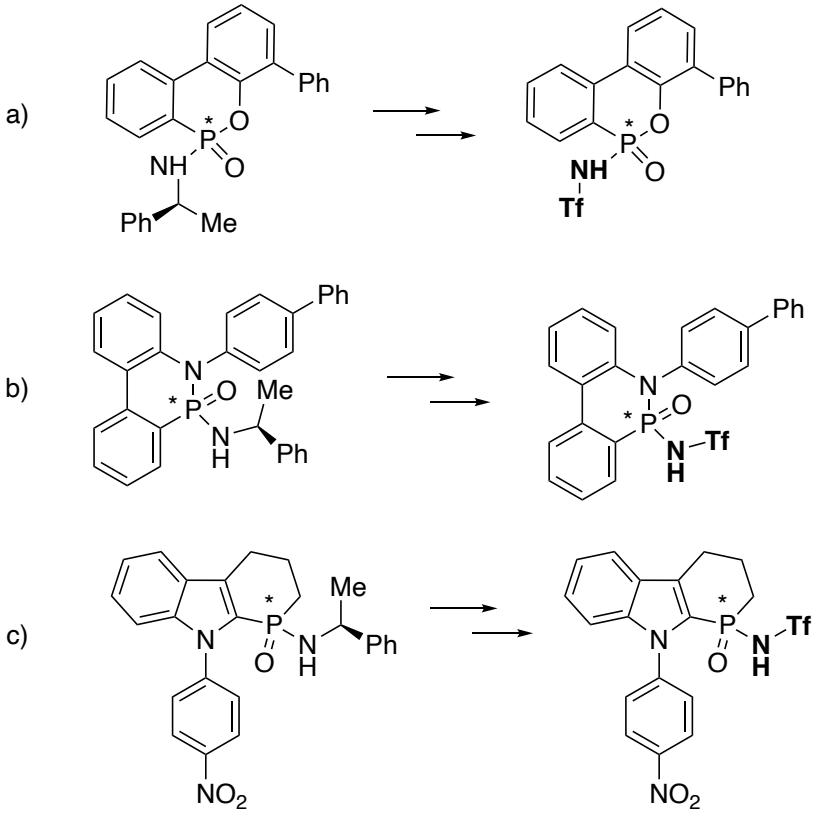


6.3 Restoring a Bidentate Mode to Rescue our CPAs

Another solution to rescue our CPAs is to introduce a second binding site to act as a Brønsted basic site into our catalyst design, *N*-sulfonylphosphoramide catalysts could be synthesized (Scheme 6.5). Phosphoramides have shown themselves to be equally powerful catalysts.[100, 101] They were first introduced by Yamamoto and coworkers with an *N*-triflyl group in the BINOL phosphate framework, and keeping oxygen instead of sulfur.[28] Thus introducing this sulfonyl group into our catalyst design, might solve the issue of dual activation, by containing an oxygen atom that is available to participate and H-bonding, while maintaining appropriate acidity. In principle this can be done through any of our

phosphonamide precursors, by reducing the benzylamine to the primary amine, followed by reacting with triflic anhydride, or going from the acid through the chloride and reacting with triflic amide.

Scheme 6.5 Proposed *N*-triflylphosphoramide *P*-stereogenic CPAs



In conclusion, despite the disappointing results of the chiral assays, there are still many possibilities to explore. We have developed several chiral catalyst platforms that can be derivatized into other phosphorus acids or phosphines. Through the synthesis of these platforms, we have learned a lot about different thiophosphorus acid methodologies, including the powerful transformation of the Wadsworth−Emmons−Stec reaction to synthesize chiral thiophosphorus acids. Chiral phosphorus acids have been employed in numerous

transformations, and instead of screening reactions for which our catalysts might give good results, we hope to determine a general catalyst that is successful in numerous organocatalytic transformations. The investigation of our CPAs is still underway, and we still believe they have the potential to become all-around superior catalysts.

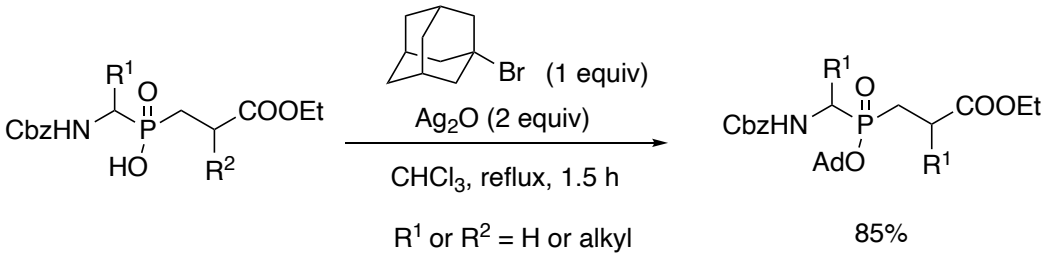
CHAPTER 7

SYNTHESIS OF ADAMANTYL *H*-PHOSPHINATE ESTERS

7.1 Adamantyl *H*-Phosphinate Esters as Precursors to *P*-Stereogenic Compounds

1-Adamantyl phosphinate esters were introduced by Yiotakis et al. in 1996, as a protecting group of the hydroxyphosphinyl functionality in disubstituted phosphinic acids $R^1R^2P(O)(OH)$.[102] 1-Adamantyl is a tertiary system that reacts through an S_N1 mechanism. Yiotakis and coworkers utilized adamantyl esters for the solid-phase synthesis of phosphinopeptides, since they are completely stable to the basic conditions required to remove the Fmoc group, and can be cleaved under relatively mild acidic conditions.[102] Their reported peptide analog synthesis used Ag_2O to form the silver salt, which reacts with 1-adamantyl bromide to generate the adamantyl ester (Scheme 7.1).

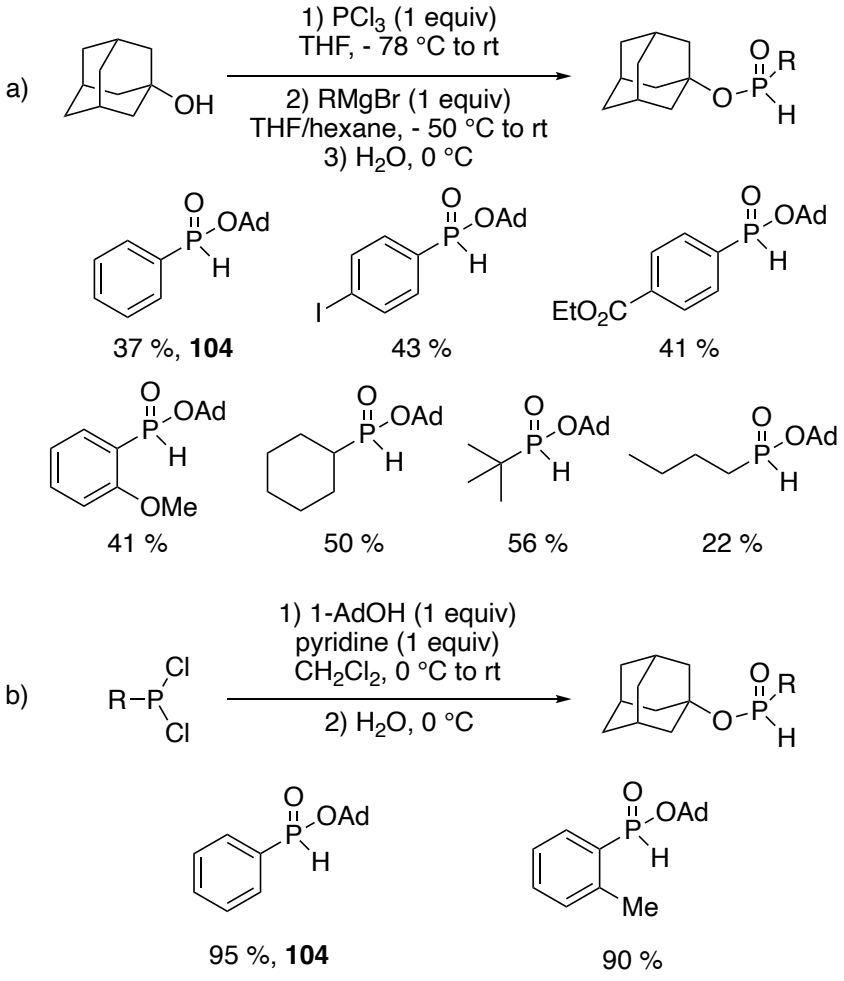
Scheme 7.1 Esterification of a peptide analog using 1-AdBr and Ag_2O reported by Yiotakis and coworkers



In 2015, Leclaire, Giordano, and coworkers introduced adamantyl *H*-phosphinate esters $R^1P(O)(OAd)H$ for use in *P*-stereogenic synthesis.[103] Eight racemic adamantyl *H*-phosphinates were prepared by one of two methods: either 1) displacement of $AdOPCl_2$ (itself made from PCl_3) with a Grignard reagent and hydrolysis, to produce the esters in low to moderate yields (Scheme 7.2, entry a), or 2) reaction of a dichlorophosphine $RPCl_2$ with 1-

adamantanol and hydrolysis (Scheme 7.2, entry b). The latter method results in excellent yields, however, is limited by the availability of the dichlorophosphine starting materials. The enantiomeric esters were resolved by semi-preparative chiral HPLC (Lux Cellulose-2 column) to obtain enantiopure *H*-phosphinates, which could then be elaborated into various *P*-stereogenic compounds.

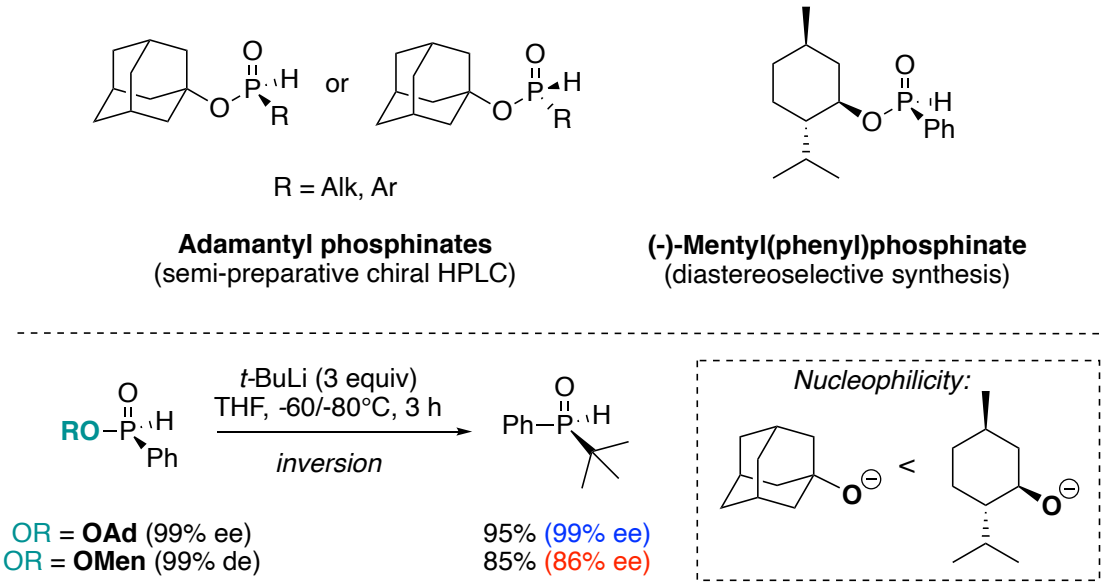
Scheme 7.2 Synthesis of adamantyl *H*-phosphinates reported by Leclaire, Giordano, and coworkers.



Leclaire, Giordano, and coworkers also examined the conversion of *H*-adamantylphosphinates into secondary phosphine oxides (SPOs) through nucleophilic addition

of an organometallic reagent. Interestingly, the displacement of adamantyl phenyl-*H*-phosphinate **104** with *t*-BuLi, resulted in significantly higher enantioselectivities than the menthyl-*H*-phosphinate equivalent (Scheme 7.3). This is due to the reduced nucleophilicity of the adamantoxide compared to the menthoxide anion, meaning substitution of an adamantyloxy group on the deprotonated phosphinate proceeds more rapidly than its racemization. In the case of the menthyl, the loss of optical purity is due to a competitive nucleophilic substitution of the menthoxide that is in the reaction medium. Therefore, using a sterically hindered tertiary alcohol, such as adamantyl, as a leaving group minimizes this competitive substitution process.

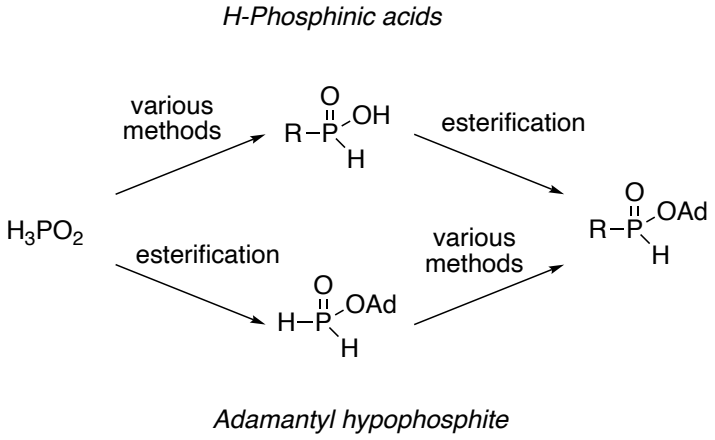
Scheme 7.3 *O*-(-)-Menthylphosphinate versus *O*-adamantyl phosphinate in the stereoselective addition of *t*-BuLi.



7.2 Synthesis of Adamantyl *H*-Phosphinate Esters

Our research began by exploring alternative synthetic methods to ones presented in Section 7.1, as the synthesis is limited in terms of available reagents and the low to moderate yields. We investigated alternatives to the synthesis of adamantyl *H*-phosphinates through either the esterification of *H*-phosphinic acids or through forming the novel adamantyl hypophosphite as an intermediate (Scheme 7.4).[104]

Scheme 7.4 Approaches to adamantyl *H*-phosphinates

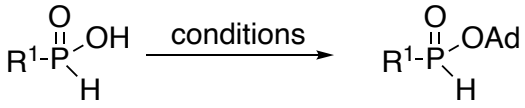


We started by exploring the esterification scope of *H*-phosphinic acids and the results are collected in Table 7.1. The first method we considered was reacting silver oxide/1-bromoadamantane with PhP(O)(OH)H since it is similar to Yiotakis' conditions (Scheme 7.1)[102] and a single example of patented conditions (1-bromo-3,5-dimethyladamantane, Ag_2O, $CHCl_3$, reflux, no yield reported).[105] As shown in Table 7.1 entries 1 vs. 2, the use of a slight excess of PhP(O)(OH)H compared to 1-bromoadamantane, and Ag_2O gave a better yield of **104**, but overall the yield was still moderate. Alternative esterification conditions were tested with 1-adamantanol as the reactant. EDC gave a moderate 72 % yield of product (Table 7.1,

entry 4). Next, pivaloyl chloride was tested and found to be a good reagent (Table 7.1, entries 6, 11, and 13-15), giving an excellent yield on multigram scales (Table 7.1 entry 6b). It was found that excess adamantanol was difficult to remove and required chromatography. By using adamantanol as the limiting reagent, a good yield of product was obtained, and the crude product was sufficiently pure to not require chromatographic purification (Table 7.1 entry 6b vs. 5). Next, 1-propanephosphonic acid cyclic anhydride (T3P) gave a good yield (Table 7.1, entry 7, 10, and 12), without the need for chromatographic purification in certain cases, even on a large 48 mmol scale (Table 7.1, 7b).

The esterification of a trityl *H*-phosphinic acid was also tried under the PivCl reaction conditions and resulted in an 88 % yield by ^{31}P-NMR (Table 7.1, entry 8). However, the product quickly decomposed. Similarly, the esterification of a hydroxymethyl phosphinic acid completely failed, which was likely due to byproducts in the starting material (Table 7.1, entry 9).[106] Overall, both T3P and PivCl were found to be the best methods to form adamantyl esters due to the high yields and satisfactory purity after workup.

Table 7.1 Esterification of $R^1P(O)OHH$ to $R^1P(O)(OAd)H$



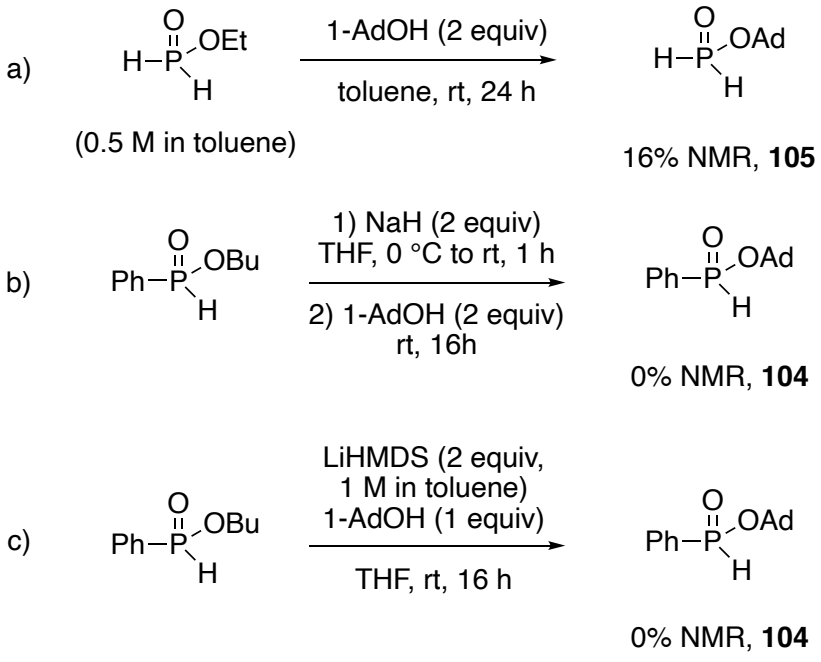
Entry	R^1	Conditions	Yield (%)[a]
1	Ph	$R^1PO_2H_2$ (1 equiv), AdBr (2.4 equiv), $CHCl_3$, brought to reflux, Ag_2O (2.4 equiv) added portion-wise, refluxed for 2 h	42
2	Ph	$R^1PO_2H_2$ (1.2 equiv), AdBr (1 equiv), $CHCl_3$, Ag_2O (1 equiv) added portion-wise, rt, 2 h	56

3	Ph	$R^1PO_2H_2$ (1 equiv), AdOH (1 equiv), EDC (1.5 equiv), DMAP (0.1 equiv), DCM, 0 °C to rt, 16 h	55
4	Ph	$R^1PO_2H_2$ (1.1 equiv), AdOH (1.8 equiv), EDC (1.5 equiv), DMAP (0.1 equiv), DCM, 0 °C to rt, overnight	72
5	Ph	$R^1PO_2H_2$ (1 equiv), PivCl (1.5 equiv), Pyr (1 equiv), AdOH (2 equiv), DCM, rt, 16 h	84
6a 6b	Ph	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16 h	80[b] 94[b,d]
7a 7b	Ph	$R^1PO_2H_2$ (1.25 equiv), T3P (1.5 equiv, 50 wt% in EtOAc), AdOH (1 equiv), DCM, rt, 16 h	90[b] 85[b,e]
8	Tr	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16 h	88[c]
9	$HOCH_2$	$R^1PO_2H_2$ (1 equiv, 60 wt% in H_2O), PivCl (2.0 equiv), Pyr (1.5 equiv), AdOH (1 equiv), toluene, rt, 16 h	0[c]
10	Bn	$R^1PO_2H_2$ (1 equiv), T3P (1.2 equiv, 50 wt% in EtOAc), AdOH (1 equiv), DCM, rt, 16 h	89[b]
11	Cin	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16h	59
12	Cin	$R^1PO_2H_2$ (1 equiv), T3P (1.2 equiv, 50 wt% in EtOAc), AdOH (1 equiv), DCM, rt, 16 h	53[b]
13	Oct	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16h	50
14	$CH_3CH_2CH{=}CCH_2CH_3$	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16h	66
15	$C_6H_5CH_2CH_2CH_2CH_2$-	$R^1PO_2H_2$ (1.2 equiv), PivCl (1.2 equiv), Pyr (1.5 equiv), AdOH (1 equiv), DCM, rt, 16h	78

[a] Isolated yield of pure $R^1P(O)(OAd)H$ from $R^1P(O)(OH)H$ (1.5 mmol) after column chromatography, unless otherwise noted; [b] No chromatography; [c] Yield by ^{31}P-NMR; [d] 8.5g (30 mmol) of $R^1P(O)(OAd)H$; [e] 13g (48 mmol) of $R^1P(O)(OAd)H$.

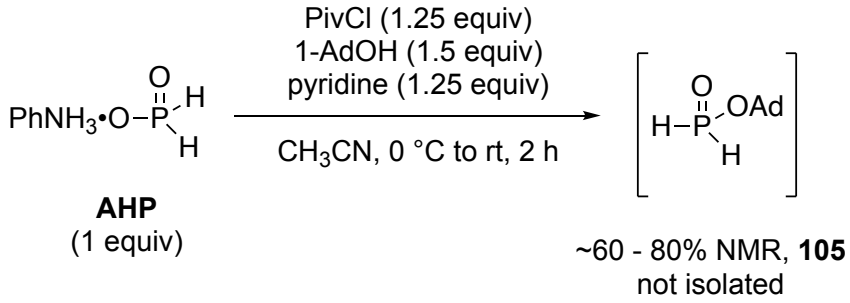
Another potential way to make adamantyl esters would be to transesterify other *H*-phosphinates with 1-adamantanol. Transesterification was first reported by Gallagher in the synthesis of *t*-BuOP(O)H_2 through transesterifying MeOP(O)H_2 with *t*-BuOH.[107] Schwabacher later perfected this reaction as a preparative procedure.[108] Unfortunately, in our hands the transesterification of EtOP(O)H_2 with AdOH was unsatisfactory, resulting in a dismal 16 % NMR yield of adamantyl hypophosphite **105** (Scheme 7.5, entry a). Attempts to transesterify PhP(O)(OBu)H with AdOH, using either NaH or LiHMDS, also failed (Scheme 7.5, entry b and c). This result may not be surprising, in light of Leclaire's and Giordano's work in which the superior resistance of adamantyl *H*-phosphinates to racemization was ascribed to the very slow reaction of the tertiary AdOLi with the RP(OAd)(OLi) intermediate, a proposal fully consistent with the failure of the transesterification under basic conditions.[103]

Scheme 7.5 Transesterification of *H*-phosphinates with 1-AdOH



Next, the preparation of adamantyl hypophosphite **105** (Scheme 7.6) was accomplished before investigating its reactivity in one-pot reactions. Hypophosphite esters cannot be isolated because they hydrolyze easily and disproportionate when concentrated. This employed Stawinski's method of reacting anilinium hypophosphite (AHP) with PivCl and 1-AdOH, to form $AdOP(O)H_2$ **105** in ~60-80 % ^{31}P-NMR yield.[109] Once formed, adamantyl hypophosphite can be converted into a variety of *H*-phosphinate esters.[2, 57]

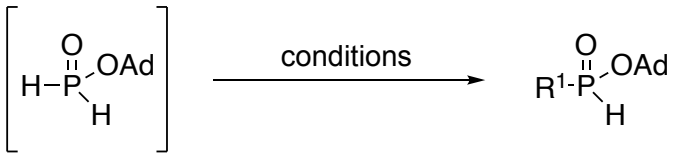
Scheme 7.6 Synthesis of adamantyl hypophosphite



Our palladium-catalyzed hydrophosphinylation of alkenes with adamantyl hypophosphite worked, but the overall isolated yields were only in the 30 % range (Scheme 7.2, entries 1-2).[2] The palladium-catalyzed cross-coupling of adamantyl hypophosphite with 2-iodoanisole gave the product in a slightly better 47% overall yield (Table 7.2, entry 3; compared to Leclaire's 41 % (Scheme 7.2, method a).[2] However, DBU and BSA- promoted alkylation failed completely with hypophosphite (Table 7.2, entry 4-5). Similarly, DBU-promoted conjugate addition to benzyl acrylate gave no product (Table 7.2, entry 6). Relatedly, our nickel-catalyzed hydrophosphinylation of 4-octyne did not proceed and resulted in the unreacted starting material (Table 7.2, entry 7).[94] These results show that the tertiary adamantyl hypophosphite ester is considerably less reactive than its primary and secondary ester

counterparts.[110] For example, the DBU-promoted methylation of *n*-BuOP(O)H_2 proceeds in 74 % overall yield.[110]

Table 7.2 Synthesis of $R^1P(O)(OAd)H$ from *in situ*-generated (AdO)P(O)H_2

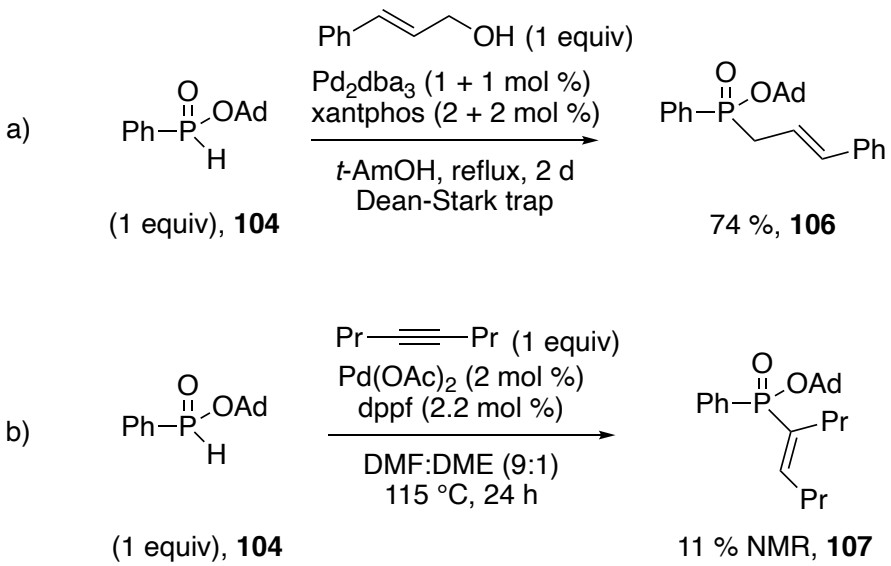


Entry	R^1	Reagents	Temp., Time	Yield (%)[a]
1	Oct	AdOP(O)H_2 (2 equiv) 1-octene (1.0 equiv), Pd_2dba_3 (1 mol%), xantphos (2 mol%)	reflux, 16 h	32
2	Dec	AdOP(O)H_2 (2 equiv) 1-decene (1.0 equiv), Pd_2dba_3 (1 mol%), xantphos (2 mol%),	reflux, 16 h	33
3	2-$MeOC_6H_4$-	AdOP(O)H_2 (1 equiv), 2-iodoanisole (1 equiv), DIPEA (1.3 equiv), $Pd(OAc)_2$ (2 mol%), dppf (2 mol%) DME	reflux, 48 h	47[b]
4	Me	1) AdOP(O)H_2 (1 equiv) BSA (1.5 equiv), 0 °C to rt, 1 h; 2) MeI (1.2 equiv)	rt, 2 h	0[c,d]
5	Me	AdOP(O)H_2 (1 equiv), DBU (1.1 equiv), MeI (1.1 equiv)	0 °C to rt, 16 h	0[d]
6	$BnO_2C(CH_2)_2$-	$R^1PO_2H_2$ (1.0 equiv), benzyl acrylate (1.1 equiv), DBU (1.5 equiv)	rt, 16 h	0[d]
7	PrC=CHPr	AdOP(O)H_2 (1 equiv), 4-octyne (1.0 equiv), $NiCl_2$ (3 mol%)	reflux, 3 h	0[d]

[a] Isolated yield of pure $R^1P(O)(OAd)H$ from AdOP(O)H_2 after column chromatography; [b] Synthesis of AdOP(O)H_2 was in toluene; [c] Synthesis of AdOP(O)H_2 was in DCM; [d] ^{31}P NMR yield

Although PhP(O)(OAd)H is less reactive than other esters, a reaction that performed well was the Pd-catalyzed allylation.[2] As shown in Scheme 7.7 entry a, cinnamylation proceeded in good yield, however it required an extended reaction time and two portions of catalyst to reach completion. For comparison, the reaction of PhP(O)(OBu)H gave a 99 % isolated yield after 24 h at reflux, and with only a portion of palladium. [111] However, the Pd-catalyzed hydrophopshinylation of 4-octyne was unsatisfactory, giving only 11 % yield by ^{31}P-NMR (the rest being starting material (Scheme 7.7, entry b).[92]

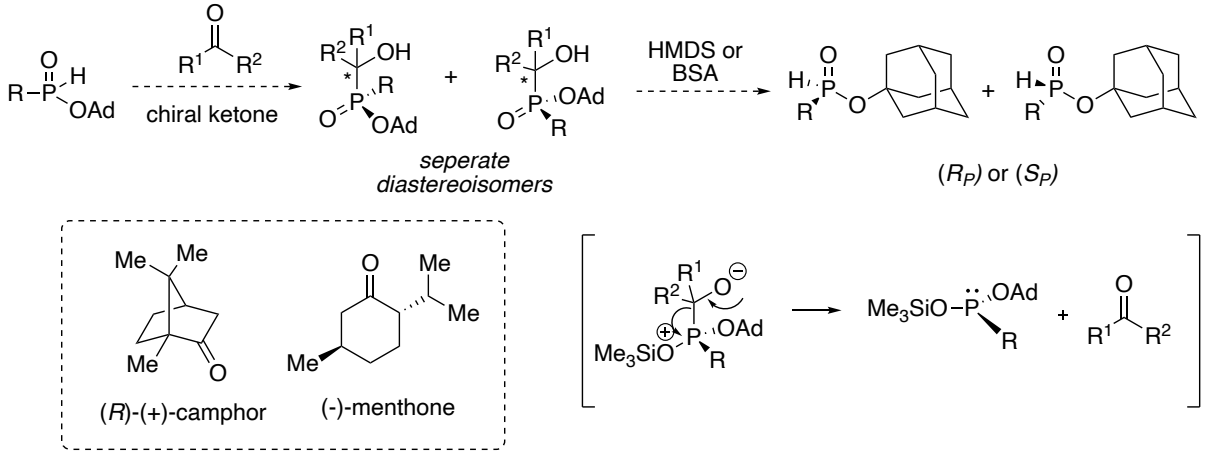
Scheme 7.7 Pd-catalyzed functionalization of PhP(O)(OAd)H to PhP(O)(OAd)R



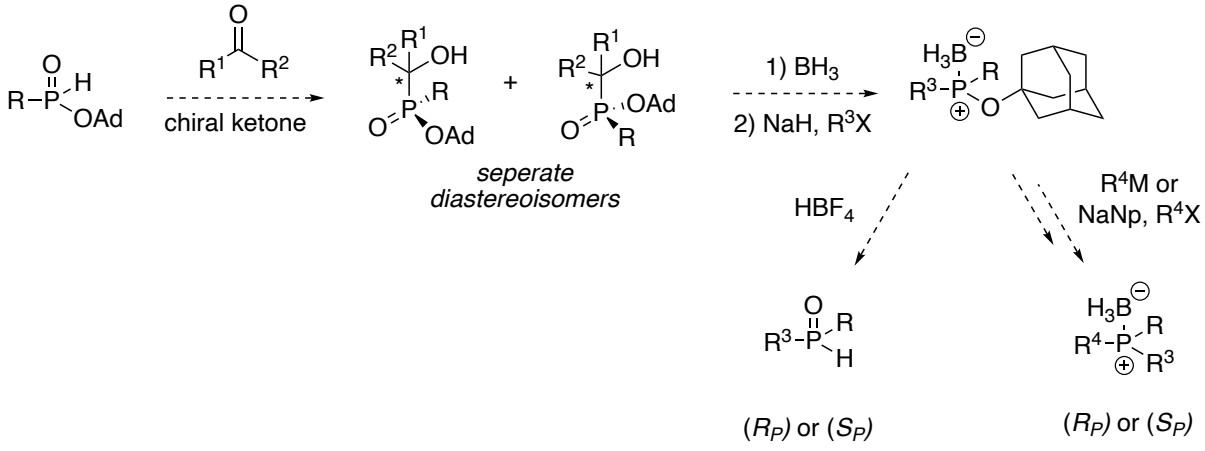
The reactivity of PhP(O)(OAd)H with a chiral ketone was also investigated, as a potential alternative to Leclaire and Giordano's resolution by semi-preparative chiral HPLC.[103] This would allow for a method to potentially resolve and obtain enantiopure *H*-phosphinates on large scale, by separating the diastereomer tertiary alcohol-adducts, then silylating with HMDS or BSA to form a zwitterion, that would rearrange to give the chiral *H*-phosphinate and

regenerate the chiral ketone (Scheme 7.8).[112] Another possible resolution method would be the reduction of the tertiary hydroxyalkyl phosphine oxides P(O) to the corresponding phosphonite-borane using BH_3 followed by alkylation (Scheme 7.9).[113, 114] The phosphonite-borane complex can be cleaved to form the *H*-phosphinate using tetrafluoroboric acid, stereospecifically.[115, 116] The adamantyl ester could also be displaced with an organometallic, or reduced with NaNp and alkylated (Scheme 7.9).

Scheme 7.8 Proposed resolution strategy of RP(O)(OAd)H with a chiral ketone then BSA

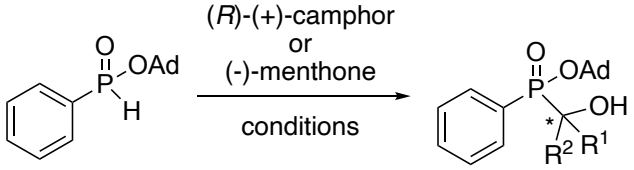


Scheme 7.9 Proposed resolution strategy of RP(O)(OAd)H with a chiral ketone then BH_3 and alkylating



Attempts to react adamantyl ester with (+)-camphor or (-)-menthone are summarized in Table 7.3, and either resulted in unreacted starting material (entries 1-4, 7-8) or low yields of the product (entries 5-6). An attempt to add the (+)-camphor to H_3PO_2 (50 wt.% in H_2O, concentrated under vacuum before use) with BSA, followed by the addition of 1-AdOH with PivCl, was marginally successful (Scheme 7.10).

Table 7.3 Conditions tested for *H*-functionalization of PhP(O)(OAd)H with (+)-camphor or (-)-menthone

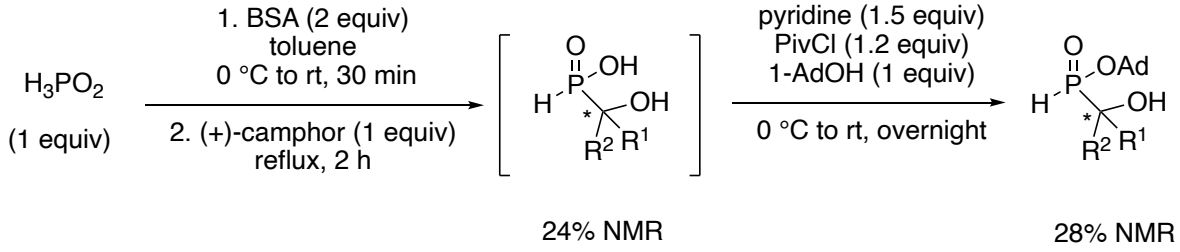


Entry	Ketone	Reagents	Solvent	Temp., Time	Yield (%)[a]
1	(+)-camphor	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), Pyr (0.1 equiv)	toluene	reflux, 3 d	0
2	(+)-camphor	1) PhP(O)(OAd)H (1 equiv), Et_3N (1.1 equiv), TMSCl (1.1 equiv) 2) ketone (4 equiv), Pyr (0.1 equiv)	THF:toluene	1) 0 °C to rt, 2 h; 2) reflux, 24 h	0
3	(-)-menthone	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), Pyr (0.1 equiv)	toluene	reflux, 2 d	0
4	(+)-camphor	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), $Ti(OiPr)_4$ (10 mol%)	toluene	rt, 16 h	0

5	(+)-camphor	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), Ti(O*i*Pr)$_4$ (1 equiv)	toluene	reflux, 24 h	18
6	(-)-menthone	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), Ti(O*i*Pr)$_4$ (1 equiv)	toluene	reflux, 24 h	29
7	(+)-camphor	PhP(O)(OAd)H (1 equiv), ketone (2 equiv), KF (40 wt% on alumina, 2 equiv)	CH_3CN	rt to reflux, 20 h	0
8	(+)-camphor	PhP(O)(OAd)H (1.3 equiv), ketone (1.0 equiv), BSA (1.0 equiv)	CH_3CN	rt to reflux, 24 h	0

[a] Yield by ^{31}P- NMR

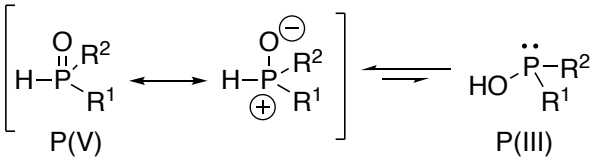
Scheme 7.10 Silylation of H_3PO_2 with BSA, followed by addition of (+)-camphor and 1-AdOH



Phosphinylidene compounds $R^1R^2P(O)H$ are important types of organophosphorus compounds and display prototropic tautomerism, in which a hydrogen atom moves from one atom to another (Scheme 7.11). In 2015, our group measured the initial rate of the deuteration of phosphinylidene-containing compounds to obtain a quantitative measure of their reactivity.[117] The P(V) form is almost always the most stable species, and the less stable P(III) form is the reactive species in most reactions involving phosphinylidenes.[2]

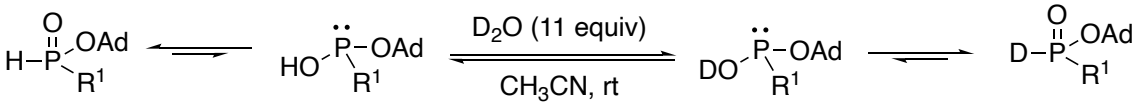
Substituent effects of R^1 and R^2 on tautomerism dramatically affect phosphinylidene reactivity. The larger the half-life of deuteration, the least reactive the compound. This is because the chemical reactivity is due to the P(III) (P-OH) tautomer. In theory, the stronger electron-donating nature of the adamantyl group should stabilize the phosphonium tautomer even more and destabilize the phosphorus lone pair in the P(III) tautomer. The electronic effect of the adamantyl group may be gauged by the pK_a of carboxylic acids RC(O)OH: 1-AdCOOH is 5.06; pivalic acid is 5.05; propionic acid is 4.88; and acetic acid is 4.76.[118, 119] The higher the pK_a, the more EDG the group.

Scheme 7.11 Tautomeric equilibrium between P(V) and P(III) form



The kinetics of phosphinylidene tautomerization is directly correlated with the rate of phosphinylidine deuteration by excess D_2O. P(III) phosphinylidenes formed by any method will readily exchange the P−OH proton for deuterium (Scheme 7.12). Deuteration rates may be directly observed and quantified over time using ^{31}P NMR spectroscopy as depicted in Figure 7.1. Using an excess D_2O ensures that tautomerization is rate-limiting.

Scheme 7.12 Deuteration of phosphinylidene adamantyl ester using an excess of D_2O



Thus, adamantyl phenyl-*H*-phosphinate was deuterated under the same conditions.[117] As deuteration progresses, the P(O)H proton, which couples to the phosphorus, is replaced with deuterium, and the signal goes from a doublet ($J^1_{P\text{-}H}$) of triplets (J^4_{PCCH}) to a triplet ($J^1_{P\text{-}D}$) of triplets ($J^4_{PCCH)}$ (Figure 7.1). The half-life of deuteration was determined to be 179 minutes (~3 hours), which is considerably longer than the ethyl ester PhP(O)(OEt)H at 1.4 hours, confirming that the former is comparably less reactive than the latter (Table 7.4 entry 10 vs entry 11).[117] This is consistent with the observed reduced reactivity of adamantyl *H*-phosphinates and hypophosphite.

Figure 7.1 Proton-coupled ^{31}P-NMR spectra at 161.97 MHz obtained during the deuteration of PhP(O)(OAd)H (1 M in CH_3CN) using D_2O (11 equiv) at room temperature

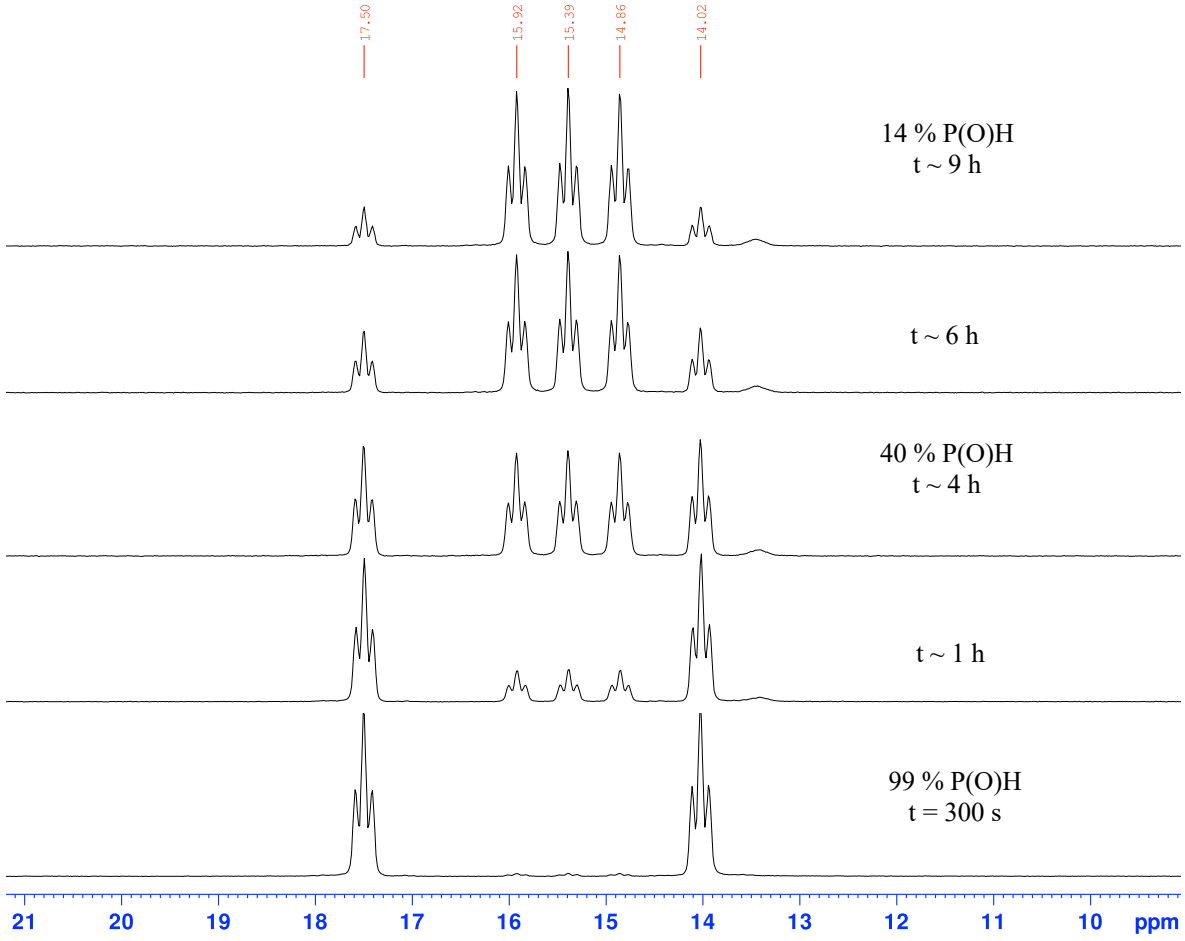
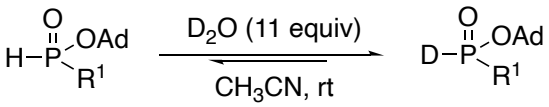


Table 7.4 Kinetic data for the initial rate of decay of the starting phosphinylidene after addition of D_2O compiled from ref 117



Entry	R^1	R^2	Rate constant (s^{-1})	Half-life (s)
1	H	NaO		> 3 days
2	Bu	Bu		> 3 days
3	OH	OH	3.91 × 10−6	177366 (49 h)
4	$Me_2C(CH_2O)_2$		8.18 × 10−6	84695 (24 h)
5	EtO	EtO	9.00 × 10−6	77025 (21 h)
6	EtO	Oct	2.35 × 10−5	29446 (8.2 h)
7[a]	$(MeO)_2P(S)H$		2.57 × 10−5	26992 (7.5 h)
8	OH	Oct	3.55 × 10−5	19525 (5.4 h)
9	BnO	BnO	4.73 × 10−5	14648 (4.1 h)
10	**AdO**	**Ph**	**6.00 × 10−5**	**10740 (3 h)**
11	EtO	Ph	1.33 × 10−4	5200 (1.4 h)
12	OH	Ph	2.09 × 10−4	3324 (55 min)
13	$(Me_2CO)_2$		7.40 × 10−4	937 (15.6 min)
14	Ph	Oct	1.16 × 10−3	596 (9.9 min)
15	PhO	PhO	2.20 × 10−3	315 (5.2 min)
16	Ph	Ph	4.61 × 10−3	150
17	H	OH	3.87 × 10−3	179
18	DOPO		2.68 × 10−3	259

[a] Dimethyl *H*-thiophosphonate

EXPERIMENTAL

Reagents 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). Unless otherwise stated, HPLC or reagent grade solvents were used. The activation of molecular sieves consisted in flame drying them under vacuum (0.5 mmHg) during 20-30 min. When common anhydrous reagents and/or solvents were employed, they were prepared as follows: Et_3N, pyridine, aniline, diisopropylethylamine, diisopropylamine, and *tert*-amyl alcohol were distilled under N_2 from CaH_2 and stored under N_2 over activated 4Å or 3Å molecular sieves. Aqueous hypophosphorous acid (50 wt.%), was purchased from Aldrich and used as received. Concentrated hypophosphorous acid (H_3PO_2) was obtained by rotary evaporation (0.5 mmHg) of the 50 wt.% aqueous solution at room temperature for 20-30 min before reaction. Stock solutions (0.5 M) of concentrated H_3PO_2 in reagent grade acetonitrile were also prepared and used for three months without any decomposition of the acid.

Purification. Flash chromatography experiments were carried out on silica gel premium R_f grade (40−75 μm). Ethyl acetate/hexanes or ethyl acetate/methanol mixtures were used as the eluent for chromatographic purifications. Hexanes were distilled before use to remove the grease residue. TLC plates were visualized by UV or immersion in permanganate potassium (3 g of $KMnO_4$, 20 g of K_2CO_3, 5 mL of 5% aq NaOH, 300 mL of water) followed by heating.

Nuclear Magnetic Resonance (NMR) Data. ^1H NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer. Chemical shifts for ^1H NMR spectra (in parts per million) are relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with deuterated chloroform. ^{13}C

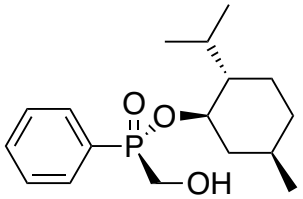
NMR spectra were recorded at 101 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts reported (in parts per million) are relative to external 85% phosphoric acid (δ = 0.0 ppm). The NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra, an approach that is valid if no phosphorus-containing gas (i.e., PH_3) evolves, or if the precipitate in a heterogeneous mixture does not contain phosphorus. The yields determined by NMR are generally accurate within ~10 % of the value indicated and are reproducible. Isolated yields are sometimes significantly lower because *H*-phosphinate esters are highly polar compounds and hydrolytically labile.

High-Resolution Mass Spectrometry (HRMS) Data. Mass spectrometry was provided by Louisiana State University Mass Spectrometry Resource. High-resolution mass spectra (HRMS) were obtained by electrospray ionization using a TOF analyzer.

High-Performance Liquid Chromatography (HPLC) Data. Chiral HPLC analyses were recorded on the Agilent 1100 or 1200 Series HPLC system. Chiral HPLC resolutions were done with an *(S,S)*-Whelk-01 Column (250 × 4.6 mm, 5 μm) from Regis Technologies or CHIRALCEL OD-H from Daicel, using hexanes/isopropanol mixtures as the mobile phase.

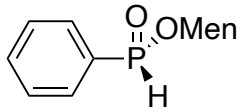
2.1 Synthesis of Diphenyl Heterocycle P-stereogenic CPA

*(S_p)-Menthyl(hydroxymethyl)-phenyl-phosphinate **45** (Scheme 2.2).*



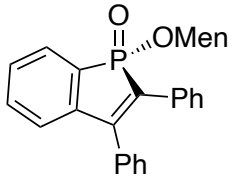
To a solution of phenylphosphinic acid (42.6 g, 300 mmol, 1 equiv) in toluene (300 mL) was added L-menthol (46.9 g, 300 mmol, 1 equiv). The reaction mixture was stirred at reflux for 24 h under N_2 in a rb flask equipped with a Dean-Stark trap. After cooling down the reaction to rt, paraformaldehyde (9.01 g, 300 mmol, 1 equiv) was added and the reaction mixture was stirred at reflux for 24 h under N_2. The solvent was then removed under vacuum and the crude obtained was recrystallized at rt in diethyl ether (200 mL) to afford the product **45** as colorless crystals (24.2 g, 26%, 97% de). Mp = 138- 139 °C; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 37.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77-7.87 (m, 2H), 7.52-7.60 (m, 1H), 7.42-7.51 (m, 2H), 4.29-4.43 (m, 2H), 3.93-4.10 (m, 2H), 2.26 (dquint., J = 2.6 and 7.0 Hz, 1H), 1.80-1.91 (m, 1H), 1.57-1.73 (m, 2H), 1.26-1.47 (m, 2H), 0.96 (d, J = 7.1 Hz, 3H), 0.74-1.13 (m, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 132.3 (d, J = 2.8 Hz), 131.7 (d, J = 9.9 Hz, 2C), 130.6 (d, J = 123 Hz), 128.3 (d, J = 12.1 Hz, 2C), 77.1 (d, J = 8.3 Hz), 60.2 (d, J = 117 Hz), 48.7 (d, J = 6.1 Hz), 43.2, 34.0, 31.4, 25.5, 22.8, 21.9, 21.1, 15.7; HRMS (EI+) m/z calcd for $C_{16}H_{28}O_3P$ ($[M+H]^+$) 311.1776, found 311.1766.

*(R_p)-Menthyl phenyl-H-phosphinate **46** (Scheme 2.3).*



To a solution of *N*-chlorosuccinimide (3.0 equiv, 53.9 mmol) in DCM (100 mL) at -78 °C and under N_2 was added dropwise a solution of dodecyl methyl sulfide (3.0 equiv, 53.9 mmol) in dichloromethane (20 mL). After 10 minutes at -78 °C, a solution of **45** (1 equiv, 17.9 mmol) in DCM (20 mL) was added over 20 minutes. After 1 h at -78 °C, Et_3N (5 equiv, 89.8 mmol) was added over 15 minutes and the reaction was allowed to warm to rt. After 1 h at rt, water was added, and the two layers were separated. The aqueous layer was then washed with dichloromethane (x2). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 90:10 to 60:40) to afford the product **46** as a colorless oil (4.7 g, 89%, 99% de). ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.4 (d); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73-7.84 (m, 2H), 7.66 (d, J = 553 Hz, 1H), 7.46-7.64 (m, 3H), 4.22-4.36 (m, 1H), 2.14-2.27 (m, 2H), 1.62-1.75 (m, 2H), 1.38-1.54 (m, 2H), 1.24 (q, J = 11.2 Hz, 1H), 0.78-1.13 (m, 2H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H).

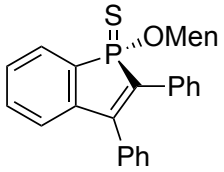
*(S_p)-1-menthyl-2,3-diphenyl-1-phosphindole **47** (Scheme 2.4).*



To **46** (1.0 equiv, 1.4 mmol) in acetic acid (13 mL) was added $Mn(OAc)_2$ (5 mol%, 0.07 mmol), MnO_2 (85% activated, 3.0 equiv, 4.2 mmol) and sodium acetate (3.0 equiv, 4.2

mmol). The suspension was stirred overnight at 70 °C under nitrogen. The reaction was cooled to ambient temperature, diluted with ethyl acetate (10 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ saturated with NaCl (10 mL) were added. The mixture was stirred for 5 min and the suspension was filtered over Celite. The organic layer was washed with aqueous solutions of aqueous solutions of $Na_2S_2O_4$ saturated with NaCl (10 mL x 2) and washed with saturated $NaHCO_3$ (10 mL x 5). The combined extracts were washed with brine, dried with $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (dichloromethane:acetone 100:0 to 98:2) to give the product **47** as an white solid (0.4 g, 61%, 99% de). ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.6 ppm (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.79 (m, 1H), 7.05-7.56 (m, 13H), 4.29- 4.42 (m, 1H), 2.25- 2.38 (s, 1H), 1.53-1.76 (m, 3H), 1.38-1.51 (m, 1H), 1.16-1.36 (m, 2H), 0.75-1.10 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H), 0.66 (d, J = 7.0 Hz, 3H), 0.43 (d, J = 6.8 Hz, 3H).

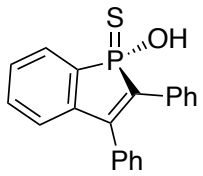
kf(R_p)-1-menthyl-2,3-diphenyl-1-thiophosphindole **48** *(Scheme 2.6).*



To a solution of **47** (1.0 equiv, 0.8 mmol) in anhydrous toluene (10 mL) was added Lawesson's Reagent (0.6 equiv, 0.5 mmol) under nitrogen. The solution was refluxed for 24 h, cooled to room temperature, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate 98:02 to 95:05) to give **48** as a yellow oil (0.3 g, 72%, 99% de). ^{31}P NMR (162 MHz, $CDCl_3$) δ 87.8 ppm (s); ^{1}H NMR (400

MHz, $CDCl_3$): δ = 7.5 (m, 1H), 7.2-7.44 (m, 13H), 4.45 (m, 1H), 2.25 (m, 1H), 1.6 (m, 3H), 1.4 (m, 1H), 1.29 (m, 2H), 1.20 (m, 2H), 0.9 (m, 3H), 0.60 (m, 3H), 0.39 (m, 3H).

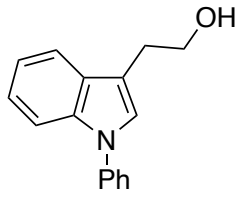
Representative Procedure for Cleavage of Menthyl Ester (Table 2.1- entry 4).



To a solution of **48** (1 equiv, 0.6 mmol) in distilled CH_2Cl_2 (16 mL) was added TMSBr (5 equiv, 3.2 mmol) dropwise at rt under nitrogen. The solution stirred at rt for 16 h, then MeOH (12 mL) was added. The reaction stirred at rt for 1 h. The reaction mixture was checked by TLC (hexanes:ethyl acetate 60:40) and showed only the starting material spot. The ^{31}P NMR of the reaction mixture affirmed this giving a singlet at 86.6 ppm corresponding to the starting material.

2.2 Synthesis of Tryptophol-derived *P*-stereogenic CPA

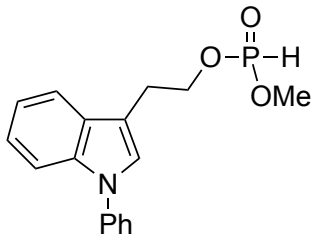
*zN-Phenyl tryptophol **50** (Scheme 2.8).*



To a screw-cap test tube was added CuI (0.05 equiv, 1.5 mmol), tryptophol **49** (1.0 equiv, 31.0 mmol), K_3PO_4 (2.1 equiv, 65.1 mmol) and the vessel was evacuated and back-filled with nitrogen. Iodobenzene (1.2 equiv, 37.2 mmol), trans-N_1,N_2-dimethylcyclohexane-1,2-diamine (10 mol%, 3.1 mmol) and toluene (32 mL) were added under nitrogen. The reaction

tube was sealed, and the contents were stirred, with heating from an oil bath at 110 °C for 24 h. The reaction was cooled to ambient temperature, diluted with ethyl acetate (20 mL), filtered through a plug of Celite, eluted with additional ethyl acetate (20 mL). The filtrate was concentrated under vacuum and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate 95:05 to 50:50) to provide **50** as a colorless oil (7.3 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (ddd, J = 7.8, 1.4, 0.8 Hz, 1H), 7.62 (dt, J = 8.2, 0.9 Hz, 1H), 7.54 (d, J = 5.7 Hz, 4H), 7.44 – 7.33 (m, 1H), 7.31 – 7.28 (m, 2H), 7.27 – 7.19 (m, 1H), 4.00 (t, J = 6.4 Hz, 2H), 3.13 (td, J = 6.4, 0.9 Hz, 2H), 1.72 (s, 1H).

N-Phenyl-H-methylphosphonate tryptophol **51** *(Scheme 2.8).*

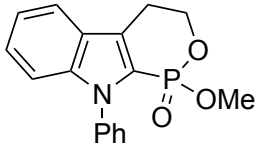


Synthesis of *tert*-butylamine methyl phosphonate salt: To a round bottom flask was added dimethyl phosphite (1.0 equiv, 54.5 mmol) and *tert*-butylamine (4.1 equiv, 218.1 mmol). This was brought to a reflux for 3 h then cooled to room temperature where it crystallized overnight. The crystals were then vacuum filtered to give a white solid (8.2 g, 88%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.6 (dm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 611 Hz, 1H), 3.49 (d, J = 12 Hz, 3H), 1.31 (s, 9H, $(CH_3)_3$).

To a solution of *tert*-butylamine methyl phosphonate salt (1.0 equiv, 1.7 mmol) in anhydrous CH_2Cl_2 (22 mL) was added pivaloyl chloride (1.0 equiv, 1.7 mmol) at room temperature under nitrogen. After stirring for 1 h, **50** (1.0 equiv, 1.7 mmol) was added at room temperature and left to stir overnight. The mixture was washed with saturated aqueous

$NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL x 2). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate 8:2 to 6:4 to 2:8) to give **51** colorless oil (0.5 g, 89 %). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.5 (dm); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 1H), 7.65 – 7.59 (m, 1H), 7.56 – 7.47 (m, 4H), 7.38 (d, J = 6.4 Hz, 1H), 7.32 – 7.20 (m, 3H), 4.44 (dtd, J = 8.7, 7.1, 1.8 Hz, 2H), 3.74 (d, J = 12.0 Hz, 3H), 3.28 (td, J = 7.0, 0.9 Hz, 2H).

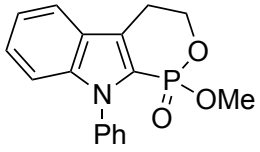
Methyl phosphonate-N-phenylcarbazole **52** *(Scheme 2.9).*



To a solution of **51** (1.0 equiv, 2.2 mmol) in acetic acid (15 mL) was added $Mn(OAc)_2$ (5 mol%, 0.111 mmol), MnO_2 (85% activated, 3.0 equiv, 6.6 mmol) and sodium acetate (3.0 equiv, 6.6 mmol). The suspension was stirred overnight at 70 °C under nitrogen. The reaction was cooled to room temperature, diluted with ethyl acetate (20 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ saturated with NaCl (20 mL) were added. The mixture was stirred for 5 min and the suspension was filtered over Celite. The organic layer was washed with aqueous solutions of aqueous solutions of $Na_2S_2O_4$ saturated with NaCl (20 mL x 2) and washed with saturated $NaHCO_3$ (20 mL x 5). The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate 90:10 to 0:100) to give **52** as a colorless oil (0.3 g, 43 %). ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.9 ppm (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 3H), 7.57 (ddd, J = 8.0, 7.1, 1.0 Hz, 2H), 7.51 – 7.43 (m, 1H), 7.42 – 7.29 (m, 2H), 7.24 (ddd,

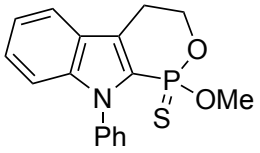
J = 7.9, 6.0, 1.9 Hz, 1H), 4.82 – 4.57 (m, 2H), 3.48 (d, J = 11.6 Hz, 3H), 3.24 (dddd, J = 16.7, 6.7, 4.4, 2.7 Hz, 2H).

Representative Procedure for Catalytic Arylation (Table 2.2 – entry 2).



To a solution of **51** (1 equiv, 0.1 mmol) in DMSO (4 mL) was added $Mn(OAc)_2$ (5 mol%, 0.005 mmol), Co(ethylhexanoate)$_2$ (5 mol%, 0.005 mmol) in air. A condenser was added, and the reaction flask was heated to 100 °C in an oil bath for 20 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL) and 0.5 M aqueous solution of $Na_2S_2O_4$ saturated with NaCl (2 mL) was added. The mixture was stirred for 5 min and the suspension was filtered over Celite. The organic layer was washed with an aqueous solution of $Na_2S_2O_4$ saturated with NaCl (2 mL x 2), and then washed with saturated $NaHCO_3$ (2 mL x 5). The combined extracts were washed with brine, dried with $MgSO_4$, filtered and concentrated under vacuum. The crude ^{31}P-NMR revealed the product peak at 6.4 ppm (17%) and the rest a complex mixture and starting material.

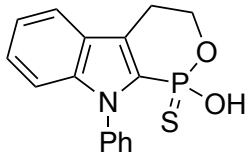
*Methylthiophosphonate-N-phenylcarbazole **53** (Scheme 2.10).*



To a solution of **52** (1.0 equiv, 6.7 mmol) in anhydrous toluene (40 mL) was added Lawesson's Reagent (0.6 equiv, 4.0 mmol) under nitrogen. The solution was refluxed for 16

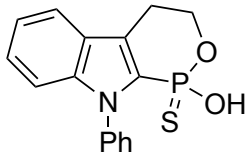
h, cooled to room temperature, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate 98:02 to 80:20) to give **53** as a colorless oil (1.2 g, 54%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 67.8 ppm (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 1H), 7.53 (m, 5H), 7.33 (dd, J = 8.6, 6.7 Hz, 1H), 7.23 (dd, J = 8.0, 6.3 Hz, 2H), 4.68 (dq, J = 17.6, 4.3 Hz, 2H), 3.66 (d, J = 14.5 Hz, 3H), 3.37 – 3.29 (m, 1H), 3.23 – 3.12 (m, 1H).

*Thiophosphonic acid N-phenylcarbazole **39** (Scheme 2.11, entry a).*



In a reaction tube was added **53** (1.0 equiv, 0.16 mmol) in anhydrous CH_3CN (6 mL) and 1,4-diazabicyclo[2.2.2]octane (1.0 equiv, 0.16 mmol). The tube was placed in a synthesizer and stirred for 12 h at 85 ^{o}C under nitrogen. The solution was cooled to room temperature, acidified with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (10 mL x 2). The combined extracts were dried with $MgSO_4$, filtered and condensed under vacuum to yield **39** (NMR yield: 100%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.0 ppm (s).

(*Diphenylmethyl)phenyl-methoxy thiophosphonate **53** (Scheme 2.13).*



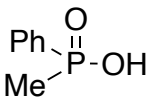
Pyridine-LR: In a rb flask was added distilled pyridine (225 mL) and brought to 80 °C in an oil bath. To the reaction was added P_4S_{10} (0.1 equiv, 0.28 mmol) portion-wise. The

reaction stirred at reflux for 1 hour, and then brought to rt. A yellow solid formed and was isolated on a Büchner funnel. The solid was washed with acetonitrile and dried in a desiccator under vacuum overnight (0.8 g, 87%).

To a rb flask was added **52** (1 equiv, 1.24 mmol) in toluene (7 mL). To this the pyridine-LR (0.6 equiv, 0.75 mmol) was added and the reaction brought to reflux for 16 h. The reaction was cooled to rt, diluted with EtOAc (10 mL) and transferred to separatory funnel. The organic layer was washed with NH_4Cl (sat. aq), H_2O (10 mL), then 1 M HCl and the layers separated. The organic layer was dried with Na_2SO_4, filtered, and concentrated under vacuum to yield **53** (NMR yield: 75%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 68.0 (s).

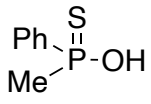
3.2 Synthesis of Thiophosphorus Acids

*Methyl-phenylphosphonic Acid **60**.*



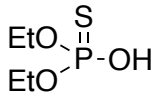
To a solution of phenyl phosphinic acid (1.0 equiv, 70.38 mmol,) in DCM (140 mL) was added bis(trimethylsilyl)acetamide (2.2 equiv, 154.83 mmol) at 0 °C under argon. The reaction mixture stirred for 30 min, and iodomethane (1.2 equiv, 84.45 mmol) was added at 0 °C and stirred overnight. The reaction mixture was quenched with methanol and concentrated under a vacuum. Ethyl acetate was added and washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford acid as a white solid **60** (7.3 g, 66%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 7.77 (ddd, J = 12.4, 8.3, 1.4 Hz, 2H), 7.51 (dd, J = 7.6, 1.4 Hz, 1H), 7.44 (ddd, J = 7.6, 3.4, 1.1 Hz, 2H), 1.63 (d, J = 14.7 Hz, 3H).

Representative procedure for the synthesis of thiophosphorus acids using M_2S from P(O)OH compounds (Table 3.2, entry 7).



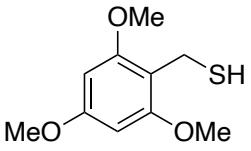
To a rb flask was added **60** (1 equiv, 0.32 mmol) in DMF (2 mL). DCC (1.5 equiv, 0.48 mmol) was added and stirred for 30 min. Next sodium sulfide nonahydrate (3 equiv, 0.9 mmol) was added and the reaction brough to 120 °C for 14 h. The reaction was cooled to rt, then an NMR of the crude reaction mixture was taken (NMR yield: 74%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 55.73; and 26% starting material at 24.35 ppm. The product was not isolated.

Representative procedure for the synthesis of thiophosphorus acids using M_2S from P(O)Cl compounds (Table 3.3, entry 5).



To a reaction tube was added Na_2S (4.5 equiv, 12.8 mmol, anhydrous) in distilled DCM (10 mL) under argon. To this Me_3SiCl (1.5 equiv, 4.27 mmol) was added dropwise and stirred at rt for 1 h. $(EtO)_2P(O)Cl$ (1 equiv, 3.1 mmol) was added and the reaction brough to reflux for 24 h. Then the reaction was cooled to rt, and an NMR of the crude reaction mixture was taken (NMR yield: 9%) ^{31}P NMR (162 MHz, D_2O) δ 64.4; the anhydride $R^1R^2P(S)OP(O)\text{-}R^1R^2$ at 53.5 (d, J = 21.4 Hz) and -14.7 (d, J = 21.0 Hz); as well as the acid P(O)OH at 3.5 ppm. The product was not isolated.

2,4,6-Trimethoxybenzyl thiol (Scheme 3.7).

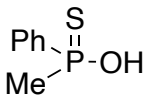


To a rb flask was added trimethoxybenzaldehyde (1 equiv, 35.5 mmol) in MeOH (100 mL) under argon. The flask was cooled to 0 °C and $NaBH_4$ (1.45 equiv, 51 mmol) was added portion-wise (5 portions, over 15 min). The reaction was brought to rt and stirred for 2 h. The mixture was concentrated under vacuum, diluted with Et_2O (40 mL), and transferred to a separatory funnel. The organic layer was washed with brine (20 mL), then the layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum

to afford the intermediate as a while solid (6.5g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.76 (d, J = 7.9 Hz, 2H), 2.03 – 1.94 (m, 1H).

The TmobOH (1 equiv, 34.8 mmol) was dissolved in distilled CH_3CN (100 mL) and cooled to 0 °C under argon. Thiourea (1.5 equiv, 52 mmol) was added, followed by *p*-toluene sulfonic acid (1 equiv, 34.8mmol) and brought to rt and stirred for 16 h. Then 3M NaOH was added (50 mL) and stirred for 5 h at rt. The mixture was transferred to a separatory funnel and 3M HCl was added (pH = 2-3). The organic layer was extracted with EtOAc and the layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (hexanes:ethyl acetate 90:10 to 80:20) to afford the pure TmobSH as a white solid (4 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.75 (d, J = 7.9 Hz, 2H), 1.99 (t, J = 7.9 Hz, 1H).

*Methyl-phenyl thiophosphorus acid **61** (Scheme 3.8, entry a).*

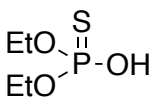


To a rb flask was added **60** (1 equiv, 0.64 mmol) in DCM (3 mL) under nitrogen. The reaction was cooled to 0 °C, and oxalyl chloride (1.2 equiv, 0.77 mmol) was added followed by DMF (10 mol %, 0.064 mmol). The reaction was brought to rt and stirred for 2 h. The TmobSH (1 equiv, 0.64 mmol) was added and the reaction stirred at rt for 16 h. The reaction mixture was transferred to a separatory funnel and washed with $NaHCO_3$ (sat. aq.), and extracted with DCM. The organic layer was separated and dried with $Na_2S_2O_4$, filtered, and concentrated under vacuum. The crude was purified by column chromatography (hexanes/ethyl acetate 90:10 to 10:90) to afford the thioester (0.28 g, 89%). ^{31}P NMR (162

MHz, $CDCl_3$) δ 46.9 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (ddd, J = 12.9, 8.2, 1.5 Hz, 2H), 7.57 – 7.42 (m, 3H), 6.01 (s, 2H), 4.21 – 4.04 (m, 1H), 3.94 (dd, J = 11.8, 8.7 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 6H), 1.93 (d, J = 13.3 Hz, 3H).

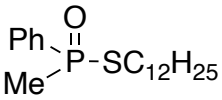
The thiophosphorus ester (1 equiv, 0.8 mmol) was dissolved in toluene (1.5 mL) under nitrogen. Thiourea (2 equiv, 1.6 mmol) and TFA (0.3 mL) were added, and the reaction stirred at rt for 6 h. The reaction was diluted with EtOAc (4 mL) and transferred to a separatory funnel. The organic layer was extracted with $NaHCO_3$ (sat. aq.), washed with EtOAc, then the basic layer acidified with 3M HCl (pH = 1), and extracted with EtOAc. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under vacuum. The NMR of the product after workup afforded the product **61** (NMR yield: 87%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.28 (s).

*Diethyl thiophosphorus acid **63** (Scheme 3.8, entry b).*



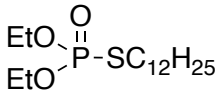
To a rb flask was added TmobSH (3 equiv, 8.6 mmol) in THF (20 mL) under nitrogen. The reaction was cooled to 0 °C, then NaH (3 equiv, 8.6 mmol, 60% in mineral oil) was added in one portion and stirred for 10 min. Following, diethyl chlorophosphate (1 equiv, 2.9 mmol) was added dropwise, and the reaction brought to rt and stirred for 3 h. The reaction was diluted with Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was washed with NH_4Cl (sat. aq), washed H_2O, washed with 3 M HCl (aq), and then with brine. The organic layer was separated and dried with $MgSO_4$, filtered, and concentrated under vacuum to afford the product **63** (NMR yield: 76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 64.51 (s).

*Dodecyl-methylphenylphosphinothioate **64** (Scheme 3.9, entry a).*



To a rb flask was added **60** (1 equiv, 0.64 mmol) in DCM (4 mL), followed by DBU (2 equiv, 1.4 mmol) under argon. Diethylcyanophosphonate (1.1 equiv, 0.7 mmol) was added dropwise followed by addition of dodecyl thiol (1.1 equiv, 0.7 mmol). The reaction stirred at rt for 18 h. The mixture was then transferred to a separatory funnel, and the organic layer washed with $NaHCO_3$ (sat. aq), then washed with brine. The organic layer was separated, dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (hexanes:ethyl acetate 90:10 to 10:90) to afford the pure product as an oil (0.16 g, 89%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.78 (m, 2H), 7.62−7.45 (m, 3H), 2.87−2.74 (m, 1H), 2.73−2.60 (m, 1H), 1.97 (d, J = 13.3 Hz, 3H), 1.65−1.50 (m, 2H), 1.36−1.13 (m, 18H), 0.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (d, J = 103.2 Hz), 132.1 (d, J = 3.2 Hz), 130.8 (d, J = 10.4 Hz), 128.7 (d, J = 13.0 Hz), 31.9, 30.6 (d, J = 4.7 Hz), 29.6, 29.5, 29.4, 29.3, 28.9, 28.7 (d, J = 2.6 Hz), 28.5, 22.7, 21.2, 20.5, 14.1; HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{19}H_{33}SOP$ 341.2062, found 341.2056.

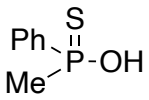
*Dodecyl-diethylphosphorothioate **65** (Scheme 3.9, entry b).*



To a solution of 1-dodecanethiol (1.0 equiv, 23.18 mmol) in THF (100 mL) was added at 0 °C NaH (60% dispersion in mineral oil, 1.5 equiv, 34.77 mmol) and stirred under argon for 1 h at rt; then diethyl chlorophosphate (1.0 equiv, 23.18 mmol) was added dropwise at rt,

and the mixture was stirred for 1 h. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified by column chromatography (hexanes/ethyl acetate 70:30) to afford pure product as a colorless oil **65** (5.5 g, 70%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24−3.94 (m, 4H), 2.78 (dt, J = 14.4, 7.4 Hz, 2H), 1.64 (p, J = 7.4 Hz, 2H), 1.32 (m, J = 7.1, 0.8 Hz, 8H), 1.21 (m, 16H), 0.93−0.76 (t, 3H).

Representative procedure for the cleavage of $R^1R^2P(O)SC_{12}H_{25}$ to $R^1R^2P(S)OH$ (Table 3.4, entry 4).



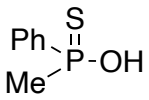
To a rb flask was added **64** (1 equiv, 0.27 mmol), sodium sulfide nonahydrate (2 equiv, 0.5 mmol) in DMF (2 mL). The reaction was brough to 100 °C in an oil bath and stirred for 14 h. The flask was then cooled to rt, EtOAc (4 mL) was added and concentrated under vacuum. The crude was solubilized with DCM and transferred to a separatory funnel. Then the organic layer was washed with 1M HCl (pH = 1), extracted with DCM, and the organic layer was dried with $Na_2S_2O_4$, filtered and concentrated under vacuum. An NMR of the crude product was taken (NMR yield: 77%) ^{31}P NMR (162 MHz, $CDCl_3$) δ 58.2; and 23% starting material at 29.5 ppm.

General Procedure for the NaNp and LiDBB Reduction of Thioesters (Scheme 3.10).

LiDBB[120] and NaNp[121] were prepared according to the literature. To a solution of the appropriate thioester, (1 equiv) in THF (0.1 M) was added dropwise to a freshly prepared 1 M

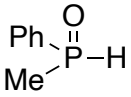
solution of LiDBB or NaNp in THF (2 - 4 equiv), at -78 °C (LiDBB) or rt (NaNp) under argon. The reaction stirred at rt for the appropriate time (3 - 16 h). Ethyl acetate was added, and the mixture was washed with 3 M HCl. The two layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under a vacuum.

*Methyl-phenylphosphinothioic acid via NaNp **61** (Scheme 3.10, entry a).*



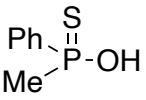
Following the general procedure, to a solution of **64** (1.0 equiv, 1.17 mmol,) in THF (10 mL) was added dropwise NaNp (1 M in THF, 2.0 equiv, 2.34 mmol,) at rt, and the mixture was stirred for 3 h at rt to afford methyl-phenylphosphinothioic acid **61** as a colorless oil (NMR yield: 89%): ^{31}P NMR (162 MHz, DMSO-d_6) δ 75.9 (s).

*Methyl-phenylphosphine oxide via NaNp **66** (Scheme 3.10, entry b).*



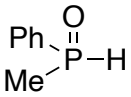
Following the general procedure, to a solution of **64** (1.0 equiv, 1.17 mmol,) in THF (10 mL) was added dropwise NaNp (1 M in THF, 4.0 equiv, 4.7 mmol) at rt, and the mixture was stirred for 3 h at rt to afford methyl-phenylphosphine oxide **66** as a colorless oil and dodecyl-methylphenylphosphinothioate **64** (NMR yield: 56% and 42% respectively): ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.3 (s), 23.0 (d, J = 485.4 Hz).

*Methyl-phenylphosphinothioic acid via LiDBB **61** (Scheme 3.10, entry c).*



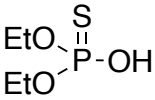
Following the general procedure, to a solution of *dodecyl-methylphenylphosphinothioate* (1.0 equiv, 0.58 mmol,) in THF (10 mL) was added dropwise LiDBB (1 M in THF, 4.0 equiv, 1.16 mmol,) at -78 °C, and stirred for 16 h at rt to afford methyl-phenylphosphinothioic acid **61** as a colorless oil and dodecyl-methylphenylphosphinothioate **64** (NMR yield: 51% and 34% respectively): ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.0 (s), 40.4 (s).

*Methyl-phenylphosphine oxide via LiDBB **66** (Scheme 3.10, entry d).*



Following the general procedure, to a solution of **64** (1.0 equiv, 0.7 mmol) in THF (10 mL) was added dropwise LiDBB (1 M in THF, 4.0 equiv, 2.8 mmol) at -78 °C, and the mixture was stirred for 16 h at rt to afford methyl-phenylphosphine oxide **66** as a colorless oil (NMR yield: 100%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.2 (d, J = 488.1 Hz).

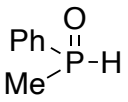
*Diethyl-phosphinothioic acid via NaNp **63** (Scheme 3.10, entry e).*



Following the general procedure, to a solution of **65** (1.0 equiv, 1.18 mmol) in THF (10 mL) was added dropwise NaNp (1 M in THF, 2.0 equiv, 2.36 mmol) at rt, and the mixture was

stirred for 3 h at rt to afford diethyl-phosphinothioic acid **63** as a light-yellow oil (NMR yield: 87%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.5 (s).

Methyl-phenylphosphine oxide via Et_3SiH and Pd/C (Scheme 3.12).

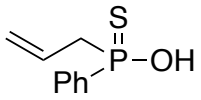


To a rb was added **64** (1 equiv, 1 mmol) in THF (5 mL). To this Pd/C (5 mol%, 10 wt.% loading) was added, followed by Et_3SiH (3 equiv, 3 mmol) dropwise. The reaction stirred at rt for 5 h then reflux for 24 h and no product formed (NMR yield: 100% sm). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.66 (s).

General Procedure for the Nucleophilic Substitution of H-Phosphinates with Organometallics, Followed by Trapping with Elemental Sulfur or Selenium (Table 3.5).

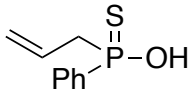
Butyl-phenyl-*H*-phosphinate[106] and ethyl-benzyl-*H*-phosphinate[110] were prepared according to the literature. To a solution of RM (2.5−3.5 equiv, M = Li or MgX) in THF or Et_2O (0.25 M) was added dropwise a solution of the appropriate *H*-phosphinate (1.0 equiv) in THF or Et_2O (0.6 M) at −78 or 0 °C, over 30 min under argon. The reaction was stirred for an additional 3 h at rt and was then quenched with elemental sulfur or selenium (3−5 equiv) and let stir overnight at rt under argon. Ethyl acetate was added to the reaction mixture and washed (3x) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate (3x). The organic layer was dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford the pure product without further purification.

Allyl-phenylphosphinothioic Acid (Table 3.5, entry 1a).



Following the general procedure, allylmagnesium bromide (1.0 M in diethyl ether, 2.4 equiv, 6.05 mmol) in THF (10 mL) at 0 °C was reacted with a solution of butyl-phenyl-H-phosphinate (1.0 equiv, 2.52 mmol) in THF (4 mL). Elemental sulfur (3.0 equiv, 7.57 mmol) was added to afford crude allyl-phenylphosphinothioic acid as a light-yellow oil (0.35 g, 57%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.85 (ddd, J = 13.1, 8.3, 1.4 Hz, 2H), 7.56−7.49 (m, 1H), 7.49−7.40 (m, 2H), 5.85−5.42 (m, 1H), 5.25−4.86 (m, 2H), 3.12−2.63 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (d, J = 103.5 Hz), 132.2 (d, J = 3.0 Hz), 131.0 (d, J = 11.2 Hz), 128.4 (d, J = 13.1 Hz), 127.1 (d, J = 9.4 Hz), 121.1 (d, J = 14.1 Hz), 43.3 (d, J = 72.5 Hz); HRMS(EI+) m/z $[M+ H]^+$ calcd for $C_9H_{11}OPS$ 199.0341, found 199.0349.

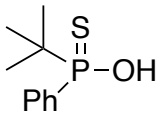
Allyl-phenylphosphinothioic Acid (Table 3.5, entry 1b).



Following the general procedure, allylmagnesium bromide (1.0 M in diethyl ether, 3.5 equiv, 8.75 mmol) in THF (10 mL) at 0 °C was reacted with a solution of butyl-phenyl-H-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental sulfur (5.0 equiv, 12.5 mmol) was then added to afford pure allyl-phenylphosphinothioic acid as a light-yellow oil (0.4 g, 67%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.85 (ddd, J = 13.1, 8.3, 1.4 Hz, 2H), 7.56−7.49 (m, 1H), 7.49−7.40 (m, 2H), 5.85−5.42 (m, 1H), 5.25− 4.86 (m, 2H), 3.12−2.63 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (d, J =

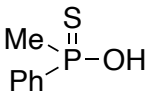
103.5 Hz), 132.2 (d, J = 3.0 Hz), 131.0 (d, J = 11.2 Hz), 128.4 (d, J = 13.1 Hz), 127.1 (d, J = 9.4 Hz), 121.1 (d, J = 14.1Hz), 43.3 (d , J = 72.5 Hz); HRMS (EI+) m/z $[M+ H]^+$ calcd for $C_9H_{11}OPS$ 199.0341, found 199.0349.

Phenyl-tert-butylphosphinothioic Acid (Table 3.5, entry 2).



Following the general procedure, *tert*-butylmagnesium chloride (1.0 M in THF, 5.0 equiv, 12.5 mmol) in THF (10 mL) at 0 °C was reacted with a solution of butyl-phenyl-*H*-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental sulfur (5.0 equiv, 12.5 mmol) was then added to afford crude phenyl-*tert*-butylphosphinothioic acid as a brown oil (NMR yield: 37%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 71.3 (s).

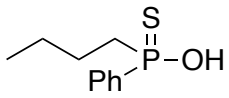
Methyl-phenylphosphinothioic Acid (Table 3.5, entry 3).



Following the general procedure, methyllithium (1.6 M in diethyl ether, 2.5 equiv, 6.25 mmol) in diethyl ether (10 mL) at -78 °C was reacted with a solution of butyl-phenyl-*H*-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental sulfur (3.0 equiv, 7.5 mmol) was then added to afford pure methyl-phenylphosphinothioic acid as a colorless oil (0.40 g, 91%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.90 (ddd, J = 13.7, 8.3, 1.4 Hz, 2H), 7.53−7.49 (m, 1H), 7.49−7.33 (m, 2H), 2.00 (d, J = 13.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (d, J = 104.6 Hz), 132.1 (d, J = 3.0 Hz), 130.3

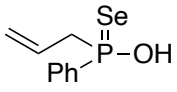
(d, J = 11.8 Hz), 128.5 (d, J = 13.2 Hz), 25.1 (d, J = 78.4 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for C_7H_9OPS 173.0184, found 173.0185.

n-Butyl-phenylphosphinothioic Acid (Table 3.5, entry 4).



Following the general procedure, n-butyllithium (2.5 M in hexanes, 2.5 equiv, 6.25 mmol) in diethyl ether (10 mL) at -78 °C was reacted with a solution of butyl-phenyl-*H*-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental sulfur (3.0 equiv, 7.5 mmol) was then added to afford pure *n*-butyl-phenylphosphinothioic acid as a light yellow oil (0.43 g, 80%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 86.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.97−7.75 (m, 2H), 7.56−7.49 (m, 1H), 7.47−7.35 (m, 2H), 2.24−1.97 (m, 2H), 1.62−1.43 (m, 2H), 1.40−1.23 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.2 (d, J = 101.2 Hz), 131.9 (d, J = 3.0 Hz), 130.7 (d, J = 11.3 Hz), 128.4 (d, J = 12.9 Hz), 36.9 (d, J = 75.2 Hz), 24.5 (d, J = 3.4 Hz), 23.4 (d, J = 18.1 Hz), 13.6; HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{10}H_{15}OPS$ 215.0654, found 215.0659.

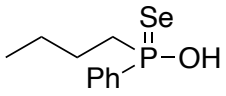
Allyl-phenylphosphinoselenoic Acid (Table 3.5, entry 5).



Following the general procedure, allylmagnesium bromide (1.0 M in diethyl ether, 3.5 equiv, 8.75 mmol) in THF (10 mL) at 0 °C was reacted with a solution of butyl-phenyl-*H*-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental selenium (5.0 equiv, 12.5 mmol) was then added to afford pure allyl-phenylphosphinoselenoic acid as an orange oil (0.50

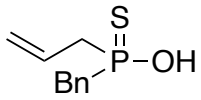
g, 65%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 78.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.87 (m, J = 13.3, 8.3, 1.5 Hz, 2H), 7.50 (dd, J = 7.3, 2.0 Hz, 1H), 7.44 (ddd, J = 6.9, 5.5, 2.6 Hz, 2H), 5.69 (ddd, J = 16.7, 9.8, 6.5 Hz, 1H), 5.16 (ddd, J = 10.2, 5.0, 1.4 Hz, 1H), 5.04 (m, J = 17.0, 6.0, 1.5 Hz, 1H), 3.11 (ddd, J = 17.1, 7.5, 2.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7 (d, J = 91.3 Hz), 132.2 (d, J = 3.1 Hz), 131.0 (d, J = 11.4 Hz), 128.3 (d, J = 13.1 Hz), 127.3 (d, J = 9.4 Hz), 121.1 (d, J = 14.1 Hz), 45.0 (d, J = 62.9 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_9H_{11}OPSe$ 246.9785, found 246.9785.

n-Butyl-phenylphosphinoselenoic Acid (Table 3.5, entry 6).



Following the general procedure, *n*-butyllithium (2.5 M in hexanes, 2.5 equiv, 6.25 mmol) in diethyl ether (10 mL) at -78 °C was reacted with a solution of butyl-phenyl-*H*-phosphinate (1.0 equiv, 2.50 mmol,) in THF (4 mL). Elemental selenium (3.0 equiv, 7.5 mmol) was then added to afford pure *n*-butyl-phenylphosphinoselenoic acid as an orange oil (0.45 g, 72%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 83.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, J = 13.3, 8.2, 1.5 Hz, 2H), 7.55−7.49 (m, 1H), 7.49− 7.42 (m, 2H), 7.26−7.22 (m, 1H), 2.45−2.12 (m, 2H), 1.68−1.44 (m, 2H), 1.46−1.17 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (d, J = 89.7 Hz), 132.0 (d, J = 3.0 Hz), 130.7 (d, J = 11.6 Hz), 128.4 (d, J = 12.9 Hz), 38.6 (d, J = 65.1 Hz), 24.9 (d, J = 3.2 Hz), 23.3 (d, J = 18.1 Hz), 13.6; HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{10}H_{15}OPSe$ 257.0158, found 257.0161.

Allyl-benzylphosphinothioic Acid (Table 3.5, entry 7).



Following the general procedure, allylmagnesium bromide (1.0 M in diethyl ether, 3.5 equiv, 8.75 mmol) in THF (10 mL) at 0 °C was reacted with a solution of ethyl-benzyl-*H*-phosphinate (1.0 equiv, 2.50 mmol) in THF (4 mL). Elemental sulfur (5.0 equiv, 12.5 mmol) was then added to afford pure allyl-benzylphosphinothioic acid as a light-yellow oil (0.33 g, 62%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 88.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.46 (m, 1H), 7.32 m, J = 11.2, 8.8, 5.0, 2.9 Hz, 5H), 6.03−5.73 (m, 1H), 5.35−5.04 (m, 2H), 3.42 (d, J = 14.9 Hz, 2H), 2.96−2.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.1 (d, J = 8.4 Hz), 130.3 (d, J = 5.8 Hz), 128.6 (d, J = 3.2Hz), 127.5 (d, J = 9.1 Hz), 127.3 (d, J = 3.7 Hz), 121.2 (d, J = 13.7 Hz), 42.2 (d, J = 64.5 Hz), 39.8 (d, J = 68.3 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{10}H_{13}OPS$ 213.0497, found 213.0497.

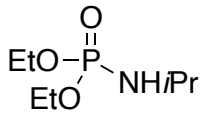
General Procedure for the Chlorination of $R^1R^2P(O)OR^3$ and Amination of $R^1R^2P(O)Cl$ (Scheme 3.15).

The appropriate phosphonate or phosphinate (1 equiv) in DCM (0.1-0.4 M) was added oxalyl chloride (1.2-2.0 equiv) and DMF (10 mol %) dropwise under argon. The reaction mixture was brought to reflux and stirred for the appropriate time (24 - 48 h). The crude product was concentrated under a vacuum to remove all volatiles and used directly in the next step.

To a solution of DIPEA (1.2 equiv), amine (1.2 equiv) in DCM (0.5 M) was added at 0 °C the appropriate chlorophosphinate or chlorophosphonate (1 equiv) dropwise under argon. The reaction mixture was brought to room temperature and stirred overnight. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and

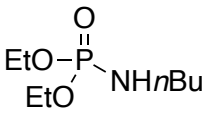
the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under a vacuum to afford the pure product either without further purification or after column chromatography.

*Diethyl-N-isopropylphosphoramidate **63** (Scheme 3.15, entry a).*



Following the general procedure, $(EtO)_2P(O)Cl$ (1 equiv, 10 mmol) was reacted with isopropylamine (1.2 equiv, 12 mmol) and DIPEA (1.2 equiv, 12 mmol,) in DCM (20 mL) to afford diethyl-*N*-isopropylphosphoramidate **63** as an orange oil (1.6 g, 98%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07−3.70 (m, 4H), 3.19 (m, J = 9.4, 8.0, 6.4 Hz, 1H), 2.84 (t, J = 10.1 Hz, 1H), 1.18 (t, J = 7.1 Hz, 6H), 1.02 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.8 (d, J = 5.4 Hz), 43.6, 25.1 (d, J = 5.7 Hz), 16.1 (d, J = 7.3 Hz).

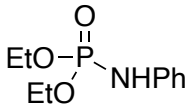
*Diethyl-N-butylphosphoramidate **64** (Scheme 3.15, entry a).*



Following the general procedure, $(EtO)_2P(O)Cl$ (1 equiv, 10 mmol) was reacted with *n*-butylamine (1.2 equiv, 12 mmol) and DIPEA (1.2 equiv, 12.0 mmol) in DCM (20 mL) to afford diethyl-*N*-butylphosphoramidate **64** as an orange oil (1.8 g, 86%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12−3.81 (m, 4H), 2.96− 2.77 (m, 3H),

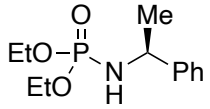
1.49−1.38 (m, 2H), 1.33 (d, J = 22.5 Hz, 2H), 1.28 (td, J=7.1,0.8 Hz, 6H), 0.87 (t, J = 7.3 Hz, 3H).

*Diethyl-N-phenylphosphoramidate **65** (Scheme 3.15, entry a).*



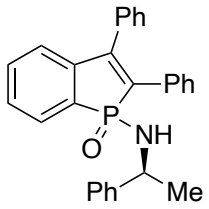
Following the general procedure, $(EtO)_2P(O)Cl$ (1 equiv, 10 mmol) was reacted with aniline (1.2 equiv, 12 mmol) and DIPEA (1.2 equiv, 12 mmol) in DCM (20 mL) to afford diethyl-*N*-phenylphosphoramidate **65** as an orange oil (1.7 g, 74%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.18 (m, 2H), 7.10−7.02 (m, 2H), 6.97 (m, J = 7.4, 1.1 Hz, 1H), 6.66 (d, J = 9.5 Hz, 1H), 4.41− 3.96 (m, 4H), 1.33 (td, J = 7.1, 0.9 Hz, 6H).

*Diethyl-N-((S)-1-phenylethyl)phosphoramidate **66** (Scheme 3.15, entry a).*



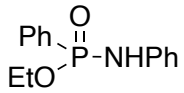
Following the general procedure, $(EtO)_2P(O)Cl$ (1 equiv, 10 mmol) was reacted with (*S*)-1-phenylethylamine (1.2 equiv, 12 mmol) and DIPEA (1.2 equiv, 12 mmol) in DCM (20 mL) to afford diethyl-*N*-((*S*)-1-phenylethyl)phosphoramidate **66** as an orange oil (1.7 g, 62%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H), 7.33−7.31 (m, 2H), 7.28−7.21 (m, 1H), 4.32 (ddd, J = 9.2, 8.5, 6.8 Hz, 1H), 4.12−4.01 (m, 2H), 3.97−3.83 (m, 1H), 3.72 (dt, J=10.0, 7.2Hz, 1H), 3.34 (t, J = 10.1 Hz, 1H), 1.48 (dd, J = 6.8, 1.0 Hz, 3H), 1.32 (td, J = 7.0, 0.8 Hz, 3H), 1.11 (td, J = 7.1, 0.9 Hz, 3H).

1-N-((S)-1-Phenylethyl)-2,3-diphenyl-1-phosphindole ***68*** *(Scheme 3.15, entry b).*



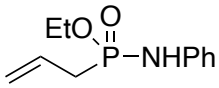
Following the general procedure, 1-butyl-2,3-diphenyl-1-phosphindole[57] **67** (1 equiv, 22.7 mmol) in DCM (200 mL) was added oxalyl chloride (2.0 equiv, 45.4 mmol) and DMF (10 mol %, 2.27 mmol), The mixture was stirred 24 h at reflux. The crude obtained was solubilized in DCM (20 mL) and reacted with DIPEA (1.2 equiv, 27.24 mmol), (*S*)-1-phenylethylamine (1.2 equiv, 27.24 mmol), and DMAP (2.27 mmol, 10 mol %) in DCM (45 mL) to afford **68** as an orange oil (6.7 g, 71%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.38 (s), 40.34 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, J = 10.2, 6.9, 1.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.39−7.35 (m, 4H), 7.21−7.05 (m, 11H), 7.04−6.95 (m, 2H), 4.30−4.07 (m, 1H), 3.22−3.05 (m, 1H), 1.35 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (dd, J = 75.7, 25.6 Hz), 144.5 (d, J = 3.6 Hz), 144.4 (d, J = 2.6 Hz), 142.4 (dd, J = 58.0, 31.9 Hz), 134.3 (dd, J = 16.9, 5.0 Hz), 133.1 (m), 132.6 (m), 129.1 (m), 128.8 (d, J = 12.2 Hz), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1 (d, J = 2.6 Hz), 128.1 (d, J = 19.7 Hz), 127.6 (d, J = 21.9 Hz), 127.0 (d, J = 12.1 Hz), 125.8 (d, J = 17.7 Hz), 123.5 (dd, J = 18.4, 12.5 Hz), 51.0 (d, J = 25.2 Hz), 25.6 (d, J = 7.2 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{28}H_{24}NOP$ 422.1668, found 422.1660.

*Ethyl-phenyl-N-phenylphosphoramidate **70** (Scheme 3.15, entry c).*



Following the general procedure, diethyl phenylphosphonate **69** (1 equiv, 10 mmol) in DCM (25 mL) was added oxalyl chloride (1.2 equiv, 12 mmol) and DMF (10 mol%, 1 mmol). The mixture was stirred 48 h at reflux. After cooling down the reaction to rt, the reaction mixture was added directly at 0 °C to the aniline (10 equiv, 100 mmol) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under a vacuum. The crude product was crystallized in a mixture of ethyl acetate and hexanes to afford ethyl-phenyl-*N*-phenylphosphoramidate **70** as a brown solid (1.8 g, 70%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.81 (m, 2H), 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.43 (m, J = 7.8, 3.8 Hz, 2H), 7.15 (m, J = 7.7 Hz, 2H), 7.01−6.94 (m, 2H), 6.89 (d, J = 7.4 Hz, 1H), 4.41−4.29 (m, 1H), 4.26−4.09 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H).

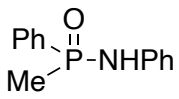
*Allyl-O-ethyl-N-phenylphosphoramidate **72** (Scheme 3.15, entry d).*



Under neat conditions allyl bromide (10 mmol, 1.0 equiv) and triethyl phosphite (10 mmol, 1.0 equiv) were brought to reflux for 24 h under argon. After concentration under a vacuum, following general procedure, the crude product was solubilized in DCM (25 mL) and oxalyl chloride (1.2 equiv, 12 mmol) and DMF (10 mol %, 1 mmol), were added and stirred at reflux for 24 h. After cooling down the reaction to rt, the reaction mixture was added directly

at 0 °C to the aniline (100 mmol, 10 equiv) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under a vacuum. The crude obtained was purified by column chromatography (ethyl acetate 100%) to afford allyl-*O*-ethyl-*N*-phenylphosphoramidate 72 as a brown oil (1.6 g, 88%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.9 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.5, 7.2 Hz, 2H), 7.09−7.02 (m, 3H), 6.98−6.86 (m, 1H), 5.91−5.69 (m, 1H), 5.19−5.00 (m, 2H), 4.23 mt, J = 10.2, 7.2 Hz, 1H), 4.06 (m, J = 10.2, 7.8, 7.0 Hz, 1H), 2.85−2.67 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 129.4, 127.1 (d, J = 10.4 Hz), 121.2, 120.3 (d, J = 14.2 Hz), 117.3 (d, J = 6.3 Hz), 60.3 (d, J = 7.2 Hz), 31.7 (d, J = 127.1 Hz), 16.2 (d, J = 6.9 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{11}H_{16}NO_2P$ 226.0991, found 226.0991.

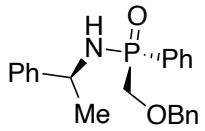
*Methyl-N,P-diphenylphosphinic amide **73** (Scheme 3.15, entry e).*



Following the general procedure, to **60** (1.0 equiv, 46.75 mmol,) in DCM (125 mL) was added dropwise oxalyl chloride (1.2 equiv, 62.52 mmol) at 0 °C under argon. The reaction mixture was stirred overnight at rt, then was added directly at 0 °C to the aniline (10.0 equiv, 467.5 mmol) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under a vacuum. The crude obtained was purified by column chromatography (ethyl acetate 100%) to afford methyl-*N,P*-diphenylphosphinic amide **73** as a brown solid (9.2 g, 85%). ^{31}P NMR (162 MHz, DMSO-d_6) δ 23.9 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 11.8 Hz, 1H), 7.79−7.71 (m, 2H),

7.49 (m, J = 7.6, 7.2, 3.9 Hz, 3H), 7.08 (dd, J = 8.5, 7.3 Hz, 2H), 7.03−6.86 (m, 2H), 6.80−6.59 (m, 1H), 1.70 (d, J = 14.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 142.8, 134.8 (d, J = 120.1 Hz), 131.9 (d, J = 2.7 Hz), 131.6 (d, J = 10.1 Hz), 129.3, 129.0 (d, J = 12.3 Hz), 120.6, 117.8 (d, J = 6.8 Hz), 17.7 (d, J = 91.7 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{13}H_{14}NOP$ 232.0886, found 232.0891.

(Sp)-N-((S)-1-phenylethyl)(benzoxymethyl)phenylphosphinic amide ***75*** *(Scheme 3.15, entry f).*



To a solution of (*S*)-1-phenylethylamine (3 equiv, 3.74 mmol) in THF (6 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 2.6 equiv 3.25 mmol,) and stirred for 1 h under argon. **74** (1 equiv, 1.25 mmol), in THF (4 mL) at -78 °C was added dropwise to the reaction mixture and stirred for 3 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under a vacuum. The crude obtained was purified by column chromatography (ethyl acetate:methanol 100:0 to 90:10) to afford (*Sp*)-*N*-((*S*)-1-phenylethyl)(benzoxymethyl)-phenylphosphinic amide **75** as a white solid (300 mg, 66%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (ddd, J = 11.7, 8.2, 1.4 Hz, 2H), 7.57 (dd, J = 7.5, 1.5 Hz, 1H), 7.53−7.46 (m, 2H), 7.45−7.40 (m, 2H), 7.36− 7.26 (m, 6H), 7.20−7.14 (m, 2H), 4.59 (td, J = 8.7, 6.7 Hz, 1H), 4.42 (s, 2H), 3.80−3.73 (m, 2H), 3.32 (t, J = 8.6 Hz, 1H), 1.49 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (d, J = 4.2 Hz), 137.1, 132.3 (d, J = 2.9 Hz), 132.1 (d, J = 9.5 Hz), 132.1, 130.9, 128.5 (d, J = 12.5 Hz), 128.4 (d, J = 12.4 Hz), 127.9, 127.9, 127.2, 126.2,

75.1 (d, J = 12.9 Hz), 67.1 (d, J = 110.0 Hz), 50.1 (d, J = 1.4 Hz), 25.6 (d, J = 5.0 Hz); HRMS (EI+) m/z [M+H]+ calcd for $C_{22}H_{24}NO_2P$ 366.1617, found 366.1631.

General Procedure of the Stec Reaction with Conditions A (Table 3.6).

To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added NaH (60% dispersion in mineral oil, 3 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (3 equiv) was then added dropwise and stirred for 2 h at rt. Ethyl acetate was then added, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford the pure product without further purification.

General Procedure of the Stec Reaction with Conditions B (Table 3.6).

To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added *n*-BuLi (2.5 M in hexanes in mineral oil, 2.0 equiv) at -78 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (3.0 equiv) was then added dropwise and stirred for 2 h at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

General Procedure of the Stec Reaction with Conditions C (Table 3.6).

To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.5 equiv) at 0 °C under argon. The

reaction mixture stirred at rt for 1 h. Carbon disulfide (3.0 equiv) was then added dropwise and stirred for 2 h at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

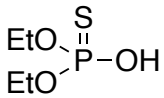
General Procedure of the Stec Reaction with Conditions D (Table 3.6).

To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.5 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (5.0 equiv) was then added dropwise and stirred overnight at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

General Procedure of the Stec Reaction with Conditions E (Table 3.6).

To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added NaH (60% dispersion in mineral oil, 2.0 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (5.0 equiv) was then added dropwise and stirred overnight at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

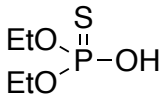
Diethyl-phosphorothioic acid (Table 3.6, entry 1a).



Following general procedure with conditions A, **63** (1 equiv, 1 mmol) was reacted with NaH (60% dispersion in mineral oil, 3 equiv, 3 mmol) in THF (10 mL). Carbon disulfide (3 equiv, 3 mmol) was added to afford the product as a light-yellow oil (0.15 g, 88%): ^{31}P NMR

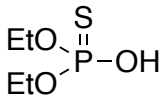
(162 MHz, $CDCl_3$) δ 65.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (dd, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

Diethyl-phosphorothioic acid (Table 3.6, entry 2b).



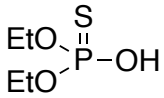
Following general procedure with conditions B, **64** (1 equiv, 1 mmol) was reacted with *n*-BuLi (2.5 M in hexanes, 2 equiv, 2 mmol) in THF (10 mL). Carbon disulfide (3 equiv, 3 mmol) was added to afford diethyl-phosphorothioic acid as a light-yellow oil (0.16 g, 95%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (dd, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

Diethyl-phosphorothioic acid (Table 3.6, entry 3b).



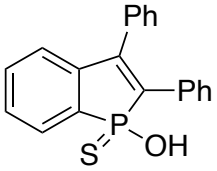
Following general procedure with conditions B, **65** (1 equiv, 1 mmol) was reacted with *n*-BuLi (2.5 M in hexanes, 2 equiv, 2 mmol,) in THF (10 mL). Carbon disulfide (3.0 equiv, 3.0 mmol) was added and stirred overnight to afford diethyl-phosphorothioic acid as a light-yellow oil (0.17 g, 99%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (dd, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

Diethyl-phosphorothioic acid (Table 3.6, entry 4b).



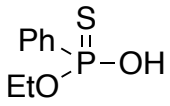
Following general procedure with conditions B, **66** (1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (2.5 M in hexanes, 2 equiv, 2 mmol) in THF (10 mL). Carbon disulfide (3 equiv, 3 mmol) was added and stirred overnight to afford diethyl-phosphorothioic acid as a light-yellow oil (0.13 g, 75%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (dd, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

2,3-Diphenyl-1-phosphindole-1-thioic acid (Table 3.6, entry 5).



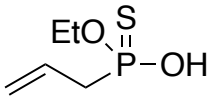
Following general procedure with conditions B, **68** (1.0 equiv, 1.0 mmol) was reacted with *n*-BuLi (2.5 M in hexanes, 2 equiv, 2 mmol) in THF (7 mL). Carbon disulfide (3 equiv 3 mmol,) was added to afford 2,3-diphenyl-1-phosphindole-1-thioic acid as a light yellow solid (0.50 g, 85%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 80.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.81 (m, 1H), 7.46 (ddt, J = 6.5, 3.1, 1.8 Hz, 4H), 7.42−7.36 (m, 3H), 7.34−7.29 (m, 2H), 7.25 (dq, J = 4.9, 1.9, 1.4 Hz, 3H), 7.23−7.16 (m, 1H), 6.28 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (d, J = 25.6 Hz), 141.3 (d, J = 31.2 Hz), 133.6 (d, J = 17.0 Hz), 133.3 (d, J = 6.9 Hz), 132.8 (d, J = 1.8 Hz), 132.1 (m), 129.7, 129.6, 129.4 (d, J = 11.9 Hz), 129.3, 128.7, 128.7, 128.3, 128.1 (d, J = 1.5 Hz), 127.7 (d, J = 10.8 Hz), 123.9 (d, J = 12.4 Hz); HRMS (EI+) m/z $[M + H]^+$ calcd for $C_{20}H_{15}OPS$ 335.0654, found 335.0648.

Ethyl-phenylphosphorothioic acid (Table 3.6, entry 6).



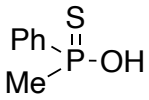
Following general procedure with conditions B, **70** (1.0 equiv, 1.0 mmol) was reacted with *n*-BuLi (2.5 M in hexanes, 2.0 mmol, 2.0 equiv) in THF (10 mL). Carbon disulfide (3.0 equiv, 3.0 mmol) was added to afford ethyl-phenylphosphorothioic acid as a light orange oil (0.24 g, 79%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 79.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.06−7.84 (m, 2H), 7.53 (m, J = 7.2, 1.6 Hz, 1H), 7.45 (m, J = 7.0, 2.3 Hz, 2H), 4.19 (m, J = 9.5, 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

Allyl-ethylphosphorothoic acid (Table 3.6, entry 7).



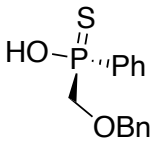
Following general procedure with conditions D, **72** (1 equiv, 5 mmol) was reacted with lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.25 equiv, 1.875 mmol) in THF (10 mL). Carbon disulfide (5.0 equiv, 7.5 mmol) was added to afford allyl-ethylphosphorothoic acid as a red oil (0.19 g, 76%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 87.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.81 (m, J = 17.0, 8.0 Hz, 1H), 5.28− 4.99 (m, 2H), 4.16 (m, J = 8.0 Hz, 2H), 2.86 (dd, J = 19.7, 7.4 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.1 (d, J = 10.6 Hz), 120.8 (d, J = 15.4 Hz), 62.5 (d, J = 7.3 Hz), 40.4 (d, J = 108.6 Hz), 16.0 (d, J = 7.3 Hz); HRMS (EI+) m/z [M + H]+ calcd for $C_5H_{11}O_2PS$ 167.0290, found 167.0290.

Methyl-phenylphosphinothioic acid (Table 3.6, entry 8b).



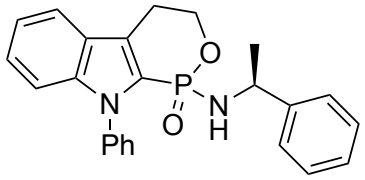
Following general procedure with conditions D, **73** (1.0 equiv, 1.5 mmol) was reacted with lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.25 equiv, 1.875 mmol) in THF (10 mL). Carbon disulfide (5.0 equiv, 7.5 mmol,) was added and stirred overnight to afford methyl-phenylphosphinothioic acid as a colorless oil (0.22 g, 85%): ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.94−7.83 (m, 2H), 7.53−7.48 (m, 1H), 7.47−7.40 (m, 2H), 2.00 (d, J = 13.7 Hz, 3H); HRMS (EI+) m/z $[M + H]^+$ calcd for C_7H_9OPS 173.0184, found 173.0185.

(S_p)-(Benzoxymethyl)phenylphosphinothioic acid (Table 3.6, entry 9).



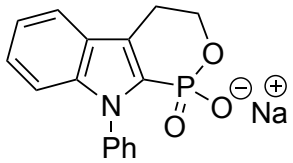
Following general procedure with conditions E, **75** (0.82 mmol, 1.0 equiv) was reacted with NaH (60% dispersion in mineral oil, 2 equiv, 1.64 mmol) in THF (5 mL). Carbon disulfide (10 equiv, 8.2 mmol) was added to afford (S_p)-(benzoxymethyl)phenylphosphinothioic acid as a light yellow oil (0.21 g, 72%, > 99% de): ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, J = 13.1, 7.6 Hz, 2H), 7.74−7.60 (s, 1H), 7.56 (m, J = 7.5 Hz, 1H), 7.47 (m, J = 7.6, 3.8 Hz, 2H), 7.37−7.26 (m, 3H), 7.22−7.13 (m, 2H), 4.79−4.44 (m, 2H), 4.27− 3.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 132.4 (d, J = 2.6 Hz), 131.6 (d, J = 11.2 Hz), 128.5, 128.5, 128.4, 128.1, 128.1, 75.0 (d, J = 9.1 Hz), 72.9 (d, J = 90.5 Hz); HRMS (EI+) m/ z $[M + H]^+$ calcd for $C_{14}H_{15}O_2PS$ 279.0603, found 279.0606.

*((S)-1-phenylethylamine)-phosphonamide-N-phenylcarbazole **76** (Scheme 3.16).*



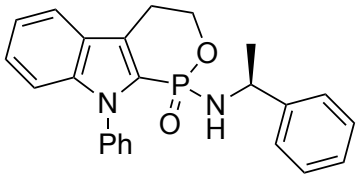
To a solution of **52** (1 equiv, 1.5 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C in an ice bath. Oxalyl chloride (1.2 equiv, 1.8 mmol) was added dropwise, followed by DMF (10 mol%, 0.15 mmol) under nitrogen. The reaction was brought to rt and stirred overnight. A ^{31}P NMR of the crude reaction mixture was taken (NMR yield: 100% SM). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.4 (s).

*Sodium methylphosphonic acid-N-phenylcarbazole salt **77** (Scheme 3.17).*



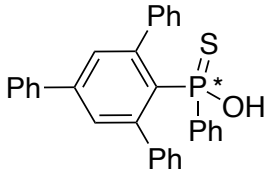
In a rb flask was added **52** (1 equiv, 1.5 mmol), NaI (1.1 equiv, 1.65 mmol) and 2-butanone (5 mL). The reaction was brought to 60 °C in an oil bath and stirred overnight. The reaction was then cooled, and the precipitant filtered to yield **77** as a white solid (0.5 g, 99%). ^{31}P NMR (162 MHz, D_2O) δ -0.72 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, J = 8.4, 1.4 Hz, 2H), 7.66 – 7.44 (m, 3H), 7.40 – 7.22 (m, 2H), 7.11 (dt, J = 22.4, 7.1 Hz, 2H), 4.29 (dt, J = 13.8, 5.6 Hz, 2H), 2.87 (td, J = 5.7, 2.4 Hz, 2H).

*((S)-1-phenylethylamine)-phosphonamide-N-phenylcarbazole **76** (Scheme 3.18, entry b).*



In a reaction tube was added **77** (1 equiv, 0.5 mmol), EDC (1.5 equiv, 0.75 mmol), DMAP (0.3 equiv, 0.15 mmol), DIPEA (2.0 equiv, 1 mmol) and (*S*)-(1)-phenylethylamine (1 equiv, 0.5 mmol) in DMF (2.5 mL), under N_2. The reaction was brought to 80 °C and stirred for 24 h. The reaction was brought to rt. The DMF was concentrated under vacuum, the crude diluted with ethyl acetate and transferred to separatory funnel. The organic layer was washed with NH_4Cl (sat. aq.) and brine, then separated and dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by column chromatography on silica gel (hexanes:ethyl acetate 50:50 to 10:90) to afford the product **76** as a mixture of diastereoisomers (NMR yield: 61%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.0 (s), 8.7 (s).

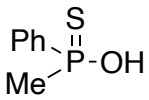
*2,4,6,-triphenyl(phenyl) thiophosphinic acid **79** (Scheme 3.20).*



To a solution of (S_p) or (R_p)- ***78*** (1.0 equiv, 0.3 mmol) in dry THF (3 mL) was added at 0 °C NaH (2.0 equiv, 0.6 mmol, 60% dispersion in mineral oil) under argon. The reaction stirred for 1 h at rt, and then carbon disulfide (5.0 equiv, 1.6 mmol) was added dropwise and stirred for 16 h at rt. Ethyl acetate and hexanes were added and washed (3×) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was

dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude mixture was solubilized in DCM and the insoluble precipitate filtered out. The filtrate was concentrated under a vacuum (NMR yield: 100% sm). ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.3 (s).

*Methyl-phenylphosphinothioic acid **61** via one-pot transamidation and CS_2 (Scheme 3.22, entry b).*

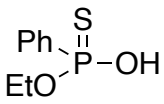


To a solution of methyl-phenylphosphonoic acid (1 equiv, 16.01 mmol) in DCM (100 mL) was added dropwise oxalyl chloride (1.2 equiv, 19.22 mmol) at 0 °C under argon. The reaction mixture stirred for 3 h, then was added directly at 0 °C to a mixture of butanol (1.2 equiv, 19.22 mmol) and Et_3N (1.2 equiv, 19.22 mmol), and was stirred overnight at rt. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford *n*-butyl-methylphenylphosphinate **80** as a colorless oil (2.1 g, 77%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, J = 12.0, 8.2, 1.5 Hz, 2H), 7.41 (dd, J = 7.4, 1.5 Hz, 1H), 7.38−7.32 (m, 2H), 3.87 (dd, J = 10.0, 6.8 Hz, 1H), 3.61 (dd, J = 10.0, 6.9 Hz, 1H), 1.53 (d, J = 14.6 Hz, 3H), 1.50−1.41 (m, 2H), 1.33−1.16 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H).

To a solution of aniline (3 equiv, 3 mmol) in THF (10 mL) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 3 equiv, 3 mmol) at 0 °C under argon. The reaction stirred at rt for 1 h; then a solution of **80** (1 equiv, 1 mmol) in THF (5 mL) was added via cannula at 0 °C and stirred for 2 h at rt. Carbon disulfide (5 equiv, 5 mmol) was then added dropwise at rt and stirred overnight. EtOAc was then added, and the organic layer was washed

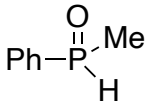
with a saturated aqueous solution of $NaHCO_3$. The two layers were separated; the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford methyl-phenylphosphinothioic acid **61** as a colorless oil (0.15 g, 85%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.94−7.83 (m, 2H), 7.53−7.48 (m, 1H), 7.47−7.40 (m, 2H), 2.00 (d, J = 13.7 Hz, 3H); HRMS (EI+) m/z $[M + H]^+$ calcd for C_7H_9OPS 173.0184, found 173.0185.

Representative Procedure for a one and trans-amination/CS_2 of $R^1R^2P(O)OR^3$ (Table 3.7, entry 4).



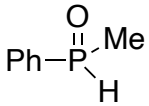
To a solution of aniline (3.0 equiv, 3.0 mmol) in THF (10 mL) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 3.0 equiv, 3.0 mmol) at 0 °C under argon. The reaction stirred at rt for 1 h; then a solution of diethylphenylphospoinate (1.0 equiv, 1.0 mmol) in THF (5 mL) was added via cannula at 0 °C and stirred for 2 h at rt. Carbon disulfide (5 equiv, 5 mmol) was then added dropwise at rt and stirred overnight. Ethyl acetate was then added, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated; the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum (NMR yield: 11%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 79.7 (s).

Methyl-phenyl-H-phosphinate (Scheme 3.24, entry a).



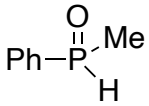
To a rb flask was added methyl-phenylphosphinyl pyrrolidine (1 equiv, 2 mmol) in distilled toluene (20 mL) under argon. Trichlorosilane (1.1 equiv, 2.2 mmol) was added dropwise at rt, then the reaction was brought to reflux for 1 h. The flask was cooled to rt and EtOAc (10 mL) was added, and the mixture transferred to a separatory funnel. The organic layer was washed with 2 M NaOH (10 mL), and brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum to afford the methyl-phenyl-*H*-phosphinate (0.04 g, 14%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4 (d).

Methyl-phenyl-H-phosphinate (Scheme 3.24, entry b).



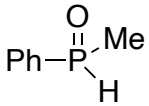
To a rb flask was added methyl-phenyl-*N*-butylphosphinamide (1 equiv, 2 mmol) in distilled toluene (20 mL) under argon. Trichlorosilane (1.1 equiv, 2.2 mmol) was added dropwise at rt, then the reaction was brought to reflux for 1 h. The flask was cooled to rt and EtOAc (10 mL) was added, and the mixture transferred to a separatory funnel. The organic layer was washed with 2 M NaOH (10 mL), and brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum to afford the methyl-phenyl-*H*-phosphinate (0.12 g, 17%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.5 (d).

Methyl-phenyl-H-phosphinate (Scheme 3.24, entry c).



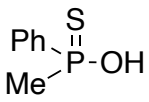
To a rb flask was added *O*-menthyl-acetylmethyl-*N*-butylphosphinamide (1 equiv, 0.57 mmol) in distilled toluene (6 mL) under argon. Trichlorosilane (1.1 equiv, 0.63 mmol) was added dropwise at rt, then the reaction was brought to reflux for 1 h. The flask was cooled to rt and EtOAc (5 mL) was added, and the mixture transferred to a separatory funnel. The organic layer was washed with 2 M NaOH (5 mL), and brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum (NMR yield: 24%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.9 (d).

Methyl-phenyl-H-phosphinate (Scheme 3.24, entry d).



To a rb flask was added methyl-phenyl-*N*-1-phenylethylphosphinamide (1 equiv, 2 mmol) in distilled toluene (20 mL) under argon. Trichlorosilane (2 equiv, 4 mmol) was added dropwise at rt, then the reaction was brought to reflux for 1 h. The flask was cooled to rt and EtOAc (10 mL) was added, and the mixture transferred to a separatory funnel. The organic layer was washed with 2M NaOH (10 mL), and brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum (NMR yield: 0%).

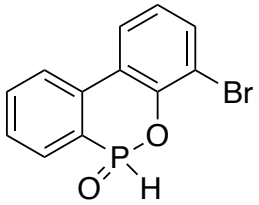
Representative procedure for the conversion of $R^1R^2P(O)OH$ to $R^1R^2P(S)OH$ via isothiocyanate rearrangement (Table 3.8, entry 4).



To a rb flask was added **60** (1 equiv, 1.3 mmol) in toluene (10 mL) under argon. DIPEA (2 equiv, 2.6 mmol) was added and stirred at rt for 10 min, following the addition of allyl isothiocyanate (1 equiv, 1.3 equiv). The flask was brought to 90 °C in an oil bath and stirred for 16 h. The reaction was cooled to rt, and an NMR of the crude was taken (NMR yield: 0%).

4.1 *O*-DOPO *P*-Stereogenic CPA

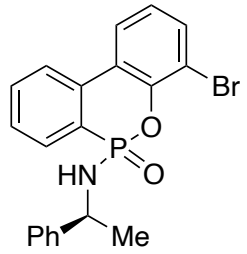
8-Bromo-DOPO-H-phosphinate ***83*** *(Scheme 4.2).*



To a rb-flask was added 2-phenylphenol (1 equiv, 25 mmol) in distilled DCM (100 mL) under argon. DIPA (0.1 equiv, 2.5 mmol) was added, followed by *N*-bromosuccinimide (1 equiv, 25 mmol). The reaction was brought to reflux for 16 h, then cooled to rt. The mixture was transferred to a separatory funnel, and the organic layer was washed with 3 M HCl (40 mL), and brine. The layers were separated, and the organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (hexanes:ethyl acetate 95:05) to afford 3-bromo-2-hydroxylbiphenyl **82** (5.6 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H), 7.53 (ddt, J = 8.1, 6.6, 1.1 Hz, 3H), 7.49 – 7.45 (m, 1H), 7.33 (dd, J = 7.7, 1.6 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 5.77 (s, 1H).

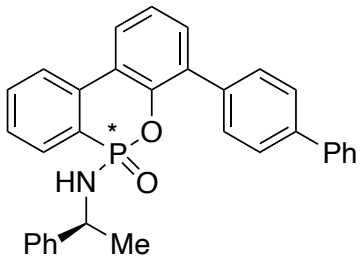
To a rb flask was added **82** (1 equiv, 20 mmol) and $ZnCl_2$ (1.5 mol%, 0.3 mmol) in air. The flask was brought to 150 °C in an oil bath, and PCl_3 (1.25 equiv, 25 mmol) was added dropwise over 1 h. The reaction stirred at 150 °C for 8 h, then cooled to rt. EtOAc (5 mL) and H_2O (5 mL) were added to the mixture and stirred for 10 min and then transferred to a separatory funnel. The organic layer was washed with brine, then the layers were separated, dried with $MgSO_4$, filtered, and concentrated under vacuum to afford the product **83** (5.3 g, 89%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 641.5, 601.9 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.90 (ddd, J = 12.7, 7.7, 1.4 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.66 (dt, J = 8.0, 1.3 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.18 (td, J = 8.0, 0.6 Hz, 1H).

*(N-(S)-1-phenylethylamino)-8-bromo-DOPO-phosphine-oxide **84** (Scheme 4.3).*



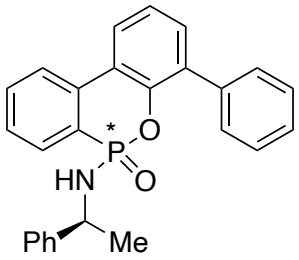
To a rb flask was added DIPEA (1.2 equiv, 21.5 mmol), iodoform (1.2 equiv, 21.5 mmol), *(S)*-1-phenylethylamine (1.2 equiv, 21.5 mmol) in distilled CH_3CN (15 mL) under argon. The reaction flask was cooled to 0 °C. In an addition funnel was added **83** (1 equiv, 18 mmol) in CH_3CN (5 mL) and added dropwise to the reaction mixture. The flask was brought to rt and stirred for 16 h. The solvent was concentrated under vacuum, and the crude residue dissolved in EtOAc (15 mL) and transferred to a separatory funnel. The organic layer was washed with NH_4Cl (sat. aq.) and brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified and resolved by column chromatography (hexanes:ethyl acetate 90:10) to afford the pure product **84** (4.4 g, 60%; resolved yield 43%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.02 (s) and 13.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.5, 1.3 Hz, 2H), 7.89 (dd, J = 8.1, 1.5 Hz, 1H), 7.73 (d, J = 1.1 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.31 (d, J = 4.3 Hz, 4H), 7.27 – 7.22 (m, 1H), 7.11 (td, J = 7.9, 0.5 Hz, 1H), 4.46 – 4.32 (m, 1H), 3.46 (s, 1H), 1.53 (dd, J = 6.8, 0.9 Hz, 3H).

8-Biphenyl-((S)-1-phenylethylamino)-DOPO-phosphine-oxide ***85*** *(Scheme 4.4, entry a).*



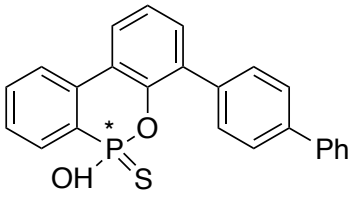
To a reaction tube was added **84** (1 equiv, 2.4 mmol), K_2CO_3 (10 equiv, 24 mmol), biphenyl boronic acid (3 equiv, 7.2 mmol) and toluene (50 mL). The reaction vessel was flushed with argon for 10 min, then $Pd(PPh_3)_4$ (4 mol%, 0.096 mmol) was added, then the tube was sealed and brought to 100 °C in an oil bath and stirred for 16 h. Once the reaction was brought to rt, EtOAc (20 mL) was added, and the mixture was transferred to a separatory funnel. The organic layer was washed with NH_4Cl (sat. aq.) and brine. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (hexanes:EtOAc 80:20 to 50:50) to afford the pure product **85** (0.3 g, 25%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.6 (s); ring-opening δ 3.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.2, 5.8 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.83 – 7.71 (m, 2H), 7.71 – 7.66 (m, 2H), 7.63 – 7.56 (m, 2H), 7.56 – 7.49 (m, 3H), 7.49 – 7.45 (m, 3H), 7.44 – 7.38 (m, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.19 (s, 4H), 4.27 (tq, J = 9.8, 6.8 Hz, 1H), 3.45 (t, J = 9.8 Hz, 1H), 1.43 (dd, J = 6.8, 0.9 Hz, 3H).

8-Phenyl-10-((S)-(1-phenylethyl)amino)dibenzo-oxaphosphinine 10-oxide ***86*** *(Scheme 4.4, entry b).*



To a reaction tube was added **84** (1 equiv, 1.2 mmol), K_2CO_3 (3.5 equiv, 4.2 mmol), phenyl boronic acid (1 equiv, 1.2 mmol) in DMF:H_2O (15:1.2 mL). The reaction tube was flushed with argon for 10 min, then $Pd(PPh_3)_4$ (2.7 mol%, 0.03 mmol) was added, then the tube was sealed and brought to 100 °C to stir for 16h. Then flask was cooled to rt and diluted with DCM. the mixture was transferred to a separatory funnel, the organic layer was washed with NH_4Cl (sat. aq.) and brine. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under vacuum (NMR yield: 0%). Ring-opened product as the major product 80%: ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.6 (s).

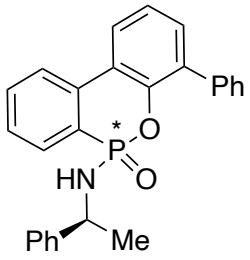
8-Biphenyl-DOPO-thiophosphorus acid ***87*** *(Scheme 4.5).*



In a rb flask was added **85** (1 equiv, 0.4 mmol) in Et_2O (15 mL) under argon. The flask was cooled to 0 °C and *n*-BuLi (2 equiv, 0.8 mmol, 2.5 M in hexanes) was added dropwise. The flask was brought to rt and stirred for 2 h. CS_2 (4 equiv, 1.6 mmol) was added at rt and stirred overnight. A crude NMR was taken to show 11% of the thiophosphorus acid **87** ^{31}P

NMR (162 MHz, $CDCl_3$) δ 68.4 (s); 40% the ring opened product ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.9 (s); and 49% unreacted starting material ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.6 (s).

(Sp)/(Rp)-8-Phenyl-10-((S)-(1-phenylethyl)amino)dibenzo-oxaphosphinine 10-oxide ***90*** *(Scheme 4.6 - path A).*

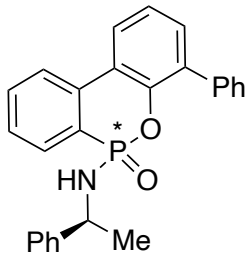


Under neat conditions 2,6-diphenylphenol (1.0 equiv, 10.0 mmol), zinc chloride (1.5 mol%, 0.15 mmol), and phosphorus trichloride (1.25 equiv, 12.50 mmol) were added to a rb flask, and brought to 150 °C in an oil bath and stirred for 8 h under argon. After cooling down the reaction to 0 °C, the reaction mixture was quenched with ethyl acetate (20 mL) and H_2O (20 mL) and stirred for 1 h. The mixture was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford the *H*-phosphinate intermediate **89** as a white solid (2.4 g, 82%). This product was used directly in the next step without further purification.

The crude mixture was dissolved in CH_3CN and added dropwise via addition funnel to a mixture of iodoform (1.2 equiv, 9.85 mmol), Et_3N (1.2 equiv, 9.85 mmol), and (*S*)-1-phenylethylamine (1.2 equiv, 9.85 mmol) at 0 °C under argon and stirred overnight at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified and resolved by column chromatography

(hexanes:ethyl acetate 45:55) to afford the product **90** as a white solid (2.4 g, 58%, resolved 22% of *Sp* and 15% of *Rp*): racemic mixture ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.86 (s), 13.53 (s); (*Sp*)- ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.46 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.96 (dd, J = 8.0, 1.7 Hz, 2H), 7.74 (d, J = 1.2 Hz, 1H), 7.63−7.46 (m, 1H), 7.44−7.30 (m, 7H), 7.21 (m, 5H), 4.38−4.20 (m, 1H), 3.37 (t, J = 9.8 Hz, 1H), 1.42 (dd, J = 6.8, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (d, J = 7.5 Hz), 143.9 (d, J = 5.5 Hz), 137.4 (d, J = 7.1 Hz), 136.9, 133.7 (d, J = 5.8 Hz), 132.7 (d, J = 2.5 Hz), 131.7, 130.1 (d, J = 9.6 Hz), 129.7, 128.5, 128.1, 127.9 (d, J = 14.7 Hz), 127.4, 127.1, 125.7, 125.4, 124.2 (d, J = 21.4 Hz), 124.0 (d, J = 11.4 Hz), 123.8, 122.8 (d, J = 11.6 Hz), 51.2, 25.2 (d, J = 4.5 Hz); (*Rp*)- ^{31}P NMR (162 MHz, CDCl3) δ 13.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.99 (m, 1H), 7.96 (dd, J = 8.1, 1.7 Hz, 1H), 7.75−7.66 (m, 2H), 7.66−7.60 (m, 2H), 7.52−7.44 (m, 3H), 7.44−7.31 (m, 3H), 7.22 (d, J = 2.0 Hz, 3H), 7.16−7.09 (m, 2H), 4.44−4.18 (m, 1H), 3.34 (t, J = 9.4 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H); HRMS (EI+) m/z [M + H]+ calcd for $C_{26}H_{22}NO_2P$ 412.1461, found 412.1473.

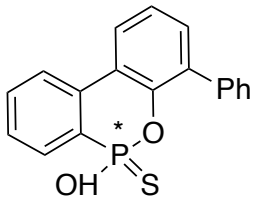
(Sp)/(Rp)-8-Phenyl-10-((S)-(1-phenylethyl)amino)dibenzo[c,e]-[1,2]oxaphosphinine 10-oxide ***90*** *(Scheme 4.6 - path B).*



Under neat conditions 2,6-diphenylphenol (1.0 equiv, 10.0 mmol) and phosphorus trichloride (2.0 equiv, 20.0 mmol) were added to a rb flask, and brought to 50 °C in an oil bath

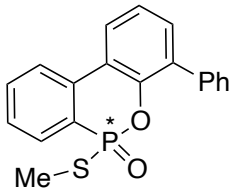
and stirred for 3 h under argon. The reaction was cooled down to rt, and zinc chloride (0.43 equiv, 4.3 mmol) was added and brought to 150 °C and stirred for 8 h under argon. After cooling to 0 °C, the crude was solubilized in toluene (20 mL), and Et_3N (2.0 equiv, 20.0 mmol) and (*S*)-1-phenylethylamine (2.0 equiv, 20.0 mmol) were added and stirred at rt for 2 h under argon. To the reaction mixture H_2O_2 (35 wt % in H_2O, 2.0 equiv, 20.0 mmol) was added at 0 °C and then stirred for 4 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified and resolved by column chromatography (hexanes:ethyl acetate 45:55) to afford pure phosphonamide **90** as a white solid (3.3 g, 78%, resolved 22% of *Sp* and 15% of *Rp*): racemic mixture ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.89 (s), 13.56 (s); (*Sp*) ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.46 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.96 (dd, J = 8.0, 1.7 Hz, 2H), 7.74 (d, J = 1.2 Hz, 1H), 7.63−7.46 (m, 1H), 7.44−7.30 (m, 7H), 7.21 (m, 5H), 4.38−4.20 (m, 1H), 3.37 (t, J = 9.8 Hz, 1H), 1.42 (dd, J = 6.8, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (d, J = 7.5 Hz), 143.9 (d, J = 5.5 Hz), 137.4 (d, J = 7.1 Hz), 136.9, 133.7 (d, J = 5.8 Hz), 132.7 (d, J = 2.5 Hz), 131.7, 130.1 (d, J = 9.6 Hz), 129.7, 128.5, 128.1, 127.9 (d, J = 14.7 Hz), 127.4, 127.1, 125.7, 125.4, 124.2 (d, J = 21.4 Hz), 124.0 (d, J = 11.4 Hz), 123.8, 122.8 (d, J = 11.6 Hz), 51.2, 25.2 (d, J = 4.5 Hz); (*Rp*) ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.99 (m, 1H), 7.96 (dd, J = 8.1, 1.7 Hz, 1H), 7.75−7.66 (m, 2H), 7.66−7.60 (m, 2H), 7.52−7.44 (m, 3H), 7.44−7.31 (m, 3H), 7.22 (d, J = 2.0 Hz, 3H), 7.16−7.09 (m, 2H), 4.44−4.18 (m, 1H), 3.34 (t, J = 9.4 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H); HRMS (EI+) m/z [M + H]+ calcd for $C_{26}H_{22}NO_2P$ 412.1461, found 412.1473.

*(S_P)/(R_P)-10-Hydroxy-8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-sulfide **41** (Scheme 4.8).*



To a solution of (*Sp*) or (*Rp*)- **90** (1.0 equiv, 2.43 mmol,) in dry THF (15 mL) was added at 0 °C NaH (3.0 equiv, 7.30 mmol, 60% dispersion in mineral oil) under argon. The reaction stirred for 1 h at rt, and then carbon disulfide (10.0 equiv, 24.30 mmol) was added dropwise and stirred for 4 h at rt. Ethyl acetate and hexanes were added and washed (3×) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude mixture was solubilized in DCM and the insoluble precipitate filtered out. The filtrate was concentrated under a vacuum to afford either the (*Sp*) or (*Rp*)- **41** product as an orange oil (0.65 g, 76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 70.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddd, J = 16.5, 7.6, 1.5 Hz, 1H), 7.99−7.82 (m, 2H), 7.77−7.56 (m, 3H), 7.51 (dddd, J = 8.6, 7.5, 3.7, 1.1 Hz, 1H), 7.52−7.40 (m, 3H), 7.35 (dddd, J = 8.2, 6.4, 3.2, 1.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (d, J = 10.5 Hz), 136.8, 134.8 (d, J = 6.2 Hz), 133.6 (d, J = 5.8 Hz), 132.9 (d, J = 2.6 Hz), 131.8, 130.3 (d, J = 13.7 Hz), 130.2 (d, J = 13.9 Hz), 129.7, 128.5, 128.3, 128.2, 127.6, 124.6, 124.2 (d, J = 11.0 Hz), 123.6 (d, J = 12.2 Hz); HRMS (EI+) m/z calcd for $C_{18}H_{13}O_2PS$ [M + H]+325.0447, found 325.0439.

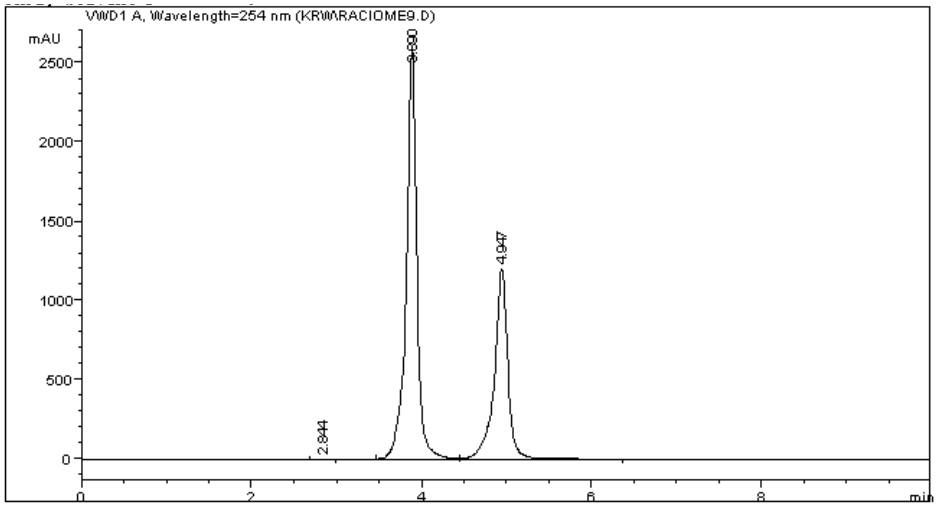
*(S_P)/(R_P)- 8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-methyl sulfide **91** (Scheme 4.9).*



The enantiomeric excess of (*Sp*)-SMe and (*Rp*)-SMe was determined and compared to the scalemic-SMe. To a solution of (*Sp*) or (*Rp*)- **41** (1.0 equiv, 0.30 mmol) in dry THF (3 mL) was added Et_3N (2 equiv, 0.62 mmol) followed by iodomethane (2.0 equiv, 0.62 mmol) at 0 °C under argon. The reaction was brought to rt and stirred for 4 h. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford the pure (*Sp*) and (*Rp*)-**91** as a white solid (0.10 g, 99%). The enantiomeric excess thus obtained was determined by a chiral HPLC analysis ((*S,S*)-Whelk-O1; eluent, hexanes/DCM = 50:50 + 0.1% TFA; flow rate, 1 mL/min; λ = 254 nm; t_1 (*Rp*) = 3.9 min, t_2 (*Sp*) = 5.0 min; (*Sp*) enantiopurity: >98% and (*Rp*) enantiopurity: >99%). (*Sp*)-SMe. ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddt, J = 8.5, 4.9, 2.3 Hz, 2H), 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.74 (dd, J = 8.4, 7.3 Hz, 1H), 7.65−7.59 (m, 2H), 7.56 (dd, J = 3.6, 1.0 Hz, 1H), 7.52−7.44 (m, 3H), 7.44−7.38 (m, 1H), 7.36 (td, J = 7.8, 0.7 Hz, 1H), 2.14 (d, J = 13.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (d, J = 9.7 Hz), 136.6 (d, J = 7.4 Hz), 136.5, 133.9 (d, J = 2.6 Hz), 133.8 (dd, J = 6.1, 0.0 Hz), 132.2, 130.4 (d, J = 10.9 Hz), 129.5, 128.7 (d, J = 14.9 Hz), 128.4, 127.8, 126.2 (d, J = 136.0 Hz), 124.9, 124.7 (d, J = 1.4 Hz), 124.4 (d, J = 11.2 Hz), 123.1 (d, J = 11.8 Hz), 11.3 (d, J = 3.7 Hz). (*Rp*)-SMe: ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15−8.01 (m, 2H), 7.94 (dd, J = 8.0, 1.7 Hz, 1H), 7.84−7.69 (m, 1H), 7.67−7.55 (m, 3H), 7.49 (ddt, J = 7.8, 6.0, 1.5 Hz, 3H),

7.46− 7.35 (m, 2H), 2.16 (d, J = 13.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 136.7 (d, J = 7.5 Hz), 136.5, 133.9, 132.2, 130.4 (d, J = 10.8 Hz), 129.5, 128.7 (d, J = 15.0 Hz), 128.3, 127.8, 126.2, 124.9, 124.6, 124.5, 124.3, 123.2 (d, J = 12.1 Hz), 11.2 (d, J = 3.8 Hz). HRMS (EI+) m/z calcd for $C_{19}H_{15}O_2PS$ $[M + H]^+$, 339.0603; found, 339.0604.

*Scalemic-**91** 8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-methyl sulfide HPLC.*



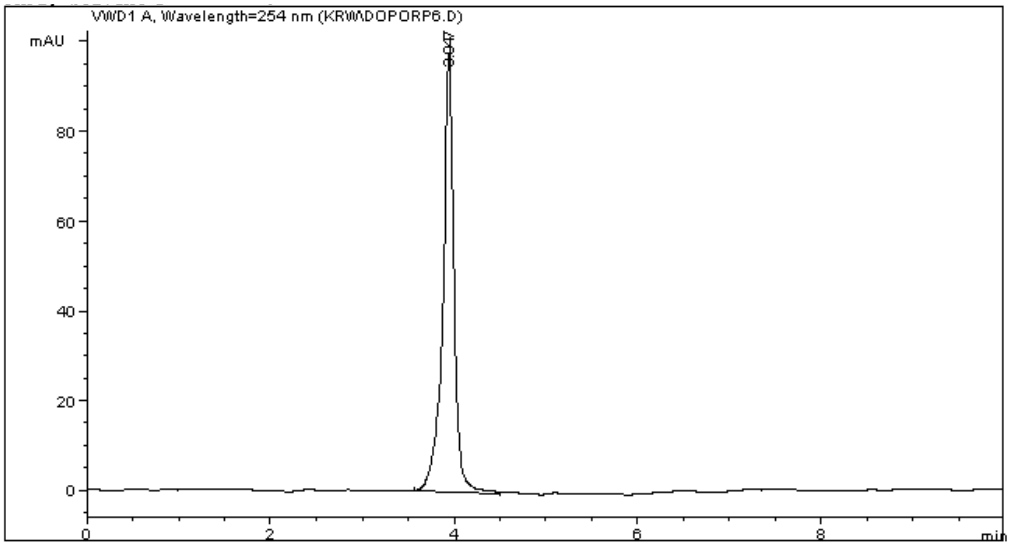
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.844	PV	0.0935	10.73883	1.78525	0.0294
2	3.890	VV	0.1297	2.29631e4	2588.10229	62.9530
3	4.947	VB	0.1630	1.35028e4	1202.93274	37.0176
Totals :				3.64766e4	3792.82029	

Results obtained with enhanced integrator!

*** End of Report ***

*(R_P)-**91** 8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-methyl sulfide HPLC.*



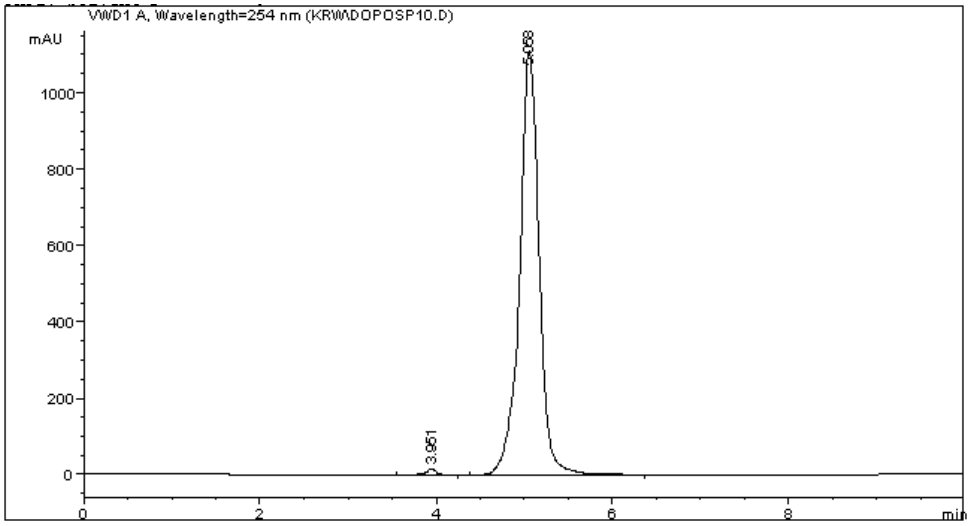
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.947	BB	0.1260	850.95898	98.03091	100.0000
Totals :				850.95898	98.03091	

Results obtained with enhanced integrator!

*** End of Report ***

*(S_P)-**91** 8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-methyl sulfide HPLC.*



Signal 1: VWD1 A, Wavelength=254 nm

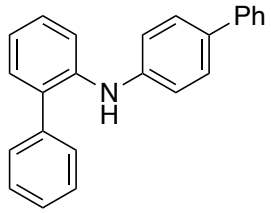
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.951	VP	0.1309	160.76207	17.90879	0.9258
2	5.058	PB	0.2330	1.72042e4	1111.31396	99.0742
Totals :				1.73650e4	1129.22275	

Results obtained with enhanced integrator!

*** End of Report ***

4.2 Synthesis of *N*-biphenyl-DOPO-derived *P*-stereogenic CPA

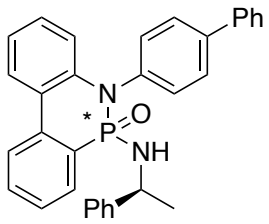
*N-(1,1'-Biphenyl-4-yl)-1,1'-biphenyl-2-amine **93** (Scheme 4.10).*



To a rb flask was added 1-aminobiphenyl (1 equiv, 36 mmol) and 4-bromobiphenyl (1 equiv, 36 mmol) in toluene (67 mL). The reaction was flushed with argon for 10 min, then $Pd(OAc)_2$ (1 mol%, 0.37 mmol), dppf (2 mol%, 0.66 mmol) and NaO*t*Bu (1.1 equiv, 47 mmol)

was added and the reaction brought to reflux for 16 h. The mixture was then cooled to rt, and H_2O (30 mL) was added then the mixture was transferred to a separatory funnel. The organic layer was washed with H_2O, extracted with toluene, and the layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuum. The crude product was purified by column chromatography to yield the product **93** (2.5 g, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.56 – 7.53 (m, 2H), 7.53 – 7.48 (m, 5H), 7.47 – 7.39 (m, 3H), 7.34 (td, *J* = 6.8, 1.6 Hz, 3H), 7.19 – 7.13 (m, 2H), 7.09 (dd, *J* = 7.4, 1.2 Hz, 1H), 5.72 (s, 1H).

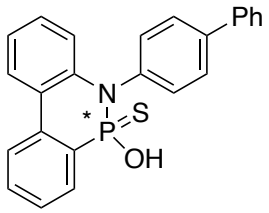
N-(1,1'-Biphenyl-4-yl)-10-((S)-(1-phenylethyl)amino)dibenzo[c,e]-phosphinine-10-oxide ***94*** *(Scheme 4.10).*



Under neat conditions to a rb flask was added **93** (1 equiv, 7.8 mmol) and phosphorus trichloride (2.3 equiv, 18.13 mmol), and brought to 50 °C in an oil bath and stirred for 3 h under argon. The reaction was cooled down to rt, and zinc chloride (0.43 equiv, 0.36 mmol) was added and brought to 150 °C and stirred for 8 h under argon. After cooling to 0 °C, the crude was solubilized in toluene (30 mL), and DIPEA (2.0 equiv, 15.6 mmol) and (*S*)-1-phenylethylamine (2.0 equiv, 15.6 mmol) were added and stirred at rt for 2 h under argon. To the reaction mixture H_2O_2 (35 wt % in H_2O5.0 equiv, 39 mmol) and THF (10 mL) was added at 0 °C and then stirred for 4 h at rt. The organic layer was poured into 1 M HCl and diluted with EtOAc then transferred to a separatory funnel. The organic layer was washed with $NaHCO_3$ (sat. aq.) and brine. The layers were separated, and the organic layer dried over

$MgSO_4$, filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (hexanes:EtOAc 50:50) to afford the phosphonamide as a white solid **94** (1.9 g, 49%). The solid was diluted in hot EtOAc and hexane was added, and the flask was placed in the refrigerator (- 18 °C) overnight. The resulting solid precipitant were filtered and washed with hexanes to afford the resolved product (0.375 g, 20%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.23 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.01 (m, 2H), 7.91 (ddd, *J* = 14.3, 7.7, 1.5 Hz, 1H), 7.70 (ddt, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* = 8.3, 6.8 Hz, 3H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.26 – 7.09 (m, 5H), 7.06 – 6.97 (m, 2H), 6.71 (dt, *J* = 8.2, 1.2 Hz, 1H), 4.41 – 4.20 (m, 1H), 3.08 (t, *J* = 9.8 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H).

*N-(1,1'-Biphenyl-4-yl)-10-dibenzo[c,e]-phosphinine-10-methyl sulfide **42** (Scheme 4.11).*

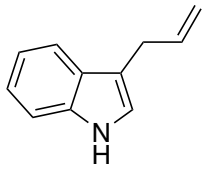


To a solution of (S_p) or (R_p)- **94** in dry THF (8 mL) was added at 0 °C NaH (3.0 equiv, 1.5 mmol, 60% dispersion in mineral oil) under argon. The reaction stirred for 1 h at rt, and then carbon disulfide (10.0 equiv, 7.7 mmol) was added dropwise and stirred for 4 h at rt. Ethyl acetate and hexanes were added and washed (3×) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude mixture was solubilized in DCM and the precipitate filtered out. The filtrate was concentrated under a vacuum to afford the product **42**

as an orange oil (0.58 g, 75%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 61.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.30 (ddd, J = 17.0, 7.7, 1.4 Hz, 1H), 8.13 – 8.05 (m, 2H), 7.73 (dd, J = 8.1, 6.6 Hz, 3H), 7.70 – 7.63 (m, 2H), 7.58 (td, J = 7.6, 3.4 Hz, 1H), 7.52 – 7.44 (m, 4H), 7.45 – 7.37 (m, 1H), 7.28 – 7.25 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H).

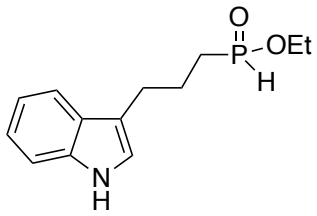
5.1 Synthesis of Indole-derived *P*-stereogenic CPA

3-Allylindole ***96*** *(Scheme 5.1).*



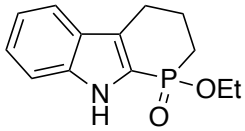
In a reaction tube was added indole (1 equiv, 20 mmol), allyl alcohol (1.5 equiv, 30 mmol) in THF (90 mL). The tube was flushed with argon for 10 minutes. Next $Pd(PPh_3)_4$ (5 mol%, 1 mmol) and Et_3B (30 mol%, 6 mmol, 1 M in THF) were added and flushed with argon for 10 minutes. The tube was sealed and brought to 50 °C in an oil bath for 16 h. The reaction was then cooled to rt and diluted with ethyl acetate (40 mL). The solution was transferred to a separatory funnel and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexanes:ethyl acetate 95:5) to give **96** as a yellow oil (2.5 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.45 – 7.27 (m, 3H), 7.01 (dt, *J* = 2.1, 1.0 Hz, 1H), 6.25 (ddt, *J* = 17.1, 10.0, 6.5 Hz, 1H), 5.44 – 5.12 (m, 2H), 3.74 – 3.65 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 136.5, 127.5, 122.1, 121.9, 119.4, 119.3, 115.4, 114.5, 111.3, 30.0.

*Ethyl-H-phosphonate indole **97** (Scheme 5.2).*



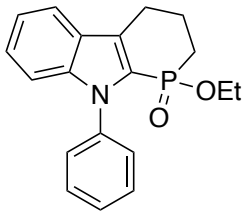
In a rb flask was added $EtO_2P(O)H_2$ (1.5 equiv, 47.7 mmol, 0.5 M in CH_3CN), **96** (1 equiv, 31.8 mmol), $Pd_2dba_3 \cdot CHCl_3$ (0.5 mol%, 0.3 mmol), and xantphos (1.2 mol%, 0.38 mmol). The flask was flushed with argon for 10 min then brought to reflux for 18 h. After cooling to rt, the mixture was diluted with ethyl acetate (60 mL). The solution was transferred to a separatory funnel and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (ethyl acetate:methanol 100:0 to 90:10) to give **97** as an oil (4.88 g, 63%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.2 (d, J = 528.3 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dt, J = 526.7, 1.9 Hz, 1H), 7.61 (dt, J = 8.0, 1.0 Hz, 1H), 7.39 (dt, J = 8.1, 1.0 Hz, 1H), 7.21 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.14 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 4.36 – 3.94 (m, 3H), 2.95 – 2.86 (m, 2H), 2.06 – 1.97 (m, 2H), 1.87 (dddd, J = 15.2, 9.3, 6.7, 3.9 Hz, 2H), 1.37 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 127.3, 122.1, 121.7, 119.3 (d, J = 54.9 Hz), 114.9, 111.2, 62.4 (d, J = 7.0 Hz), 28.9, 27.9, 25.8 (d, J = 16.5 Hz), 21.4 (d, J = 2.8 Hz), 16.3 (d, J = 6.2 Hz).

*Carbazole-ethylphosphonate **98** (Scheme 5.4).*



In a reaction tube was added **97** (1 equiv, 1.2 mmol), silver (I) acetate (3 equiv, 3.5 mmol) in DCE (8 mL) and flushed with argon for 10 min. The tube was brought to 90 °C in an oil bath for 18 h. The reaction was then cooled to rt and diluted with DCM (15 mL) and filtered over Celite. The filtrate was concentrated under vacuum and the crude product purified by column chromatography on silica gel (hexanes:ethyl acetate 20:80 to 10:90) to afford **98** as a tan solid (0.2 g, 73%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (d, J = 6.6 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.36 – 7.25 (m, 1H), 7.14 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 4.36 – 4.10 (m, 2H), 3.19 – 2.82 (m, 2H), 2.68 – 2.25 (m, 3H), 2.23 – 2.00 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (d, J = 11.6 Hz), 126.1 (d, J = 12.0 Hz), 125.7 (d, J = 15.0 Hz), 124.6, 123.5, 122.2, 120.1 – 119.3 (m), 112.7 (d, J = 1.4 Hz), 61.9 (d, J = 6.8 Hz), 27.5, 26.5, 22.6 (dd, J = 10.0, 5.0 Hz), 16.5 (d, J = 6.7 Hz).

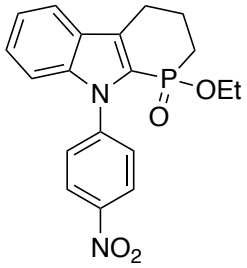
*N-phenyl carbazole-ethylphosphonate **99** (Scheme 5.5).*



To a rb flask was added **98** (1 equiv, 4 mmol), iodobenzene (1.2 equiv, 4.8 mmol), K_3PO_4 (2.1 equiv, 8.4 mmol), CuI (5 mol%, 0.2 mmol), and DMEDA (10 mol %, 0.4 mmol) in toluene (20 mL). The reaction was flushed with argon for 10 min then brought to reflux for 18 h. After cooling to rt, the solvent was evaporated under vacuum. The crude was dissolved

in DCM and transferred to a separatory funnel. The organic was washed with NH_4Cl (aq), then washed with brine. The organic layer was separated and dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexanes:ethyl acetate 25:75) to afford the pure product **99** as a colorless oil (1 g, 77%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, J = 8.7 Hz, 2H), 7.55 (t, J = 7.7 Hz, 2H), 7.49 – 7.41 (m, 1H), 7.35 – 7.25 (m, 3H), 7.20 (ddd, J = 7.8, 6.3, 1.6 Hz, 1H), 3.89 – 3.73 (m, 1H), 3.67 – 3.50 (m, 1H), 3.12 – 2.98 (m, 2H), 2.50 – 2.28 (m, 2H), 2.26 – 2.06 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (d, J = 9.2 Hz), 138.5, 129.2, 128.0, 127.8 (d, J = 8.1 Hz), 127.6 (d, J = 3.8 Hz), 126.5 (d, J = 12.5 Hz), 126.2, 125.3, 120.4, 120.0 (d, J = 1.7 Hz), 111.1, 60.9 (d, J = 6.2 Hz), 28.4 (d, J = 99.1 Hz), 23.1 (d, J = 4.0 Hz), 21.8 (d, J = 5.8 Hz), 16.4 (d, J = 6.2 Hz).

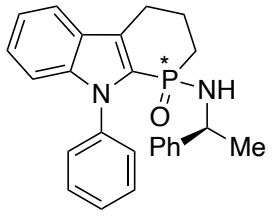
*N-(p-nitrophenyl)carbazole-ethylphosphonate **100** (Scheme 5.5).*



To a rb flask was added **98** (1 equiv, 1.5 mmol), iodo-nitrobenzene (1.2 equiv, 1.8 mmol), K_3PO_4 (2.1 equiv, 3.1 mmol), CuI (5 mol%, 0.075 mmol), and DMEDA (10 mol%, 0.15 mmol) in toluene (10 mL). The reaction was flushed with argon for 10 min then brought to reflux for 18 h. After cooling to rt, the solvent was evaporated under vacuum. The crude was dissolved in DCM and transferred to a separatory funnel. The organic was washed with NH_4Cl (sat. aq), then washed with brine. The organic layer was separated and dried with

$MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexanes:ethyl acetate 25:75) to afford **100** as a yellow solid (0.4 g, 73%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.38 (m, 2H), 7.97 – 7.89 (m, 2H), 7.67 (dt, J = 8.0, 1.1 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.30 – 7.22 (m, 1H), 3.96 – 3.73 (m, 2H), 3.05 (td, J = 6.0, 3.1 Hz, 2H), 2.38 (s, 2H), 2.29 – 2.04 (m, 2H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 144.4, 138.8 (d, J = 8.8 Hz), 129.8 (d, J = 14.0 Hz), 127.8, 127.2 (d, J = 12.3 Hz), 126.9 (d, J = 137.5 Hz), 126.3, 124.8, 121.5, 120.4 (d, J = 1.5 Hz), 110.7 (d, J = 1.6 Hz), 61.1 (d, J = 6.0 Hz), 27.9 (d, J = 98.2 Hz), 23.1 (d, J = 4.1 Hz), 21.5 (d, J = 6.1 Hz), 16.5 (d, J = 5.9 Hz).

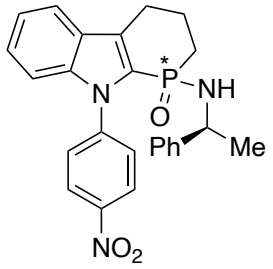
*(S)-1-(phenylethyl)phosphonamide N-phenyl carbazole **101** (Scheme 5.6).*



To a rb was added **99** (1 equiv, 2 mmol) in DCM (5 mL). Oxalyl chloride (2 equiv, 4 mmol) was added dropwise followed by DMF (10 mol%, 0.2 mmol). The reaction mixture was brought to reflux and stirred for 24 h under argon. In a separate flask was added (*S*)-1-phenylethylamine (2 equiv, 4 mmol), Et_3N (2 equiv, 4 mmol), and DMAP (0.1 equiv, 0.2 mmol) in DCM (5 mL). To this the P(O)Cl mixture was added via cannula at rt and stirred for 24 h. The reaction mixture was transferred to a separatory funnel and washed with $NaHCO_3$ (sat. aq), NH_4Cl (sat. aq), and then brine. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under vacuum. The mixture was concentrated under vacuum and directly purified and resolved by column chromatography on silica gel (hexanes:ethyl acetate

30:70) to afford the phosphoramide **101** as a beige solid (0.7 g, 85%, resolved yield 47%). *Mixture:* ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.53 (s), 20.46 (s); *Resolved:* ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.33 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.56 (m, 2H), 7.55 – 7.39 (m, 3H), 7.36 – 7.28 (m, 3H), 7.26 – 7.18 (m, 4H), 7.16 (d, J = 1.9 Hz, 2H), 4.28 (dtt, J = 13.6, 9.1, 4.6 Hz, 1H), 3.02 – 2.80 (m, 2H), 2.65 (dd, J = 10.6, 8.9 Hz, 1H), 2.26 (ddtdd, J = 17.0, 8.0, 6.0, 4.1, 2.1 Hz, 1H), 2.11 (dddd, J = 20.6, 9.4, 4.4, 2.0 Hz, 1H), 2.04 – 1.83 (m, 1H), 1.82 – 1.66 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (d, J = 2.9 Hz), 139.3 (d, J = 8.2 Hz), 138.5, 129.2, 128.8, 128.5, 127.9, 127.7 (d, J = 3.8 Hz), 126.9, 126.7 (d, J = 11.4 Hz), 126.2, 125.8, 125.3, 120.5, 120.0 (d, J = 1.5 Hz), 111.1 (d, J = 1.5 Hz), 49.9, 30.6 (d, J = 93.6 Hz), 25.5 (d, J = 6.0 Hz), 23.3 (d, J = 3.4 Hz), 21.5 (d, J = 5.8 Hz).

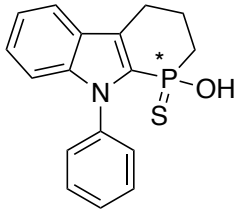
*(S)-1-(phenylethyl)phosphonamide-N-(p-nitrophenyl)carbazole **102** (Scheme 5.6).*



To a rb was added **100** (1 equiv, 0.4 mmol) in DCM (2 mL). Oxalyl chloride (2 equiv, 0.81 mmol) was added dropwise followed by DMF (10 mol%, 0.04 mmol). The reaction mixture was brought to reflux and stirred for 24 h under argon. In a separate flask was added (*S*)-1-phenylethylamine (2 equiv, 0.81 mmol), Et_3N (2 equiv, 0.81 mmol), and DMAP (0.1 equiv, 0.04 mmol) in DCM (1 mL). To this the P(O)Cl mixture was added via cannula at rt, and stirred for 24 h. The reaction mixture was transferred to a separatory funnel and washed with $NaHCO_3$ (sat. aq), NH_4Cl (sat. aq), and then brine. The organic layer was separated, dried

with $MgSO_4$, filtered, and concentrated under vacuum. The mixture was concentrated under vacuum and directly purified and resolved by column chromatography on silica gel (hexanes:ethyl acetate 30:70) to afford the product **102** (0.12 g, 67%, resolved 20%). *Mixture:* ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.3 (s), 21.3 (s); *Resolved:* ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.24 (td, J = 13.6, 8.1 Hz, 5H), 7.06 – 7.01 (m, 2H), 6.96 (d, J = 7.1 Hz, 1H), 3.88 (q, J = 8.0 Hz, 1H), 3.08 (dd, J = 16.9, 4.4 Hz, 2H), 2.40 (s, 3H), 2.22 – 2.17 (m, 1H), 2.07 – 1.92 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 144.8, 144.1, 138.6 (d, J = 7.5 Hz), 131.0, 130.5, 128.6 (d, J = 4.0 Hz), 127.2 (d, J = 8.3 Hz), 126.3, 125.5, 124.8, 121.6, 120.5, 110.8 (d, J = 8.8 Hz), 50.5 (d, J = 15.4 Hz), 30.6 (d, J = 9.1 Hz), 29.7 (d, J = 8.9 Hz), 26.1 (dd, J = 13.0, 5.9 Hz), 23.3 (dd, J = 7.3, 3.7 Hz), 21.2 (d, J = 5.8 Hz), 20.8 (d, J = 5.8 Hz).

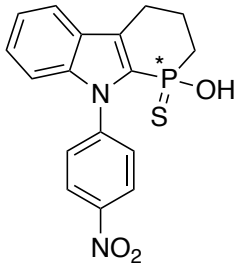
*Thiophosphonic acid N-phenyl carbazole **103** (Scheme 5.7).*



To a rb was added the (R_p) or (S_p) – **101** (1 equiv, 0.9 mmol) in THF (3 mL) under argon. The reaction was cooled to 0 °C in an ice bath. NaH (3 equiv, 2.7 mmol, 60% in mineral oil) was added in one portion and the mixture brought to rt and stirred for 1 h, then CS_2 (10 equiv, 9 mmol) was added dropwise and the reaction stirred at rt overnight. Ethyl acetate (3 mL) was added to the reaction and transferred to a separatory funnel. The product was extracted into the basic layer with $NaHCO_3$ (sat. aq), the layers were separated, and the basic layer was

acidified with 3 M HCl (pH = 1). The product was extracted into the organic layer with DCM (3x), dried with $MgSO_4$, filtered, and concentrated under vacuum to give **103** as an oil (NMR yield: 45%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 60.3 (s).

*N-(p-nitrophenyl)carbazole-ethylthiophosphonic acid **40** (Scheme 5.7).*

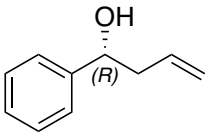


To a rb was added the (R_p) or (S_p) – **102** (1 equiv, 0.9 mmol) in THF (3 mL) under argon. The reaction was cooled to 0 °C in an ice bath. NaH (3 equiv, 2.7 mmol, 60% in mineral oil) was added in one portion and the mixture brought to rt and stirred for 1 h, then CS_2 (10 equiv, 9 mmol) was added dropwise and the reaction stirred at rt overnight. The reaction was cooled to rt and diluted with ethyl acetate (30 mL) and transferred to a separatory funnel. The organic layer was extracted with $NaHCO_3$ (sat. aq, 3x), and the layers separated. The basic layer was acidified with 3 M HCl (pH = 1) and extracted with ethyl acetate. The organic layer was separated and dried with $MgSO_4$, filtered and concentrated under vacuum to afford the product **40** as a yellow solid (0.3 g, 80%). ^{31}P NMR (162 MHz, DMSO-d_6) δ 58.1 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.45 – 8.36 (m, 2H), 7.91 – 7.83 (m, 2H), 7.71 (dt, J = 7.9, 1.0 Hz, 1H), 7.42 – 7.27 (m, 2H), 7.24 (ddd, J = 7.9, 6.6, 1.3 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.99 – 2.86 (m, 1H), 2.39 (ddt, J = 17.3, 9.8, 3.4 Hz, 1H), 2.33 – 2.08 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.4, 144.6, 138.6 (d, J = 7.9 Hz), 130.4 (d, J = 109.2 Hz), 128.9, 126.9

(d, J = 11.0 Hz), 126.2, 125.1, 124.9 (d, J = 11.8 Hz), 121.7, 121.0, 110.8, 37.3 (d, J = 78.5 Hz), 23.1 (d, J = 3.3 Hz), 20.9 (d, J = 7.0 Hz).

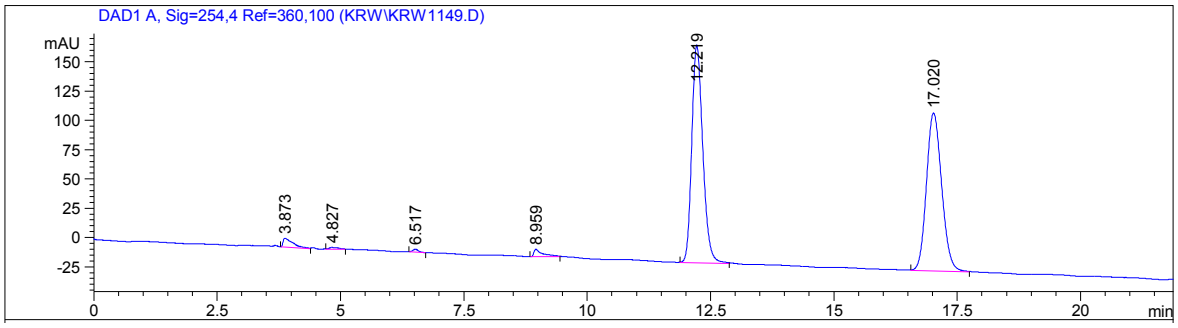
6.1 Allylation of Aldehydes

Representative Procedure for the Allylation of Aldehydes with Boronates (Table 6.1).



To a reaction tube was added the CPA catalyst (2 mol%, 0.01 mmol), benzaldehyde (1 equiv, 0.5 mmol), activated 4 Å MS (20 mg) and toluene (5 mL) under argon. The reaction was cooled to -30 °C (xylenes/dry ice bath), then allyl boronate pinacol ester (1.2 equiv, 0.6 mmol) was added dropwise. The reaction was slowly brought to rt and followed by TLC (hexanes:ethyl acetate, 90:10) until complete (24 h). The solvent was evaporated under vacuum, and the crude product was purified directly by column chromatography (hexanes:ethyl acetate, 95:5) to yield the (*R*)-1-phenyl-but-3-en-1-ol in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H), 5.82−5.64 (m, 1H), 5.15−5.02 (m, 2H), 4.67 (dd, J = 7.7, 5.3 Hz, 1H), 2.52−2.40 (m, 2H), 1.81 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/iPrOH = 99/1, 0.7 mL/min).

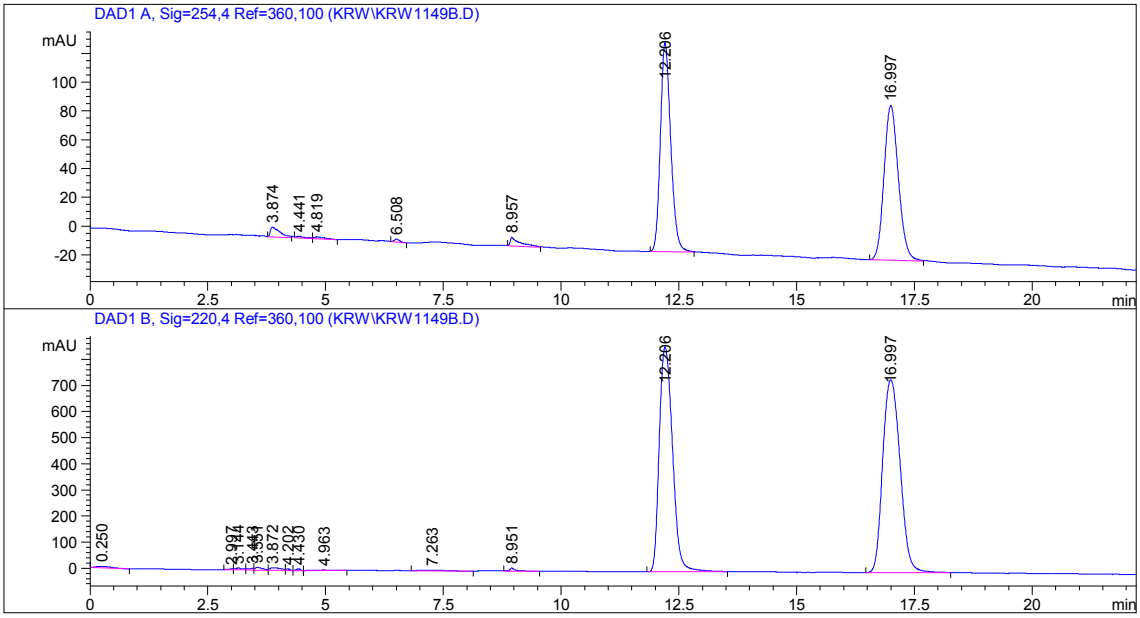
Racemic 1-phenyl-but-3-en-1-ol HPLC.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.873	VB	0.1943	104.68627	7.52438	1.7582
2	4.827	BB	0.1726	19.37492	1.50069	0.3254
3	6.517	BB	0.1242	19.93586	2.46982	0.3348
4	8.959	BB	0.1813	84.61065	6.35768	1.4210
5	12.219	BB	0.2374	2857.72046	185.79608	47.9942
6	17.020	BB	0.3304	2867.97876	134.72221	48.1665
Totals :				5954.30692	338.37087	

*1-phenyl-but-3-en-1-ol from CPA **40** HPLC.*



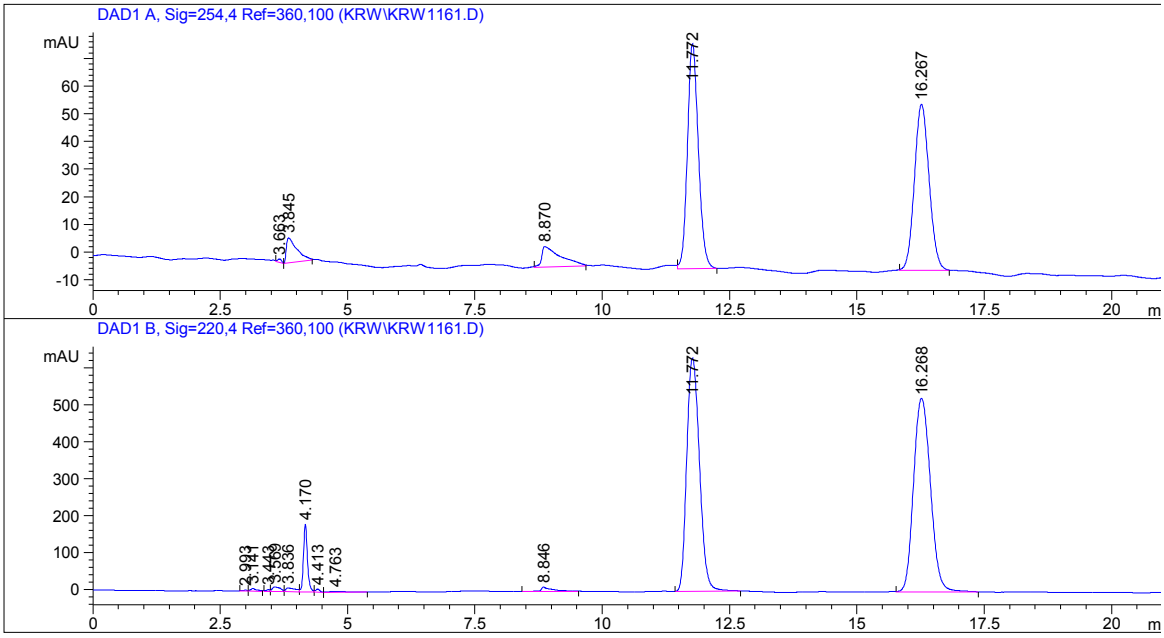
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.874	VB	0.1896	94.48878	6.73972	1.9989
2	4.441	BB	0.1739	15.17316	1.18102	0.3210
3	4.819	BB	0.1972	19.34159	1.27320	0.4092
4	6.508	BB	0.1168	15.54608	1.99807	0.3289
5	8.957	BB	0.1826	83.24170	5.82910	1.7610
6	12.206	BB	0.2364	2222.21753	145.30453	47.0106
7	16.997	BB	0.3291	2277.04614	107.52035	48.1705
Totals :				4727.05498	269.84598	

Signal 2: DAD1 B, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.250	BB	0.3319	127.63654	5.72896	0.3469
2	2.997	BV	0.0888	25.62219	3.99504	0.0696
3	3.144	VV	0.1312	78.89687	7.99147	0.2145
4	3.443	VV	0.1092	54.22726	6.64374	0.1474
5	3.551	VV	0.1462	120.12178	11.10192	0.3265
6	3.872	VV	0.2110	158.75404	9.79736	0.4315
7	4.202	VV	0.0865	33.81984	5.75977	0.0919
8	4.430	VV	0.0870	38.94765	6.99354	0.1059
9	4.963	VV	0.4300	66.66944	1.86089	0.1812
10	7.263	BV	0.4469	92.81048	2.45605	0.2523
11	8.951	BB	0.1263	123.38642	12.82018	0.3354
12	12.206	VB	0.3162	1.68450e4	861.18024	45.7878
13	16.997	BB	0.4180	1.90234e4	739.83600	51.7090
Totals :				3.67893e4	1676.16514	

*1-phenyl-but-3-en-1-ol from CPA **41** HPLC.*



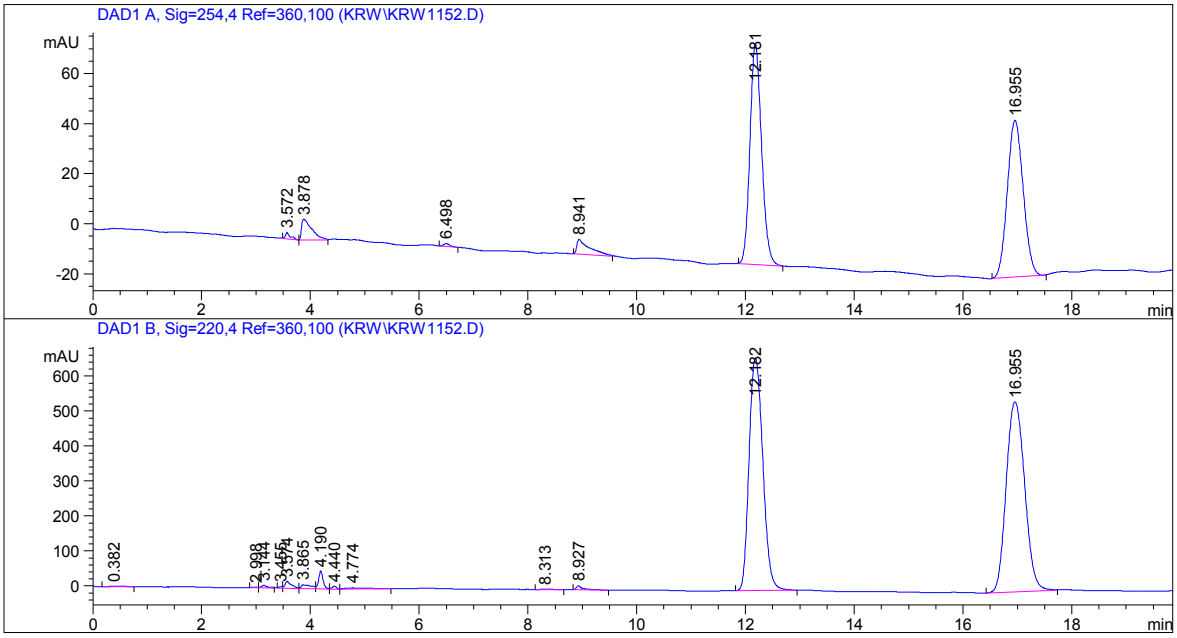
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.663	BV	0.0861	6.57638	1.23627	0.2389
2	3.845	VB	0.2086	130.08208	9.00142	4.7264
3	8.870	BB	0.3426	191.65184	7.38976	6.9635
4	11.772	BB	0.2301	1213.92419	81.32825	44.1067
5	16.267	BB	0.3126	1210.01233	60.16453	43.9645
Totals :				2752.24682	159.12023	

Signal 2: DAD1 B, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.993	BV	0.0905	13.52811	2.11905	0.0547
2	3.141	VB	0.1175	62.47178	7.32434	0.2527
3	3.443	BV	0.0768	24.24316	4.50226	0.0981
4	3.569	VV	0.1539	134.47997	12.08215	0.5440
5	3.836	VV	0.1906	134.66576	9.66459	0.5448
6	4.170	VV	0.0836	1004.00195	184.24559	4.0615
7	4.413	VV	0.0857	45.06975	8.00084	0.1823
8	4.763	VB	0.3091	43.18069	1.69560	0.1747
9	8.846	VB	0.2058	191.91740	11.92349	0.7764
10	11.772	BB	0.2794	1.09934e4	630.57642	44.4713
11	16.268	BB	0.3690	1.20732e4	523.56342	48.8396
Totals :				2.47201e4	1395.69776	

*1-phenyl-but-3-en-1-ol from CPA **42** HPLC.*



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

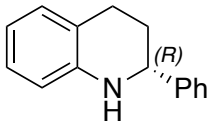
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.572	BV	0.0939	16.40731	2.45603	0.5827
2	3.878	VB	0.1886	109.48818	8.26213	3.8886
3	6.498	BB	0.1231	8.54272	1.09380	0.3034
4	8.941	BB	0.2153	99.23512	5.98971	3.5244
5	12.181	BB	0.2299	1314.91040	88.19972	46.7002
6	16.955	BB	0.3163	1267.05627	62.55633	45.0006
Totals :				2815.64001	168.55772	

Signal 2: DAD1 B, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.382	BB	0.2642	23.01851	1.07340	0.0904
2	2.998	BV	0.0924	14.31236	2.12934	0.0562
3	3.144	VB	0.1095	60.31436	7.52280	0.2368
4	3.455	BV	0.0692	21.31656	4.50348	0.0837
5	3.574	VV	0.1158	164.93797	19.66690	0.6476
6	3.865	VV	0.1693	138.19089	10.37892	0.5426
7	4.190	VV	0.0861	290.92294	51.33925	1.1422
8	4.440	VV	0.0828	43.46848	8.07522	0.1707
9	4.774	VB	0.3613	91.31042	3.04986	0.3585
10	8.313	BB	0.1671	14.71632	1.27060	0.0578
11	8.927	BB	0.1246	97.63156	10.89003	0.3833
12	12.182	BB	0.2836	1.17083e4	664.47028	45.9700
13	16.955	BB	0.3790	1.28011e4	543.09552	50.2603
Totals :				2.54695e4	1327.46559	

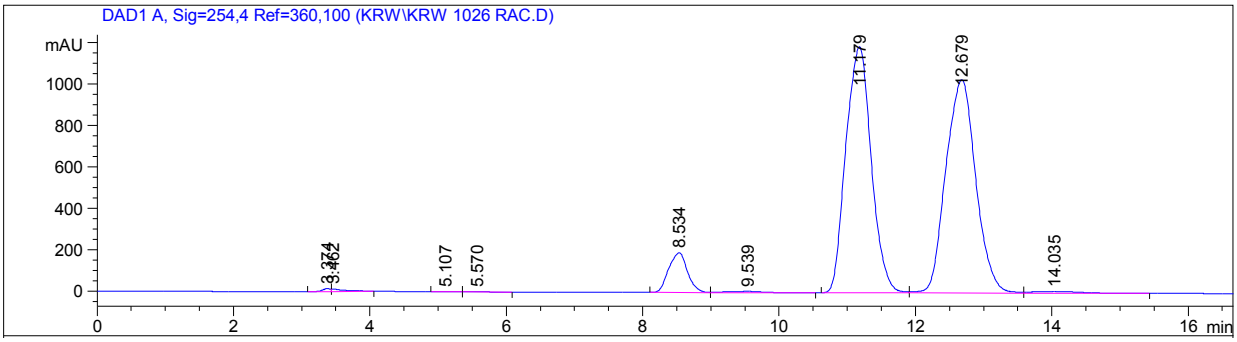
6.2 Hydrogen Transfer of Quinolines

Representative Procedure for the Asymmetric Hydrogenation of 2-Phenylquinoline (Table 6.3).



To a reaction tube was added 2-phenylquinoline (1 equiv, 0.25 mmol), the Hantzch ester (2.4 equiv, 0.58 mmol) in toluene (5 mL) under argon. The reaction was cooled to 0 °C, then the CPA catalyst (0.005 mmol, 2 mol%) was added. The reaction was brought to rt and stirred 24 h. The reaction was concentrated under vacuum, and the crude product was purified directly by column chromatography (hexanes:ethyl acetate, 95:5) to yield the 2-phenyl-1,2,3,4-tetra-hydroquinoline as a colorless oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.40 (m, 4H), 7.36 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 7.5, 1.0 Hz, 2H), 6.72 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.63 – 6.56 (m, 1H), 4.49 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.08 (s, 1H), 2.98 (td, *J* = 10.7, 5.3 Hz, 1H), 2.80 (dt, *J* = 16.4, 4.7 Hz, 1H), 2.24 – 2.11 (m, 1H), 2.11 – 1.96 (m, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min),

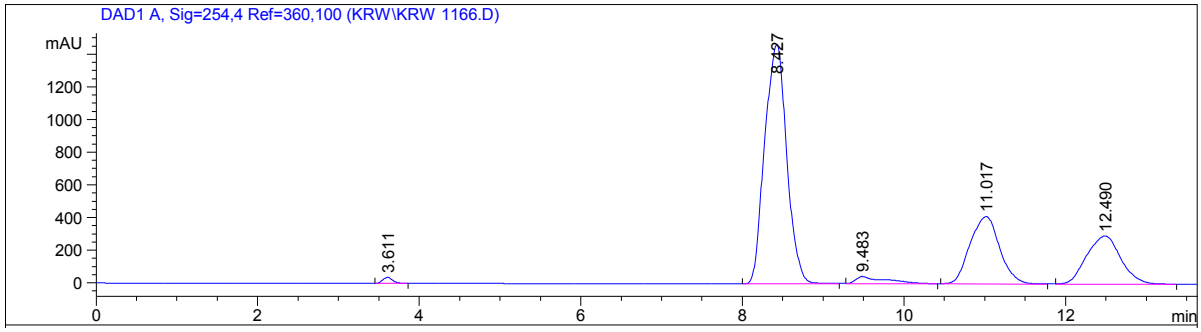
Racemic 2-phenyl-1,2,3,4-tetra-hydroquinoline HPLC.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.374	BV	0.1217	107.46756	13.67281	0.1607
2	3.462	VB	0.1805	162.36674	11.80467	0.2428
3	5.107	BV	0.1814	17.68106	1.47967	0.0264
4	5.570	VB	0.1998	16.04880	1.21773	0.0240
5	8.534	BV	0.3105	3673.62305	192.60971	5.4927
6	9.539	VB	0.4760	226.74150	6.26831	0.3390
7	11.179	BV	0.4184	3.08269e4	1189.19141	46.0919
8	12.679	VB	0.4916	3.14381e4	1031.29443	47.0057
9	14.035	BB	0.5761	412.46259	8.56110	0.6167
Totals :				6.68814e4	2456.09984	

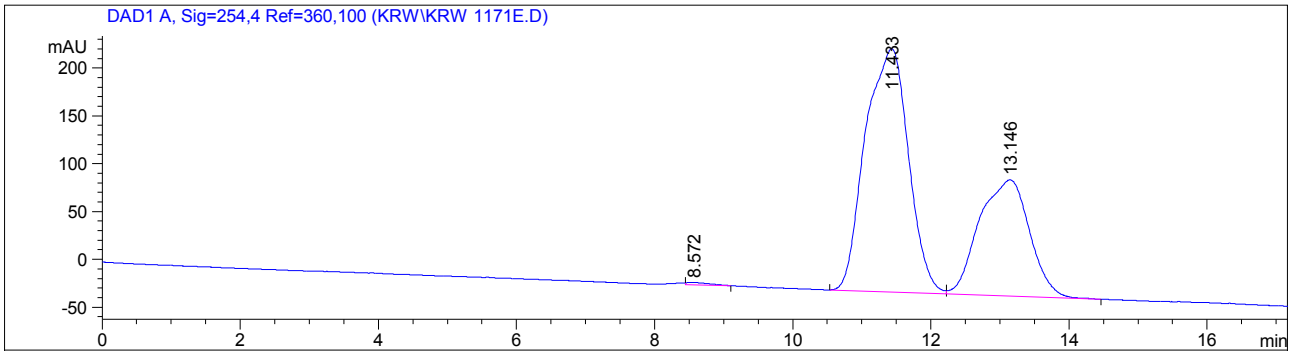
*2-phenyl-1,2,3,4-tetra-hydroquinoline from CPA **40** HPLC*



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.611	BB	0.1295	311.49915	38.06655	0.6414
2	8.427	BB	0.3080	2.78476e4	1463.50867	57.3414
3	9.483	BB	0.3455	1234.98560	45.95943	2.5430
4	11.017	BB	0.4118	1.05513e4	413.30026	21.7262
5	12.490	BB	0.4731	8619.25293	294.80676	17.7480
Totals :				4.85646e4	2255.64167	

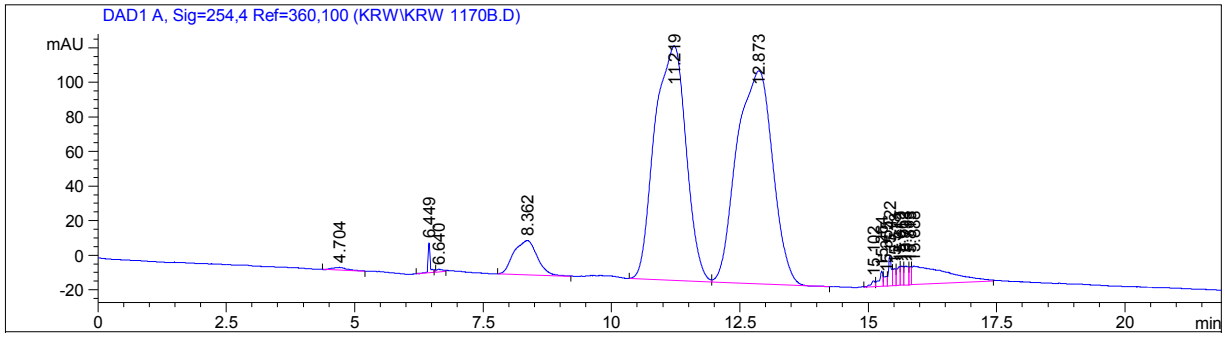
*2-phenyl-1,2,3,4-tetra-hydroquinoline from CPA **41** HPLC.*



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.572	BB	0.3008	65.14135	2.63140	0.3780
2	11.433	BV	0.5957	1.10346e4	254.57335	64.0239
3	13.146	VB	0.6986	6135.39111	121.60060	35.5982
Totals :				1.72351e4	378.80535	

*2-phenyl-1,2,3,4-tetra-hydroquinoline from CPA **42** HPLC:*

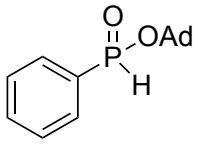


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.704	BB	0.2404	29.89528	1.54059	0.2247
2	6.449	BB	0.0466	50.97886	17.19250	0.3832
3	6.640	BB	0.1065	12.50844	1.54424	0.0940
4	8.362	BB	0.4317	627.11212	19.89706	4.7134
5	11.219	BV	0.5768	5721.33643	135.43665	43.0020
6	12.873	VB	0.6832	5966.75293	123.16451	44.8466
7	15.102	VV	0.0800	19.11582	3.37819	0.1437
8	15.264	VV	0.0691	43.87333	8.66000	0.3298
9	15.355	VV	0.0607	26.47861	5.65116	0.1990
10	15.422	VV	0.0582	67.97022	17.16884	0.5109
11	15.518	VV	0.0551	39.45806	9.77429	0.2966
12	15.613	VV	0.0622	50.56691	10.89502	0.3801
13	15.662	VV	0.0565	41.87500	10.97777	0.3147
14	15.733	VV	0.0802	61.59865	10.85541	0.4630
15	15.813	VV	0.0508	34.66135	10.41127	0.2605
16	15.888	VB	0.5615	510.62433	10.80262	3.8379
Totals :				1.33048e4	397.35012	

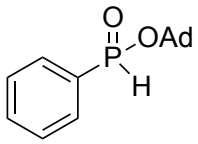
7.2 Synthesis of Adamantyl *H*-phosphinate esters

*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 1).*



To a solution of phenyl phosphinic acid (1 equiv, 1.2 mmol) and 1-BrAd (2.4 equiv, 2.9 mmol) was added in $CHCl_3$ (22 mL) at rt under N_2. The reaction was brought to reflux and Ag_2O (2.4 equiv, 2.9 mmol) was added potion-wise (5x over 1 h) was added. The reaction was stirred at reflux for 2 h, then brought to rt. Then Et_2O (10 mL) was added, and the reaction mixture filtered over celite. The filtrate was transferred to a separatory funnel, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes:EtOAc 70:30 to 50:50) to afford **104** as a white solid (0.14 g, 42%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2 (dt, *J* = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

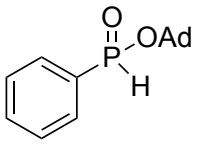
*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 2).*



To a solution of phenyl phosphinic acid (2.4 mmol, 1.2 equiv) and 1-BrAd (2 mmol, 1 equiv) was added in $CHCl_3$ (10 mL) at rt under N_2. The reaction was brought to reflux and

Ag_2O (1 equiv, 2 mmol) was added potion-wise (5x over 1 h) was added. The reaction was stirred at reflux for 2 h, then brought to rt. Then Et_2O (10 mL) was added, and the reaction mixture filtered over celite. The filtrate was transferred to a separatory funnel, the organic layer was washed with $NaHCO_3$ (sat. aq.), then brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes:EtOAc 75:25) to afford **104** as a white solid (0.32 g, 42%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2 (dt, *J* = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

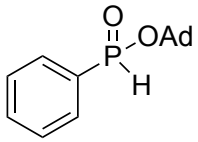
*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 3).*



To a solution of phenyl phosphinic acid (1 equiv, 35 mmol) and 1-AdOH (35 mmol, 1 equiv) in DCM (70 mL) was added 4-dimethylaminopyridine (0.1 equiv, 3.5 mmol) at rt under N_2. The reaction was brought to 0 °C and EDC (1.5 equiv, 2.25 mmol) was added. The reaction brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes/EtOAc 90:10) to afford **104** as a white solid (5.3 g, 55%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2 (dt, *J* = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ

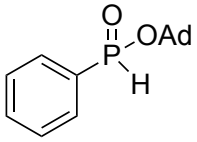
8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 4).*



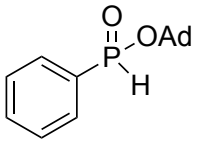
To a solution of phenyl phosphinic acid (1.0 equiv, 1.5 mmol) and 1-AdOH (1.8 equiv, 2.7 mmol) in DCM (3 mL) was added DMAP (0.1 equiv, 0.15 mmol) at rt under N_2. The reaction was brought to 0 °C and EDC (1.5 equiv, 2.25 mmol) was added. The reaction brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes:EtOAc 90:10) to afford **104** as a white solid (0.3 g, 72%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, *J* = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 5).*



To a solution of phenyl phosphinic acid (1 equiv, 1.5 mmol) and 1-AdOH (2.0 equiv, 2 mmol) in DCM (10 mL) was added pyridine (1 equiv, 1.5 mmol) and PivCl (1.5 equiv, 3 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution then washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. **104** was obtained as a white solid without further purification needed (0.35 g, 84%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, J = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

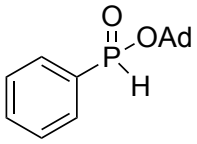
*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 6b).*



To a solution of phenyl phosphinic acid (1.2 equiv, 39 mmol) and 1-AdOH (1.0 equiv, 33 mmol) in DCM (200 mL) was added pyridine (1.5 equiv, 49 mmol) and PivCl (1.2 equiv, 39 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the

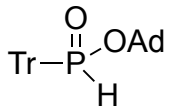
organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. **104** was obtained as a white solid without further purification needed (8.5 g, 94%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, J = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

*Adamantyl-phenyl-H-phosphinate **104** (Table 7.1, entry 7b).*



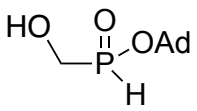
To a solution of phenyl phosphinic acid (1.25 equiv, 70 mmol) and 1-AdOH (1.0 equiv, 56 mmol) in DCM (100 mL) was added T3P (1.5 equiv, 84 mmol, 50 wt% in EtOAc) at 0 °C under N_2. The reaction was brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$ (2x). The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. **104** was obtained as a white solid without further purification needed (13 g, 85%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, *J* = 553.0, 13.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.33 (m, 2H), 2.24 – 2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1.

Adamantyl-trityl-H-phosphinate (Table 7.1, entry 8).



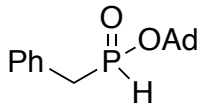
To a solution of trityl phosphinic acid (1.2 equiv, 2.4 mmol) and 1-AdOH (1.0 equiv, 2 mmol) in DCM (20 mL) was added pyridine (1.5 equiv, 3 mmol) and PivCl (1.2 equiv, 2.4 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to give the adamantyl-trityl-*H*-phosphinate (^{31}P NMR yield: 88%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.05 (d, J = 586.7 Hz). Product not stable on silica gel.

Hydroxymethyl-adamantyl ester H-phosphinate (Table 7.1, entry 9).



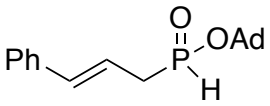
To a solution of hydroxymethyl-phosphinic acid (1.0 equiv, 2 mmol, 60 wt.% in H_2O) and 1-AdOH (1.0 equiv, 2 mmol) in DCM (10 mL) was added pyridine (1.5 equiv, 3 mmol) and PivCl (2 equiv, 4 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h and ^{31}P NMR of the crude reaction mixture showed 0 % conversion to product.

Benzyl-adamantyl ester H-phosphinate (Table 7.1, entry 10).



In a rb flask was added benzyl-phosphinic acid (1.25 equiv, 4.3 mmol) and 1-AdOH (1.0 equiv, 3.5 mmol) in DCM (8 mL) was added T3P (1.5 equiv, 5.25 mmol, 50 wt% in EtOAc) at 0 °C under N_2. The reaction was brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$ (2x). The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to afford the product without further purification (0.9 g, 89%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.4 (d, J = 538.8 Hz); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (tt, J = 6.9, 1.1 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.24 (ddt, J = 8.0, 2.7, 1.5 Hz, 2H), 6.55 (dt, J = 537.1, 2.1 Hz, 1H), 3.38 – 3.13 (m, 2H), 2.22 – 2.15 (m, 3H), 1.99 (d, J = 3.0 Hz, 6H), 1.63 (t, J = 3.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7 (d, J = 7.0 Hz), 129.8 (d, J = 6.5 Hz), 128.7 (d, J = 3.4 Hz), 127.0 (d, J = 3.9 Hz), 82.0 (d, J = 9.4 Hz), 43.8 (d, J = 4.7 Hz), 37.7 (d, J = 92.7 Hz), 35.7, 31.0; HRMS (EI+): m/z calcd for $C_{17}H_{23}O2P$: 291.1508 $[M+H]^+$; found 291.1513.

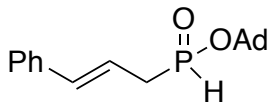
Cinnamyl-adamantyl ester H-phosphinate (Table 7.1, entry 11).



To a rb was added cinnamyl-*H*-phosphinic acid (1.0 equiv, 1.5 mmol) and 1-AdOH (1.0 equiv, 1.5 mmol) in DCM (7.5 mL) was added pyridine (1.5 equiv, 2.25 mmol) and PivCl (1.2 equiv, 1.8 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the

organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude product was purified on column chromatography (hexanes:EtOAc 55:45) to afford the product as a clear oil (0.28 g, 59%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.8 (dtt, J = 538.0, 19.6, 6.6 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dt, J = 538.3, 2.1 Hz, 1H), 7.46 – 7.27 (m, 4H), 7.26 – 7.17 (m, 1H), 6.52 – 6.37 (m, 1H), 6.06 (dd, J = 15.6, 7.6 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.21 – 2.15 (m, 3H), 2.05 (d, J = 3.0 Hz, 6H), 1.62 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (d, J = 4.3 Hz), 135.4 (d, J = 14.6 Hz), 128.6, 127.7 (d, J = 1.4 Hz), 126.2 (d, J = 2.3 Hz), 117.9 (d, J = 10.1 Hz), 81.9, 43.9 (d, J = 4.4 Hz), 35.7, 35.3 (d, J = 95.3 Hz), 31.0; HRMS (EI+): m/z calcd for $C_{19}H_{25}O_2P$: 317.1665 $[M+H]^+$; found: 317.1659.

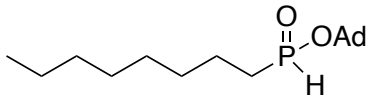
Cinnamyl-adamantyl ester H-phosphinate (Table 7.1, entry 12).



To a rb was added cinnamyl-*H*-phosphinic acid (1.25 equiv, 3 mmol) and 1-AdOH (1.0 equiv, 2.4 mmol) in DCM (5 mL) was added T3P (1.5 equiv, 4.8 mmol, 50 wt.% in EtOAc) at 0 °C under N_2. The reaction was brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$ (2x). The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum to give the pure product without further purification (0.4 g, 53%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.8 (dtt, J = 538.0, 19.6, 6.6 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dt, J = 538.3, 2.1 Hz, 1H), 7.46 – 7.27 (m, 4H), 7.26 – 7.17 (m, 1H), 6.52 – 6.37 (m, 1H), 6.06 (dd, J = 15.6, 7.6 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.21 – 2.15 (m, 3H), 2.05 (d, J = 3.0 Hz, 6H), 1.62 (t, J = 3.1

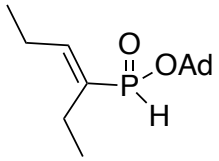
Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (d, J = 4.3 Hz), 135.4 (d, J = 14.6 Hz), 128.6, 127.7 (d, J = 1.4 Hz), 126.2 (d, J = 2.3 Hz), 117.9 (d, J = 10.1 Hz), 81.9, 43.9 (d, J = 4.4 Hz), 35.7, 35.3 (d, J = 95.3 Hz), 31.0; HRMS (EI+): *m*/*z* calcd for $C_{19}H_{25}O_2P$: 317.1665 [*M*+H]$^+$; found: 317.1659.

Octyl-adamantyl ester H-phosphinate (Table 7.1, entry 13).



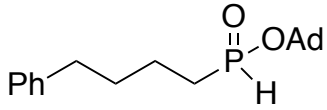
The appropriate octyl-*H*-phosphinic acid (1.0 equiv, 14 mmol) and 1-AdOH (1.0 equiv, 14 mmol) in DCM (70 mL) was added pyridine (1.5 equiv, 18 mmol) and PivCl (1.2 equiv, 16.8 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (hexanes;EtOAc 80:20) to give the product as a clear oil (2.2 g, 50%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.4 (d, J = 521.7 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 523.3 Hz, 1H), 2.21 – 2.13 (m, 3H), 2.03 (d, J = 2.9 Hz, 6H), 1.70 (tdd, J = 10.2, 5.0, 1.8 Hz, 2H), 1.63 (t, J = 3.1 Hz, 6H), 1.52 (dddd, J = 13.1, 9.4, 5.5, 2.2 Hz, 2H), 1.37 (d, J = 7.6 Hz, 2H), 1.34 – 1.17 (m, 8H), 0.92 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 81.3 (d, J = 8.7 Hz), 43.9 (d, J = 4.5 Hz), 35.7 (d, J = 4.2 Hz), 31.8, 31.0 (d, J = 3.4 Hz), 30.4 (d, J = 15.8 Hz), 29.9, 29.1 (d, J = 8.0 Hz), 28.9, 22.6, 21.1 (d, J = 2.9 Hz), 14.1; HRMS (EI+): m/z calcd for $C_{18}H_{33}O_2P$: 313.2291 [M+H]$^+$; found: 313.2287.

1-Ethyl-1-buten-1-yl-adamantyl ester H-phosphinate (Table 7.1, entry 14).



To a rb was added appropriate 1-ethyl-1-buten-1-yl-phosphinic acid (1.0 equiv, 10.7 mmol) and 1-AdOH (1.0 equiv, 10.7 mmol) in DCM (54 mL) was added pyridine (1.5 equiv, 16 mmol) and PivCl (1.2 equiv, 12.8 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified by column chromatography (hexanes:EtOAc 70:30) to afford the product as an beige oil (1.9 g, 66%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8 (dd, J = 533.5, 25.7 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 532.1 Hz, 1H), 6.41 – 6.26 (m, 1H), 2.19 (m, 7H), 2.07 (q, J = 2.5 Hz, 6H), 1.64 (q, J = 2.6 Hz, 6H), 1.10 – 0.97 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (d, J = 13.7 Hz), 134.1, 132.8, 81.2 (d, J = 8.9 Hz), 43.9 (d, J = 4.7 Hz), 35.8, 31.0, 21.6 (d, J = 19.1 Hz), 19.6 (d, J = 12.6 Hz), 13.6 (dd, J = 84.5, 2.1 Hz); HRMS (EI+): m/z calcd for $C_{16}H_{27}O_2P$: 283.1821 $[M+H]^+$; found: 283.1820.

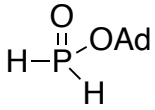
4-Phenylbutyl-adamantyl ester H-phosphinate (Table 7.1, entry 15).



To a rb was added 4-phenylbutyl phosphinic acid (1.0 equiv, 9.2 mmol) and 1-AdOH (1.0 equiv, 9.2 mmol) in DCM (46 mL) was added pyridine (1.5 equiv, 13.8 mmol) and PivCl

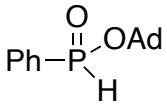
(1.2 equiv, 11 mmol) dropwise at rt under N_2. The reaction stirred at rt for 16 h. The organic layer was washed with a 0.1 M HCl aq. solution. The two layers were separated, and the organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified by column chromatography (hexanes:EtOAc 70:30) to afford the product as a colorless oil (2.4 g, 78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.7 (d, J = 522.2 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 525.4 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.19 (dd, J = 10.3, 7.7 Hz, 3H), 2.65 (t, J = 7.2 Hz, 2H), 2.21 (s, 3H), 2.05 (t, J = 2.6 Hz, 6H), 1.83 – 1.70 (m, 4H), 1.66 (d, J = 2.9 Hz, 6H), 1.63 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 128.4 (d, J = 3.3 Hz), 125.9, 81.4 (d, J = 9.0 Hz), 43.9 (d, J = 4.7 Hz), 35.7, 35.5, 32.2 (d, J = 15.7 Hz), 31.0, 29.9, 28.9, 20.8 (d, J = 2.9 Hz); HRMS (EI+): m/z calcd for $C_{20}H_{29}O_2P$: 333.1978 $[M+H]^+$ found: 333.1975.

*Adamantyl hypophosphite **105** via transesterification (Scheme 7.5, entry a).*



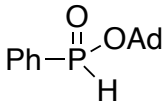
To a rb flask was added ethyl hypophosphite (2 mmol, 1 equiv, 0.5 M in toluene) followed by addition of 1-AdOH (4 mmol, 2 equiv) at rt under nitrogen. The reaction stirred at rt for 24 h (NMR yield: 16 %). ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.99 (t, J = 560.9 Hz).

*Adamantyl phenyl H-phosphinate **104** via transesterification (Scheme 7.5, entry b).*



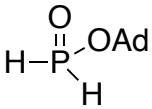
To a rb flask was added butyl-phenyl phosphonate (1 equiv) in THF under nitrogen. The reaction was cooled to 0 °C and NaH (2 equiv, 60% in mineral oil) was added and stirred at rt for 1 h. 1-AdOH (2 equiv) was added and stirred at rt for 16 h. A ^{31}P NMR of the reaction mixture was taken and showed 0 % conversion of the sm to the product.

*Adamantyl phenyl H-phosphinate **104** via transesterification (Scheme 7.5, entry c).*



To a rb flask was added butyl-phenyl phosphonate (2 mmol, 1 equiv), 1-AdOH (2 mmol, 1 equiv) in THF (10 mL) under nitrogen. LiHMDS (4 mmol, 2 equiv, 1 M in toluene) was added at rt and stirred at for 16 h. A ^{31}P NMR of the reaction mixture was taken and showed 0 % conversion of the sm to the product.

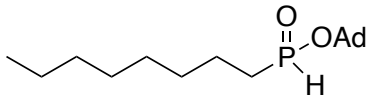
*Adamantyl hypophosphite **105** from AHP (Scheme 7.6).*



To a rb flask was added AHP (2 mmol, 1.0 equiv) and 1-AdOH (3.0 mmol, 1.5 equiv) in toluene (10 mL). To this was added pyridine (2.5 mmol, 1.25 equiv) and PivCl (2.5 mmol, 1.25 equiv) dropwise at 0 °C then brought to rt under N_2. The reaction stirred at rt for 2 h to

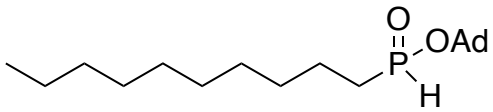
form the adamantyl hypophosphite with a conversion of sm to product ~ 60 – 80 %. ^{31}P-NMR δ 4.0 (t, *J* = 568 Hz).

Octyl-adamantyl ester H-phosphinate (Table 7.2, entry 1).



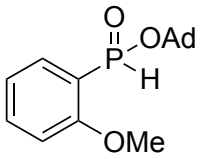
To a solution of AHP (2 mmol, 2.0 equiv) and 1-AdOH (3 mmol, 3.0 equiv) in CH_3CN or toluene (10 mL) was added pyridine (2.5 mmol, 2.5 equiv) and PivCl (2.2 mmol, 2.2 equiv) dropwise at 0 °C under N_2. The reaction was brought to rt and stirred for 2 h. 1-octene (1 mmol, 1.0 eq), tris(dibenzylideneacetone)dipalladium(0) $Pd_2(dba)_3$ (0.01 mmol, 1.0 mol %), and Xantphos (0.02 mmol, 2.0 mol %) were added and the reaction brought to reflux for 16 h. The reaction was cooled down to rt. EtOAc was added, the organic layer was washed with 1 M aq. HCl (1x), the layers were separated. The organic layer was washed with aq. solution of $NaHCO_3$ (1x), washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified by column chromatography (hexanes:EtOAc 50:50) to afford the product as a clear oil (0.11 g, 32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 523.3 Hz, 1H), 2.21 – 2.13 (m, 3H), 2.03 (d, *J* = 2.9 Hz, 6H), 1.70 (tdd, *J* = 10.2, 5.0, 1.8 Hz, 2H), 1.63 (t, *J* = 3.1 Hz, 6H), 1.52 (dddd, *J* = 13.1, 9.4, 5.5, 2.2 Hz, 2H), 1.37 (d, *J* = 7.6 Hz, 2H), 1.34 – 1.17 (m, 8H), 0.92 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 81.3 (d, *J* = 8.7 Hz), 43.9 (d, *J* = 4.5 Hz), 35.7 (d, *J* = 4.2 Hz), 31.8, 31.0 (d, *J* = 3.4 Hz), 30.4 (d, *J* = 15.8 Hz), 29.9, 29.1 (d, *J* = 8.0 Hz), 28.9, 22.6, 21.1 (d, *J* = 2.9 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.4 (d, *J* = 521.7 Hz); HRMS (EI+): *m*/*z* calcd for $C_{18}H_{33}O_2P$: 313.2291 $[M+H]^+$; found: 313.2287.

Decyl-adamantyl ester H-phosphinate (Table 7.2, entry 2).



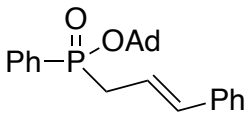
To a solution of AHP (2 mmol, 2.0 equiv) and 1-AdOH (3 mmol, 3.0 equiv) in CH_3CN or toluene (10 mL) was added pyridine (2.5 mmol, 2.5 equiv) and PivCl (2.2 mmol, 2.2 equiv) dropwise at 0 °C under N_2. The reaction was brought to rt and stirred for 2 h. 1-decene (1 mmol, 1.0 eq), tris(dibenzylideneacetone)dipalladium(0) $Pd_2(dba)_3$ (0.01 mmol, 1.0 mol %), and Xantphos (0.02 mmol, 2.0 mol %) were added and the reaction brought to reflux for 16 h. The reaction was cooled down to rt. EtOAc was added, the organic layer was washed with 1 M aq. HCl (1x), the layers were separated. The organic layer was washed with aq. solution of $NaHCO_3$ (1x), washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The crude was purified by column chromatography (hexanes:EtOAc 50:50) to afford the product as a clear oil (0.113 g, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dt, J = 521.0, 2.0 Hz, 1H), 2.20 (s, 3H), 2.06 (d, J = 2.9 Hz, 6H), 1.78 – 1.65 (m, 2H), 1.65 (t, J = 3.1 Hz, 6H), 1.6-1.5 (m, 2H), 1.38 (t, J = 7.1 Hz, 2H), 1.31 – 1.22 (m, 12H), 0.94 – 0.80 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 81.2 (d, J = 9.1 Hz), 43.9 (d, J = 4.6 Hz), 35.7, 31.9, 31.0, 30.5, 30.3, 30.0, 29.5 (d, J = 24.8 Hz), 29.4 (d, J = 22.0 Hz), 29.0 , 22.7, 21.1 (d, J = 2.9 Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3 (dd, J = 520.9, 5.1 Hz); HRMS (EI+): *m*/*z* calcd for $C_{20}H_{37}O_2P$: 341.2604 $[M+H]^+$; found: 341.2595.

Adamantyl-2-methoxyphenyl-H-phosphinate (Table 7.2, entry 3).



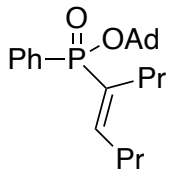
To a solution of AHP (2 mmol, 1.0 equiv) and 1-AdOH (3.0 mmol, 1.5 equiv) in toluene (5 mL) was added pyridine (2.5 mmol, 1.25 equiv) and PivCl (2.2 mmol, 1.1 equiv) dropwise at 0 °C then brought to rt under N_2. The reaction stirred at rt for 2 h, then $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 2.0 mol%), dppf (22.2 mg, 0.04 mmol, 2.0 mol%), and 1,2-dimethoxyethane (1 mL), DIPEA (2.6 mmol, 1.3 equiv.) and iodoanisole (1 mmol, 1 equiv.). The mixture was stirred under a flow of N_2 for 10 min and then heated at 115 °C for 24 h before cooling to room temperature. The solvent was then removed under vacuum and the resulting residue was dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexanes/EtOAc 50:50 to 0:100) to afford the product as a beige solid (0.29 g, 47 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 572.0 Hz, 1H), 7.83 (ddd, J = 14.4, 7.5, 1.8 Hz, 1H), 7.52 (tdd, J = 7.4, 1.8, 0.7 Hz, 1H), 7.11 – 7.01 (m, 1H), 6.97 – 6.88 (m, 1H), 3.89 (s, 3H), 2.21 (d, J = 2.9 Hz, 3H), 2.12 (d, J = 3.4 Hz, 6H), 1.66 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, J = 4.5 Hz), 134.3 (d, J = 1.9 Hz), 133.1 (d, J = 6.7 Hz), 120.7 (d, J = 13.0 Hz), 119.5 (d, J = 138.6 Hz), 110.8 (d, J = 7.2 Hz), 81.9 (d, J = 8.4 Hz), 55.6, 44.0 (d, J = 4.8 Hz), 35.8, 31.1;^{31}P NMR (162 MHz, $CDCl_3$) δ 9.3 (ddd, J = 571.3, 14.5, 6.4 Hz); HRMS (EI+): m/z calcd for $C_{17}H_{23}O_3P$: 307.1458 $[M+H]^+$; found: 307.1455.

Adamantyl-cinnamylphenyl-phosphinate ***106*** *(Scheme 7.7, entry a).*



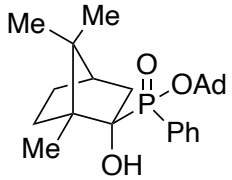
To a solution of **104** (2.0 mmol, 1 equiv) in *t*-amyl alcohol (10 mL), tris(dibenzylideneacetone)dipalladium(0) $Pd_2(dba)_3$ (1.0 mol %), Xantphos (2.0 mol %), and the cinnamyl alcohol (1 equiv) were added. The reaction mixture was stirred at reflux for 24 h under N_2 in a flask equipped with a Dean-Stark trap. The reaction was brought to rt and another portion of $Pd_2(dba)_3$ (1.0 mol %) and Xantphos (2.0 mol %) was added and brought to reflux for 24 h (48 h total reaction time). The reaction was cooled down to rt. EtOAc was added, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes/ethyl acetate 80:20) to afford **106** as a yellow solid (0.58 g, 74 %). M.p 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.58 – 7.50 (m, 1H), 7.48 – 7.42 (m, 2H), 7.34 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 6.42 – 6.27 (m, 1H), 6.21 – 6.04 (m, 1H), 2.85 (ddd, *J* = 18.5, 7.7, 1.3 Hz, 2H), 2.13 (s, 3H), 2.06 (d, *J* = 3.7 Hz, 6H), 1.59 (d, *J* = 3.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (d, *J* = 3.6 Hz), 134.5 (d, *J* = 13.1 Hz), 133.3, 131.7 (d, *J* = 2.9 Hz), 131.6, 128.5, 128.2 (d, *J* = 12.5 Hz), 127.3, 126.1 (d, *J* = 2.0 Hz), 119.7 (d, *J* = 10.3 Hz), 82.8, 44.6 (d, *J* = 3.8 Hz), 37.6 (d, *J* = 99.1 Hz), 35.7, 31.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.0; HRMS (EI+): *m*/*z* calcd for $C_{25}H_{29}O_2P$: 393.1978 $[M+H]^+$; found: 393.1975.

*Phenyl-(1-propyl-1-pentenyl)-ethyl ester phosphinic acid **107** (Scheme 7.7, entry b).*



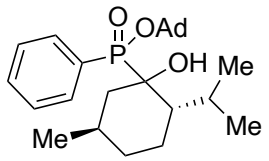
To a reaction tube was added **104** (2 mmol, 1 equiv), 4-octyne (2 mmol, 1 equiv), $Pd(OAc)_2$ (0.04 equiv, 2 mol%), dppf (0.044 equiv, 2.2 mol%) in DMF (9 mL) and DME (1 mL). The tube was flushed was argon for 10 min and then sealed. The reaction was brought to 115 °C in an oil bath and stirred for 24 h. The reaction was then cooled to rt, and a ^{31}P NMR of the reaction mixture showed 11 % yield of product **107**. ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.5 (s); and 89 % of unreacted sm product ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.1 (d).

Representative procedure for the H-functionalization of PhP(O)(OAd)H with (+)-camphor (Table 7.3, entry 5).



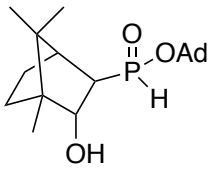
To a rb was added **104** (2 mmol, 1 equiv), Ti(O*i*Pr)$_4$ (2 mmol, 1 equiv) and (+)-camphor (4 mmol, 2 equiv) in toluene (8 mL). The flask was brought to refluc and stirred for 24 h. The reaction was then cooled to rt, and a ^{31}P NMR of the reaction mixture showed 18 % yield of product ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.3 (s); and 75 % of unreacted sm product ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9 (d).

Representative procedure for the H-functionalization of PhP(O)(OAd)H with (-)-menthone (Table 7.3, entry 6).



To a rb was added **104** (3 mmol, 1 equiv), Ti(O*i*Pr)$_4$ (3 mmol, 1 equiv) and (-)-menthone (6 mmol, 2 equiv) in toluene (12 mL). The flask was brought to refluc and stirred for 24 h. The reaction was then cooled to rt, and a ^{31}P NMR of the reaction mixture showed 29 % yield of product ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.3 (s); and 33 % of unreacted sm product ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8 (d).

Silylation of H_3PO_2 with BSA, followed by addition of (+)-camphor and 1-AdOH (Scheme 7.10).



In a rb flask was added H_3PO_2 (20 mmol, 1 equiv, concentrated under high vacuum for 30 min) in toluene (8 mL) under argon. The flask was cooled to 0 °C and BSA (40 mmol, 2 equiv) was added dropwise. The reaction was brought to rt and stirred for 30 min. (+)-camphor (1 equiv, 20 mmol) was added and the reaction brought to reflux for 2 h. (note: (+)-camphor emits flammable gas above 66 °C*)*. A ^{31}P NMR of the reaction mixture and showed 24% yield to the intermediate R^{1}P(O)(OH)H ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.06 (ddd, *J* = 524.8, 18.2, 8.9 Hz); HRMS (EI+): *m*/*z* calcd for $C_{10}H_{19}O_2P$: 218.1072 $[M+H]^+$; found: 219.1144.

The reaction was then cooled to 0 °C and pyridine (1.5 equiv, 30 mmol), 1-AdOH (1 equiv, 20 mmol), and PivCl (1.2 equiv, 24 mmol) was added, and the flask was brought to rt and stirred for 18 h. EtOAc (10 mL) was added, and the reaction mixture transferred to separatory funnel. The organic layer was washed with $CuSO_4$ (sat. aq), 1 M NaOH (aq.), and then brine. The layers were separated, and the organic layer dried with $MgSO_4$, filtered, and concentrated under vacuum. A ^{31}P NMR of the crude mixture resulted in a 28% yield to the final $R^1P(O)(OH)(OAd)$ product. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.01 (ddd, J = 554.1, 19.7, 11.3 Hz); HRMS (EI+): m/z calcd for $C_{20}H_{33}O_3P$: 352.2167 $[M-H_2O]^+$; found: 335.2134.

Kinetic Study Data of adamantyl-phenyl-H-phosphinate (Table 7.4)

NMR kinetics were recorded at room temperature on a 400 MHz spectrometer, at 161.97 MHz for ^{31}P using D_2O as a solvent lock, with four repetitions, a 2 s relaxation delay, and a 45° pulse angle. The NMR spectra were individually processed and integrated using appropriate software. Each resonance for the P(O)−H compound and the forming P(O)−D compounds was individually integrated, and the total sum of integrals was normalized to 100%. The kinetics were calculated on the basis of the decay of starting P(O)−H compound (i.e., total integrals for starting material (SM)/100 × concentration of sample, 1 M). The NMR yields are determined by integration of all the resonances in the ^{31}P spectra.

Spectrum #	P(O)-H Integral 1	P(O)-D Integral 1	P(O)-D Integral 2	P(O)-D Integral 3	P(O)-H Integral 2	Time (s)	[C]/[C]0	Ln([C]/[C]0)	Time (hh:mm:ss)
0	50	0	0	0	50	0	1	0	0:00:00
1	47.9673241	0.782257	0.81421144	0.94290256	49.4933049	300	0.97460629	-0.0257217	0:05:00
2	47.5581114	1.11502923	1.14650971	1.18741194	48.9929377	484	0.96551049	-0.0350983	0:08:04
3	47.022035	1.4352615	1.5657447	1.52504194	48.4519169	669	0.95473952	-0.0463167	0:11:09
4	46.4347206	1.81632576	1.9310246	2.0210773	47.7968517	853	0.94231572	-0.0594149	0:14:13
5	46.0432576	2.19781443	2.23050833	2.32925948	47.1991601	1037	0.93242418	-0.0699674	0:17:17
6	45.461752	2.55533153	2.63529124	2.69963118	46.6479941	1221	0.92109746	-0.0821894	0:20:21
7	45.061155	2.8836774	2.9263611	2.96517477	46.1636317	1405	0.91224787	-0.0918435	0:23:25
8	44.4943754	3.27017181	3.35527279	3.34901787	45.5311621	1589	0.90025538	-0.1050768	0:26:29
9	44.0013682	3.53050281	3.64696082	3.66734501	45.1538232	1773	0.89155191	-0.1147916	0:29:33
10	43.4594907	3.87855637	3.980522	4.04608342	44.6353475	1957	0.88094838	-0.1267562	0:32:37
11	42.9197738	4.2643315	4.37717392	4.32686065	44.1118601	2141	0.87031634	-0.1388985	0:35:41
12	42.3719476	4.57641214	4.67766291	4.67364699	43.7003304	2325	0.86072278	-0.1499828	0:38:45
13	41.9005691	4.94141649	5.02643033	5.04107397	43.0905101	2509	0.84991079	-0.1626239	0:41:49
14	41.4343317	5.30455295	5.38096222	5.39257108	42.487582	2693	0.83921914	-0.1752834	0:44:53
15	40.9091408	5.6135637	5.70558007	5.69917618	42.0725393	2877	0.8298168	-0.1865503	0:47:57
16	40.5340509	5.86741731	5.98697676	6.0011376	41.6104174	3061	0.82144468	-0.1966907	0:51:01
17	40.0478223	6.24458957	6.32450772	6.32332071	41.0597597	3245	0.81107582	-0.2093937	0:54:05
18	39.6184332	6.50487965	6.60261442	6.58496528	40.6891075	3429	0.80307541	-0.2193067	0:57:09
19	39.179658	6.81672348	6.95416792	6.88723744	40.1622132	3613	0.79341871	-0.2314042	1:00:13
20	38.7337933	7.04426065	7.21263165	7.18597519	39.8233392	3797	0.78557133	-0.241344	1:03:17
21	38.253583	7.40183262	7.56077751	7.47074204	39.3130648	3981	0.77566648	-0.2540326	1:06:21
22	37.7959086	7.69188037	7.81412242	7.79915609	38.8989325	4165	0.76694841	-0.2653357	1:09:25
23	37.4646272	7.94787185	8.09035803	8.05793988	38.4392031	4349	0.7590383	-0.275703	1:12:29
24	36.9555087	8.25428787	8.41342772	8.38104219	37.9957335	4533	0.74951242	-0.2883324	1:15:33
25	36.6170109	8.45669287	8.66651847	8.57258713	37.6871906	4717	0.74304202	-0.2970027	1:18:37
26	36.1223081	8.80821665	8.94414095	8.87626047	37.2490738	4901	0.73371382	-0.3096362	1:21:41
27	35.7482828	9.0459651	9.211583	9.17488005	36.8192891	5085	0.72567572	-0.320652	1:24:45
28	35.3073576	9.34457202	9.52311546	9.42544099	36.3995139	5269	0.71706872	-0.3325836	1:27:49
29	35.0182621	9.56559914	9.74116619	9.70162059	35.973352	5453	0.70991614	-0.3426084	1:30:53
30	34.5729499	9.85981989	10.0825882	9.99909304	35.485549	5637	0.70058499	-0.3558396	1:33:57
31	34.1541576	10.1178317	10.2969181	10.2269212	35.2041713	5821	0.69358329	-0.3658839	1:37:01
32	33.7449072	10.3943962	10.6120268	10.5146902	34.7339795	6005	0.68478887	-0.3786447	1:40:05
33	33.3658161	10.6995332	10.8189572	10.7609031	34.3547904	6189	0.67720606	-0.3897797	1:43:09
34	32.9750789	10.8959463	11.1014136	11.0149968	34.0125644	6373	0.66987643	-0.400662	1:46:13
35	32.6326667	11.1329417	11.334724	11.2756038	33.6240637	6557	0.6625673	-0.4116331	1:49:17
36	32.2507421	11.4356064	11.6108177	11.5063414	33.1964924	6741	0.65447235	-0.4239259	1:52:21
37	31.8356319	11.6755406	11.8719882	11.8045566	32.8122828	6925	0.64647915	-0.4362143	1:55:25

38	31.5445501	11.9585275	12.1163948	12.0209862	32.3595414	7109	0.63904091	-0.4477868	1:58:29
39	31.1150816	12.1389805	12.3212036	12.2528625	32.1718719	7293	0.63286953	-0.457491	2:01:33
40	30.6887103	12.4252653	12.6441681	12.5190184	31.7228379	7477	0.62411548	-0.4714199	2:04:37
41	30.3629082	12.6692097	12.905555	12.7990582	31.2632689	7661	0.61626177	-0.4840835	2:07:41
42	30.0006096	12.8949506	13.1397962	12.998704	30.9659396	7845	0.60966549	-0.4948448	2:10:45
43	29.7170459	13.1479592	13.3204678	13.2245446	30.5899825	8029	0.60307028	-0.5057215	2:13:49
44	29.3089222	13.3777784	13.5509325	13.4762318	30.2861351	8213	0.59595057	-0.5175975	2:16:53
45	28.9620258	13.6114802	13.7753244	13.7424104	29.9087592	8397	0.58870785	-0.5298252	2:19:57
46	28.6709627	13.8612286	14.0120839	13.9445709	29.5111538	8581	0.58182117	-0.5415922	2:23:01
47	28.2966058	14.0717042	14.3052921	14.155998	29.1703998	8765	0.57467006	-0.5539592	2:26:05
48	27.9494251	14.2344807	14.5194885	14.4026517	28.8939539	8949	0.56843379	-0.5648704	2:29:09
49	27.5918159	14.4876592	14.7646389	14.6349712	28.5209148	9133	0.56112731	-0.5778075	2:32:13
50	27.3113984	14.7416613	14.9623172	14.8806864	28.1039367	9317	0.55415335	-0.5903138	2:35:17
51	26.9322383	14.9427274	15.1847552	15.0740206	27.8662586	9501	0.54798497	-0.6015074	2:38:21
52	26.6098499	15.1615525	15.4152804	15.2940828	27.5192345	9685	0.54129084	-0.6137985	2:41:25
53	26.348162	15.3328796	15.6182249	15.5451002	27.1556333	9869	0.53503795	-0.6254176	2:44:29
54	26.0148874	15.6088622	15.9050003	15.6494066	26.8218436	10053	0.52836731	-0.6379636	2:47:33
55	25.7474129	15.8682274	16.0825151	15.8885597	26.4132849	10237	0.52160698	-0.6508409	2:50:37
56	25.4087206	15.9845705	16.2656545	16.1367521	26.2043024	10421	0.51613023	-0.6613962	2:53:41
57	25.0984938	16.1907578	16.4407788	16.3477601	25.9222095	10605	0.51020703	-0.6729387	2:56:45
58	**24.7894635**	**16.4284617**	**16.6696092**	**16.5291597**	**25.583306**	**10789**	**0.50372769**	**-0.6857194**	**2:59:49**
59	**24.5183128**	**16.5776298**	**16.8507986**	**16.7224**	**25.3308589**	**10973**	**0.49849172**	**-0.6961683**	**3:02:53**
60	24.1945161	16.8032268	17.0531346	16.9457073	25.0034151	11157	0.49197931	-0.7093186	3:05:57
61	23.9395912	17.0201646	17.2605681	17.0950862	24.6845899	11341	0.48624181	-0.7210492	3:09:01
62	23.6069651	17.1537191	17.4772351	17.3430302	24.4190504	11525	0.48026016	-0.7334273	3:12:05
63	23.3511685	17.4391078	17.6792153	17.5068159	24.0236925	11709	0.47374861	-0.7470785	3:15:09
64	23.0258355	17.5382546	17.8870351	17.712836	23.8360388	11893	0.46861874	-0.7579658	3:18:13
65	22.7783813	17.7488835	17.9956404	17.9260946	23.5510002	12077	0.46329382	-0.7693938	3:21:17
66	22.5394544	17.9499258	18.2038564	18.0683253	23.2384381	12261	0.45777893	-0.7813689	3:24:21
67	22.2437945	18.1167694	18.3731672	18.2742344	22.9920345	12445	0.45235829	-0.7932807	3:27:25
68	21.9676109	18.2718823	18.6170794	18.442159	22.7012684	12629	0.44668879	-0.8058931	3:30:29
69	21.7041013	18.3950374	18.7056638	18.6841742	22.5110232	12813	0.44215125	-0.8161033	3:33:33
70	21.4589429	18.6347931	18.9504559	18.7317556	22.2240525	12997	0.43682995	-0.8282113	3:36:37
71	21.1383375	18.8234846	19.1413298	18.9734145	21.9234336	13181	0.43061771	-0.8425346	3:39:41
72	20.9045781	18.9456844	19.3016601	19.1432474	21.70483	13365	0.42609408	-0.8530951	3:42:45
73	20.6249579	19.1583187	19.4549431	19.3308899	21.4308904	13549	0.42055848	-0.8661717	3:45:49
74	20.3989891	19.3733804	19.6893876	19.4440036	21.0942393	13733	0.41493228	-0.8796399	3:48:53
75	20.1433083	19.564478	19.8081706	19.6286958	20.8553474	13917	0.40998656	-0.8916309	3:51:57
76	19.9221979	19.6339283	19.9916616	19.8218699	20.6303424	14101	0.4055254	-0.9025718	3:55:01

77	19.6300204	19.7927183	20.165512	19.9537983	20.4579509	14285	0.40087971	-0.9140939	3:58:05
78	19.4840955	19.9615347	20.3266599	20.0897456	20.1379643	14469	0.3962206	-0.9257842	4:01:09
79	19.2101402	20.1310706	20.4908355	20.3059295	19.8620243	14653	0.39072164	-0.9397599	4:04:13
80	18.9404117	20.324745	20.6601605	20.4665266	19.6081563	14837	0.38548568	-0.9532512	4:07:17
81	18.6641733	20.3586084	20.7607504	20.6710376	19.5454302	15021	0.38209604	-0.9620833	4:10:21
82	18.5033129	20.5725837	20.9164805	20.8000991	19.2075239	15205	0.37710837	-0.9752227	4:13:25
83	18.2611691	20.6994285	21.1023641	20.9393395	18.9976988	15389	0.37258868	-0.9872802	4:16:29
84	18.1810919	21.0023557	21.2364061	20.9243169	18.6558293	15573	0.36836921	-0.9986695	4:19:33
85	17.8693608	21.0575736	21.4134329	21.1477834	18.5118492	15757	0.3638121	-1.0111178	4:22:37
86	17.6688924	21.3024068	21.5437473	21.2230365	18.2619169	15941	0.35930809	-1.0235751	4:25:41
87	17.3640503	21.3698578	21.6539977	21.5526953	18.0593989	16125	0.35423449	-1.0377962	4:28:45
88	17.275469	21.4734795	21.8070491	21.5673463	17.8766561	16309	0.35152125	-1.0454851	4:31:49
89	16.9594602	21.5748161	21.9584884	21.8138194	17.6934158	16493	0.34652876	-1.0597895	4:34:53
90	16.7280719	21.729823	22.1247444	21.935968	17.4813928	16677	0.34209465	-1.0726678	4:37:57
91	16.52242	21.8856358	22.2490952	22.0274344	17.3154145	16861	0.33837835	-1.0835906	4:41:01
92	16.3260149	22.0524036	22.3902721	22.1808555	17.0504539	17045	0.33376469	-1.0973191	4:44:05
93	16.1686147	22.1505067	22.4976264	22.3205248	16.8627274	17229	0.33031342	-1.1077133	4:47:09
94	15.9485129	22.260084	22.6657468	22.4838493	16.641807	17413	0.3259032	-1.1211549	4:50:13
95	15.7530304	22.4708149	22.7583282	22.6141496	16.4036768	17597	0.32156707	-1.1345491	4:53:17
96	15.5589002	22.5576021	22.9175281	22.7329971	16.2329725	17781	0.31791873	-1.1459595	4:56:21
97	15.3902778	22.7545284	23.0715841	22.7559486	16.0276611	17965	0.31417939	-1.1577912	4:59:25
98	15.199881	22.8232388	23.1546766	22.9440608	15.8781428	18149	0.31078024	-1.1686692	5:02:29
99	15.0271045	22.9674319	23.2876828	23.0881116	15.6296692	18333	0.30656774	-1.1823165	5:05:33
100	14.8141718	22.9564774	23.4368124	23.2464907	15.5460476	18517	0.30360219	-1.192037	5:08:37
101	14.7354938	23.1407123	23.5915206	23.232848	15.2994254	18701	0.30034919	-1.2028095	5:11:41
102	14.5173311	23.2231616	23.6175487	23.475751	15.1662077	18885	0.29683539	-1.2145775	5:14:45
103	14.3480389	23.3563282	23.7044794	23.5737869	15.0173666	19069	0.29365406	-1.2253529	5:17:49
104	14.120144	23.4679765	23.9170668	23.6640506	14.8307621	19253	0.28950906	-1.2395687	5:20:53
105	13.9158686	23.5489151	23.9996308	23.8112206	14.7243649	19437	0.28640233	-1.2503577	5:23:57
106	13.7941231	23.7020612	24.0706249	23.9301498	14.503041	19621	0.28297164	-1.2624086	5:27:01
107	13.6346621	23.7511221	24.212248	24.0679288	14.334039	19805	0.27968701	-1.2740841	5:30:05
108	13.4671705	23.8997924	24.3161299	24.1312214	14.1856858	19989	0.27652856	-1.2854412	5:33:09
109	13.4231904	24.1257856	24.3917142	24.1649892	13.8943207	20173	0.27317511	-1.2976423	5:36:13
110	13.1695335	24.1508859	24.5531175	24.3386476	13.7878156	20357	0.26957349	-1.3109142	5:39:17
111	13.0470703	24.1446579	24.6494802	24.494191	13.6646007	20541	0.26711671	-1.3200696	5:42:21
112	12.8408575	24.2825968	24.7596005	24.5762129	13.5407323	20725	0.2638159	-1.3325038	5:45:25
113	12.7577887	24.4736049	24.8814313	24.5856892	13.3014859	20909	0.26059275	-1.3447965	5:48:29
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115	12.4412356	24.708992	25.019363	24.7988533	13.0315561	21277	0.25472792	-1.3675593	5:54:37

116	12.3545304	24.7514536	25.1508669	24.8625305	12.8806186	21461	0.25235149	-1.3769324	5:57:41
117	12.133018	24.875887	25.252849	25.0482818	12.6899642	21645	0.24822982	-1.3934003	6:00:45
118	11.9595943	24.8816042	25.3939237	25.1405302	12.6243476	21829	0.24583942	-1.4030767	6:03:49
119	11.8388601	24.9413045	25.4527169	25.2631885	12.50393	22013	0.2434279	-1.4129345	6:06:53
120	11.6712618	25.0201627	25.4927616	25.4018815	12.4139324	22197	0.24085194	-1.4235729	6:09:57
121	11.6805532	25.2636252	25.5907954	25.3558113	12.1092149	22381	0.23789768	-1.4359146	6:13:01
122	11.3729257	25.2345742	25.6932206	25.5770545	12.1222251	22565	0.23495151	-1.4483761	6:16:05
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126	10.871681	25.6028265	26.0833788	25.8460919	11.5960218	23301	0.22467703	-1.4930913	6:28:21
127	10.7816332	25.6781713	26.1786612	25.9334244	11.42811	23485	0.22209743	-1.5046391	6:31:25
128	10.7239027	25.8177573	26.1809568	26.0162127	11.2611704	23669	0.21985073	-1.5148065	6:34:29
129	10.5549659	25.8354637	26.2917384	26.126959	11.1908731	23853	0.21745839	-1.5257478	6:37:33
130	10.4883039	25.865282	26.4265397	26.2169357	11.0029387	24037	0.21491243	-1.5375247	6:40:37
131	10.2415806	25.8537827	26.4944643	26.3766004	11.0335719	24221	0.21275153	-1.5476303	6:43:41
132	10.2385408	26.1207326	26.5595569	26.2596072	10.8215625	24405	0.21060103	-1.5577898	6:46:45
133	10.0748104	26.2031015	26.6273991	26.4207719	10.6739172	24589	0.20748728	-1.5726853	6:49:49
134	9.97598689	26.2409351	26.734854	26.4582407	10.5899833	24773	0.2056597	-1.5815324	6:52:53
135	9.98504107	26.4079046	26.8148758	26.458449	10.3337296	24957	0.20318771	-1.5936251	6:55:57
136	9.81538138	26.3785067	26.8854175	26.589151	10.3315435	25141	0.20146925	-1.6021185	6:59:01
137	9.68244918	26.4352056	26.922999	26.6559338	10.3034124	25325	0.19985862	-1.6101451	7:02:05
138	9.60920118	26.5375675	26.9760542	26.7592495	10.1179277	25509	0.19727129	-1.6231754	7:05:09
139	9.48066098	26.581567	27.0591133	26.8167565	10.0619022	25693	0.19542563	-1.6325754	7:08:13
140	9.388773	26.5855399	27.1166548	26.9398989	9.96913337	25877	0.19357906	-1.6420693	7:11:17
141	9.27660075	26.8017988	27.1951068	26.9253687	9.80112491	26061	0.19077726	-1.6566487	7:14:21
142	9.24210465	26.8496164	27.2614539	26.9277767	9.7190483	26245	0.18961153	-1.6627779	7:17:25
143	9.12981533	26.8772286	27.3233583	26.9981518	9.67144596	26429	0.18801261	-1.6712462	7:20:29
144	9.0709401	26.9493721	27.3756774	27.1317178	9.47229256	26613	0.18543233	-1.6850653	7:23:33
145	8.82405754	26.9383881	27.4695738	27.2851809	9.48279961	26797	0.18306857	-1.6978945	7:26:37
146	8.74664768	27.0925956	27.5451167	27.2803503	9.33528959	26981	0.18081937	-1.7102567	7:29:41
147	8.77197788	27.1876369	27.5297609	27.2558074	9.25481684	27165	0.18026795	-1.7133109	7:32:45
148	8.68118723	27.109715	27.6247862	27.3387959	9.24551563	27349	0.17926703	-1.7188788	7:35:49
149	8.53153427	27.1845373	27.6828066	27.4704356	9.13068622	27533	0.1766222	-1.7337423	7:38:53
150	8.48122996	27.3490409	27.7291311	27.3981943	9.04240382	27717	0.17523634	-1.7416197	7:41:57
151	8.3935104	27.377086	27.814449	27.5048576	8.91009701	27901	0.17303607	-1.7542552	7:45:01
152	8.31165087	27.3988119	27.8900938	27.5762849	8.82315853	28085	0.17134809	-1.7640582	7:48:05
153	8.22542543	27.4612923	27.9104139	27.6840453	8.71882303	28269	0.16944248	-1.7752417	7:51:09
154	8.15653155	27.5665676	28.0040067	27.6488553	8.62403881	28453	0.1678057	-1.7849485	7:54:13

155	8.09281225	27.6673371	28.0208908	27.7035246	8.51543532	28637	0.16608248	-1.7952708	7:57:17
156	7.94210188	27.5621159	28.0875806	27.8766306	8.53157101	28821	0.16473673	-1.8034067	8:00:21
157	7.91647929	27.6316311	28.1371081	27.8882009	8.42658067	29005	0.1634306	-1.8113668	8:03:25
158	7.86258064	27.835449	28.1990518	27.8503773	8.25254126	29189	0.16115122	-1.8254121	8:06:29
159	7.793338	27.7242996	28.2058011	27.9837742	8.29278709	29373	0.16086125	-1.8272131	8:09:33
160	7.64950881	27.7541374	28.2850748	28.072349	8.23892994	29557	0.15888439	-1.8395785	8:12:37
161	7.62219267	27.899496	28.3212275	28.0440079	8.113076	29741	0.15735269	-1.8492656	8:15:41
162	7.48951108	27.829636	28.3922642	28.1829206	8.10566812	29925	0.15595179	-1.8582083	8:18:45
163	7.51246872	28.0157062	28.427769	28.0956933	7.94836273	30109	0.15460831	-1.8668604	8:21:49
164	7.38081605	28.0153882	28.5151752	28.1965755	7.89204498	30293	0.15272861	-1.8790927	8:24:53
165	7.36613433	28.0280889	28.5177128	28.2831325	7.80493145	30477	0.15171066	-1.8857801	8:27:57
166	7.24318542	28.079824	28.5550481	28.3323557	7.78958678	30661	0.15032772	-1.8949376	8:31:01
167	7.09115109	27.9862067	28.6115808	28.4673036	7.84375783	30845	0.14934909	-1.9014688	8:34:05
168	7.23241665	28.3254013	28.6826957	28.2129051	7.5465813	31029	0.14778998	-1.9119631	8:37:09
169	7.13295811	28.2208906	28.7319397	28.3939492	7.52026236	31213	0.1465322	-1.92051	8:40:13
170	6.99551151	28.2631935	28.7917314	28.4356827	7.51388088	31397	0.14509392	-1.930374	8:43:17
171	6.95725883	28.3394324	28.8410452	28.5068515	7.35541215	31581	0.14312671	-1.944025	8:46:21
172	6.83814963	28.2923516	28.7911518	28.6020629	7.47628407	31765	0.14314434	-1.9439018	8:49:25
173	6.81196944	28.3977907	28.8904789	28.592019	7.30774199	31949	0.14119711	-1.9575984	8:52:29
174	6.80859661	28.5055888	28.8734023	28.5769985	7.23541386	32133	0.1404401	-1.9629742	8:55:33
175	6.74213496	28.5353743	28.9144244	28.6260883	7.18197803	32317	0.13924113	-1.9715481	8:58:37
176	6.6648596	28.5081369	28.990855	28.7248312	7.11131722	32501	0.13776177	-1.9822294	9:01:41
177	6.5645166	28.4996598	28.9654009	28.7737926	7.19663022	32685	0.13761147	-1.983321	9:04:45
178	6.4645844	28.5205596	29.0597926	28.8421879	7.11287547	32869	0.1357746	-1.9967591	9:07:49
179	6.48994585	28.6521949	29.1143681	28.7773119	6.96617921	33053	0.13456125	-2.0057358	9:10:53
180	6.49114144	28.8061295	29.1257393	28.7640409	6.81294894	33237	0.1330409	-2.0170987	9:13:57
181	6.39110744	28.7838553	29.2119038	28.8273029	6.78583058	33421	0.13176938	-2.026702	9:17:01
182	6.27836862	28.5824621	29.1948729	28.9971953	6.94710111	33605	0.1322547	-2.0230257	9:20:05
183	6.2789622	28.8005653	29.224889	28.9252075	6.77037606	33789	0.13049338	-2.0364328	9:23:09
184	6.21670636	28.7893313	29.2392944	29.0036856	6.75098227	33973	0.12967689	-2.0427094	9:26:13
185	6.22346436	28.853784	29.2676069	29.0039193	6.65122545	34157	0.1287469	-2.0499068	9:29:17
186	6.14835003	28.8263907	29.2994077	29.0915457	6.63430597	34341	0.12782656	-2.0570809	9:32:21
187	6.08615909	28.9843406	29.3875498	29.0055406	6.5364099	34525	0.12622569	-2.0696838	9:35:25
188	6.02464301	28.9191907	29.3590732	29.1104452	6.58664788	34709	0.12611291	-2.0705777	9:38:29
189	6.02342327	28.9441216	29.4002854	29.117437	6.51473275	34893	0.12538156	-2.0763937	9:41:33
190	5.98454957	29.0271094	29.451881	29.0969539	6.4395061	35077	0.12424056	-2.0855356	9:44:37
191	5.89009159	29.0658674	29.4568593	29.1779913	6.40919046	35261	0.12299282	-2.0956293	9:47:41
192	5.87587858	29.1086936	29.5381188	29.182766	6.29454294	35445	0.12170422	-2.1061616	9:50:45
193	5.82912217	29.0995756	29.5111156	29.2584397	6.30174687	35629	0.12130869	-2.1094168	9:53:49

194	5.78521195	29.0034887	29.5467807	29.3320478	6.33247084	35813	0.12117683	-2.1105044	9:56:53
195	5.79507827	29.202414	29.5900747	29.2636183	6.14881476	35997	0.11943893	-2.1249501	9:59:57
196	5.71194136	29.0367629	29.5825649	29.4140373	6.25469355	36181	0.11966635	-2.1230478	10:03:01
197	5.61820518	29.1840836	29.6584358	29.4245341	6.11474133	36365	0.11732947	-2.1427694	10:06:05
198	5.65687555	29.1703063	29.6577941	29.4365833	6.07844073	36549	0.11735316	-2.1425674	10:09:09
199	5.5854125	29.2284873	29.684029	29.4043815	6.09768979	36733	0.11683102	-2.1470266	10:12:13
200	5.55358647	29.3057393	29.6671695	29.4482738	6.02523086	36917	0.11578817	-2.1559928	10:15:17
201	5.4601884	29.2958571	29.780661	29.52713	5.93616354	37101	0.11396352	-2.1718769	10:18:21
202	5.51859768	29.3743559	29.7577582	29.4651746	5.8841136	37285	0.11402711	-2.171319	10:21:25
203	5.38687413	29.299943	29.7835906	29.5575479	5.97204433	37469	0.11358918	-2.175167	10:24:29
204	5.39000968	29.3170704	29.8357209	29.6088806	5.84831834	37653	0.11238328	-2.1858401	10:27:33
205	5.39449646	29.4061767	29.9169306	29.457259	5.8251372	37837	0.11219634	-2.1875049	10:30:37
206	5.35536302	29.3274166	29.8247422	29.6398501	5.85262817	38021	0.11207991	-2.1885432	10:33:41
207	5.34110009	29.4226027	29.910924	29.5841933	5.74117993	38205	0.1108228	-2.1998227	10:36:45
208	5.28737102	29.5280105	29.913027	29.5958089	5.67578253	38389	0.10963154	-2.2106302	10:39:49
209	5.23749191	29.3699398	29.9192153	29.7409042	5.73244873	38573	0.10969941	-2.2100113	10:42:53
210	5.18803615	29.4695173	29.9737174	29.6806759	5.6880532	38757	0.10876089	-2.2186034	10:45:57
211	5.20425191	29.568378	29.9683435	29.6573338	5.60169279	38941	0.10805945	-2.2250738	10:49:01
212	5.11064917	29.5124907	29.9721721	29.7940023	5.61068585	39125	0.10721335	-2.2329345	10:52:05
213	5.04566942	29.4976703	30.020196	29.825808	5.61065642	39309	0.10656326	-2.2390165	10:55:09
214	5.09772699	29.5331287	30.0768511	29.7371881	5.55510521	39493	0.10652832	-2.2393444	10:58:13
215	5.06444416	29.5006752	30.0450012	29.8061639	5.58371553	39677	0.1064816	-2.2397831	11:01:17
216	5.01282283	29.6379289	30.1184885	29.7399929	5.49076687	39861	0.1050359	-2.2534531	11:04:21
217	4.95283583	29.5485767	30.130852	29.9193972	5.44833825	40045	0.10401174	-2.2632515	11:07:25
218	4.97868945	29.617614	30.1428701	29.860976	5.39985041	40229	0.1037854	-2.26543	11:10:29
219	4.85540399	29.5679474	30.0591012	29.9537543	5.56379311	40413	0.10419197	-2.2615202	11:13:33
220	4.89579125	29.7473805	30.1672108	29.8475101	5.34210732	40597	0.10237899	-2.2790738	11:16:37
221	4.96449036	29.7773973	30.163028	29.7559642	5.33912021	40781	0.10303611	-2.2726758	11:19:41
222	4.86881753	29.658513	30.1853194	29.9405918	5.34675826	40965	0.10215576	-2.2812566	11:22:45
223	4.83799333	29.6514944	30.2300679	29.9883565	5.29208787	41149	0.10130081	-2.2896609	11:25:49
224	4.76837307	29.7475723	30.1831807	30.0124067	5.2884673	41333	0.1005684	-2.2969171	11:28:53
225	4.76375212	29.7285849	30.2731843	29.9951212	5.23935752	41517	0.1000311	-2.3022742	11:31:57
226	4.74201167	29.7766274	30.2527695	29.9922567	5.23633471	41701	0.09978346	-2.3047528	11:35:01
227	4.67945191	29.8263762	30.2387164	30.0362063	5.21924917	41885	0.09898701	-2.3127666	11:38:05
228	4.68557599	29.8815693	30.3433205	29.9755319	5.11400228	42069	0.09799578	-2.3228308	11:41:09
229	4.73052072	29.8778285	30.2608315	29.9553893	5.1754299	42253	0.09905951	-2.3120345	11:44:13
230	4.69409448	29.9867371	30.3205461	29.9627966	5.03582576	42437	0.0972992	-2.3299645	11:47:17
231	4.66190864	29.9052331	30.3725403	29.9952223	5.06509557	42621	0.09727004	-2.3302642	11:50:21
232	4.61585661	29.7848886	30.3450781	30.0899563	5.16422035	42805	0.09780077	-2.3248228	11:53:25

233	4.63878929	29.9250305	30.4018315	30.0620382	4.97231053	42989	0.096111	-2.3422515	11:56:29
234	4.51190929	29.90285	30.3681637	30.1541165	5.06296044	43173	0.0957487	-2.3460283	11:59:33
235	4.61448935	30.0642757	30.3829321	30.0122588	4.92604393	43357	0.09540533	-2.3496208	12:02:37
236	4.54259211	29.995538	30.4232776	30.1131706	4.92542169	43541	0.09468014	-2.357251	12:05:41
237	4.51883848	29.8689848	30.4047582	30.2112445	4.99617411	43725	0.09515013	-2.3522994	12:08:45
238	4.46678642	29.9063598	30.400707	30.1873219	5.0388249	43909	0.09505611	-2.3532879	12:11:49
239	4.45931967	29.9756429	30.4343388	30.1885854	4.94211322	44093	0.09401433	-2.3643081	12:14:53
240	4.51564562	29.942434	30.4107206	30.2093461	4.92185377	44277	0.09437499	-2.3604791	12:17:57

Figure S7.1. Concentration versus time plot for the deuteration of adamantyl-phenyl-H-phosphinate.

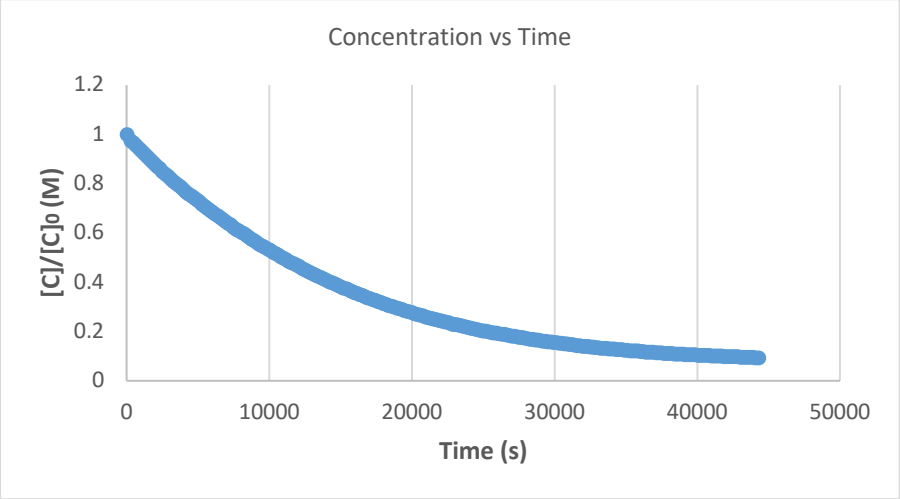
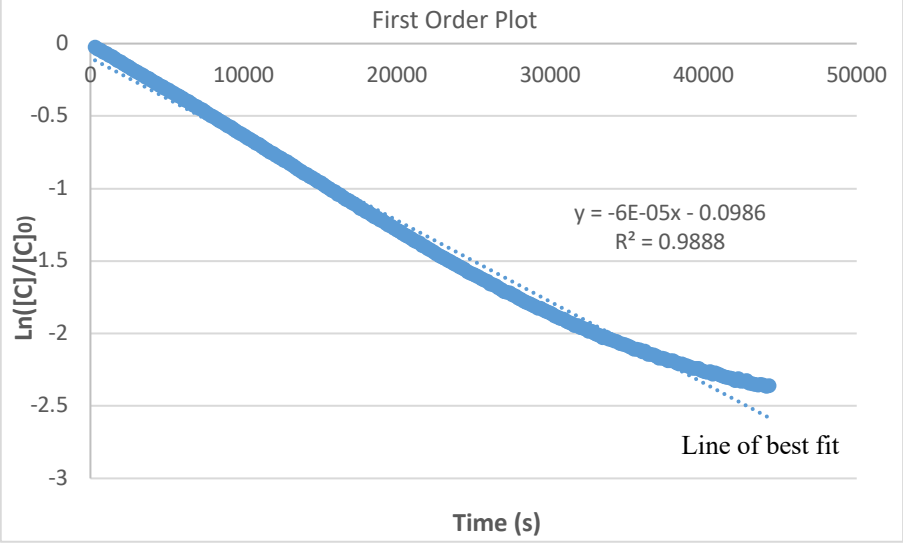


Figure S7.2. First order plot for the deuteration of adamantyl-phenyl-H-phosphinate. For a 1st order reaction, rate = k[A] (k = - slope of line).



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VITA

Born and raised in Tucson, Arizona, Karen Winters received her Bachelor of Science degree in Chemistry from Northern Arizona University (NAU) in Flagstaff, AZ, *summa cum laude*, in the spring 2016. At NAU, Karen received the NAU Department of Chemistry and Biochemistry Senior Scholar Award, Nancy and Henry Wettaw Award, and participated in undergraduate research with Professor Michael V. Lee.

In fall 2016, Karen began the doctoral degree program at Texas Christian University (TCU) in Fort Worth, TX, working with Professor Jean-Luc Montchamp in Organic Chemistry. In April 2021, Karen received the first TCU College of Science and Engineering Graduate Research and Creative Activities Award. That year she also participated in a summer research internship with Pfizer Inc. working in medicinal chemistry, in San Diego, CA.

ABSTRACT

NEW METHODOLOGIES FOR THE SYNTHESIS OF CHIRAL PHOSPHORUS ACIDS AND RELATED COMPOUNDS

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Organocatalysis has become a major subdiscipline in (asymmetric) organic synthesis. Among chiral organocatalysts, C_2-symmetrical chiral phosphorus acids (CPAs) occupy a rather special place because they can catalyze numerous transformations as Brønsted acids, however they suffer from serious limitations such as: extremely high cost (they are much too expensive for use on an industrial scale, and often too expensive even on much smaller academic scales), very high molecular weight, inability to access both enantiomers without a significant and separate synthetic effort, difficulty in catalyst-immobilization, etc. In order to solve these problems, which hamper the broader uses and applications of CPAs, our proposed approach is to rely on compounds in which the phosphorus atom is chiral (called *P*-stereogenic, *P*-chiral, or *P*-chirogenic) but the rest of the molecule is not. This dissertation presents our development and research findings for the synthesis of chiral phosphorus acids as well as their application in asymmetric organocatalysis.