Enantioselective Synthesis of Stereogenic-at-Phosphorus(V) Compounds via Hydrogen-Bond-Donor Catalysis

HARVARD UNIVERSITY
Graduate School of Arts and Sciences

DISSERTATION ACCEPTANCE CERTIFICATE

The undersigned, appointed by the

Department of Chemistry & Chemical Biology

have examined a dissertation entitled:

Enantioselective Synthesis of Stereogenic-at-Phosphorus(V) Compounds via Hydrogen-Bond-Donor Catalysis

presented by: Katherine Carmen Forbes

candidate for the degree of Doctor of Philosophy and hereby certify that it is worthy of acceptance.

Signature _____
Typed name: Professor Eric N. Jacobsen

Signature _____
Typed name: Professor Emily P. Balskus

Signature _____
Typed name: Professor Daniel E. Kahne

Date: 1 Feb 2023

Enantioselective Synthesis of Stereogenic-at-Phosphorus(V) Compounds via Hydrogen-Bond-Donor Catalysis

A dissertation presented by

Katherine Carmen Forbes

to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

February 2023

Enantioselective Synthesis of Stereogenic-at-Phosphorus(V) Compounds via Hydrogen-Bond-Donor Catalysis

Abstract

In Chapter 1, we review organocatalytic approaches for the enantioselective synthesis of stereogenic-at-P(V) compounds. General organocatalytic activation modes used for constructing P(V) stereocenters are discussed, including covalent catalysis, hydrogen-bond-donor catalysis, and general base catalysis. Existing synthetic methods applying these modalities for the enantioselective synthesis of stereogenic-at-P(V) compounds are reviewed, and the proposed mechanisms for these reactions are discussed.

In Chapter 2, we report the development of a hydrogen-bond-donor catalyzed desymmetrization of phosphonic dichlorides with amines to enantioselectively furnish chlorophosphonamidate building blocks using a commercially available catalyst. We demonstrate that chlorophosphonamidates possess two leaving groups which can be displaced sequentially and stereospecifically. Furthermore, we explore the use of chlorophosphonamidates as bifunctional stereogenic-at-P(V) building blocks which can serve as synthetic precursors to access a diverse array of stereogenic-at-P(V) targets. The synthetic utility of this methodology is established through its application to the synthesis of bioactive *P*-stereogenic targets.

In Chapter 3, we detail the development of a hydrogen-bond-donor catalyzed desymmetrization of phosphinic acids via an enantioselective alkylation reaction with sulfonium reagents to generate chiral phosphinate esters. Evaluation of different sulfonium reagents revealed a significant effect of the sulfonium structure on enantioselectivity, with a thianthrene-derived sulfonium reagent yielding the phosphinate products with the highest levels of enantioenrichment. Moderate levels of enantioselectivity are observed with sterically hindered and unhindered phosphinic acids.

Table of Contents

Acknowledgements

I am extraordinarily grateful for my advisor, Professor Eric N. Jacobsen, for his mentorship during my time at Harvard. While maintaining his many responsibilities as a professor, Eric somehow still had energy left to give to me for my development. When I began my first project as a first year, Eric mentored me on my project, guiding me through each step of the way. Eric taught me to think deeply about which efforts I chose to invest my time in, always emphasizing that there should be a good reason for conducting a given experiment. I don't know which direction my project would have taken without Eric's pragmatism, a virtue which I am grateful he has passed onto me. Eric's crystallized knowledge and expertise helped rein in the ambitions and creativity I possessed as a first-year graduate student, and his critical feedback helped me improve immensely as a researcher. One of my friends in college who was an English major used to say, "Almost every piece of writing begins as a bad first draft—good writing comes from good editors." I think Eric is, both literally and figuratively, a great editor which leads to excellent research and researchers alike to emerge from his lab. He has a keen eye for issues and knows exactly how to identify rooms for improvement; this not only enables him to turn a chaotic first draft into a well-written publication, but also allows him to help develop young students into well-trained researchers.

I also benefitted from Eric's precise training as his teaching fellow for Chemistry 105 in the Fall of 2020. Having identified that I was a nervous presenter, Eric made a point to help me improve my presentation skills as his teaching fellow. Every week, I gave Chem 105 section presentations where I presented a publication and facilitated discussions amongst the students. Eric attended every section and provided me with detailed feedback afterwards on how I could improve my presentation skills. I look back on those weekly sections with a deep appreciation for how much I benefitted from that feedback. Beyond that, Eric also challenged me to be the best I could be—if he sensed I was not accurately articulating how I really thought about things, he called me out on it. It is very difficult to find people who see your potential and are willing to put in

the work to extract it from you—it's grueling work for both parties and takes unyielding commitment. I am a significantly better scientific communicator today than I was in my first year, and I have Eric's mentorship to thank for that.

I would like to express my gratitude to my other committee members, Professor Emily Balskus and Professor Dan Kahne, for helping support my development during my time at Harvard. I have been inspired by Emily Balskus ever since I took her Biological Synthesis class during my first year at Harvard and feel so privileged to have her on my committee. Emily was generous with her time and has been very encouraging as I navigated my next steps after graduate school, and I deeply appreciate her kindness. I am also thankful for Professor Dan Kahne's scientific insight and warmth. Ever since my qualifying exams, he has been very positive and encouraging to me, and I feel very fortunate to have had the opportunity receive his feedback and support.

I have been lucky to work with so many amazing people during my time in the Jacobsen lab. Jake Essman was the first friend I made in the Harvard graduate program, and I feel so lucky to have started in the lab with him at the same time. Jake has been there for me through thick and thin, and his dry sense of humor has made me laugh through even the worst of times. He is honest, kind, and cares deeply about people he is close with. I am so grateful to call him my friend, while also thoroughly impressed by the exorbitant number of hours he so generously spent listening and helping me work through difficult times in graduate school. Russ Algera was my officemate and informal mentor during my first year of graduate school and helped me discover my first project. Russ spent hours discussing chemistry with me, helping me come up with new ideas, and chatting about music (among many other subjects of which he possessed boundless knowledge). Russ is one of the most intelligent and kind people I have ever met, and I will always be grateful for his munificence with his time and attention. My other officemate Elias Picazo was like an older brother to me, and he is everything you could want in an older brother: compassionate, trustworthy, thoughtful, and helpful. Elias and I were each other's cheerleaders

in office 202E for 2 years, and I am excited to see what he achieves as a professor. Mark Levin was a key role model who I looked up to in my first year of graduate school, always bursting with enthusiasm and a deep knowledge of chemistry. Mark's infectious laugh, appreciation for absurdity, and kindness made the lab a better place. Mark was (and has continued to be) so helpful and generous with his time (even helping edit my manuscript while he was still an assistant professor!) and his scientific acumen combined with his creativity are inspiring. I am very grateful for Hayden Sharma, one of my best friends from the Jacobsen lab. Hayden and I share a chaotic yet disciplined nature, so naturally we shared countless hilarious moments that made our sides ache intermixed with philosophical discussions and chemistry arguments. Hayden's boisterous spirit and enthusiasm are contagious. However, our friendship never prevented him from supplying me with honest criticism, which challenged me to constantly improve and push my project forward.

Adam Trotta, a former postdoc in the lab, and Michaelyn Lux have also been such kind, supportive, and generous friends who have become like family to me. I cannot think of anyone who is more understanding or patient than Adam and Michaelyn are. I will never forget the time they drove to Harvard to bring me a large bag filled with homemade baked goods and treats one day when I was working nonstop in lab while I was otherwise subsisting predominantly on kale chips. When Adam was a postdoc in the lab and I was a first/second-year graduate student, he was one of the few people that treated me as an equal. Adam comforted me through many difficult emotional periods, one time even taking me on a long mental health walk in the pouring rain.

During the pandemic in 2020 when the lab had to work in shifts of ~6 people at a time, I became very close with my shift mates, particularly Corin Wagen and Joe Gair. Joe Gair is one of the purest souls I have ever met—he is not only an excellent scientist, but also a thoughtful, patient, supportive, and earnest listener. Joe has always been kind to me through difficult times—he genuinely cares about gender equality in chemistry and is extraordinarily selfless. Joe and his wife, Mary, as well as his daughter Joan, are some of the loveliest people I have gotten to know

in Cambridge. Corin Wagen is perhaps one of the people I have learned the most from during my time in the Jacobsen lab. Corin and I possess complementary strengths and perspectives, and we always have productive conversations where I leave with a greater understanding of the discussion topic. I deeply appreciate Corin's commitment to morals, especially his honesty and compassion. Aside from being a fundamentally good person, Corin is remarkably well-rounded, and I admire his commitment to his family and friends. I have also appreciated the privilege of getting to know his kindhearted wife, Chloe, and his son, Nico.

Martin Reiterer is one of the most helpful people I have gotten to work with in graduate school. Martin's kindness runs deep: he cares about people immensely, and is constantly thinking of others in ways they do not even realize. I am in awe of Martin's many talents: he is a fastidious chemist with a firm dedication to efficiency, and his knack for fixing machines has kept the lab running since I joined. Martin is also a devoted friend, and it was wonderful to have him join Thanksgiving with my family along with Jonathan Wong. Jonathan has been so much fun to work with for the past year; he is both a considerate lab mate and a curious researcher. Most importantly, Jonathan has a refreshing sense of humor and a devious playfulness that make time spent in lab significantly more interesting. Jonathan is also a dutiful friend with a strong sense of justice which I thoroughly respect. My former undergraduate mentee, Nour Khachemoune has also been such a delight to spend time with. Nour is vivacious, caring, and filled with a refreshing zest for discovery; I am so excited to see what she accomplishes next in her archaeological research. In the past year, I have also been thankful to share time with Sam Angle, Agata Bikovtseva, and Peyton Beyer. I am grateful to Sam for her compassion and optimism—she is a caring lab mate with a big heart. It has been such a joy to share an office with Agata, who is a smart, determined, and considerate person. I have also enjoyed getting to know Peyton, who is both thoughtful and eccentric with excellent taste in music (and not to mention an awesome trivia teammate!).

I have had the opportunity to work with some amazing postdocs in the past couple years, including Mayuko Isomura, Melanie Short, and Michael Nielsen. Both Melanie and Michael have been benevolent and supportive presences in the lab, contributing to a positive work environment. Michael's commitment to promoting a healthy group culture has had a very positive impact, and I have had a great time attending his purple house parties. Mayuko Isomura has been such a pleasure to share a bay with; she is a talented chemist with outstanding work ethic, while also being a thoughtful, considerate, and genuinely sweet person who has reassured me with notes of encouragement accompanied by lovely gifts in times of distress. Nicole Minotti, our lab administrator, is a truly kind woman who has made herculean efforts to keep the lab operating and take care of us. No matter how busy she was, she was consistently caring and never flinched when someone asked for help.

I would also like to thank my friends outside of the Jacobsen lab for their support and compassion. Anne Marie Crooke, my roommate and friend from college, has been a loyal and trustworthy companion through the rollercoaster of a PhD. Anne Marie's strong moral compass helped guide me through times of confusion, and her reassurance helped calm me in times of stress. She is a great friend and roommate, and I am grateful to have spent the past four years with her. I have also cherished my friendship with Michelle Wang, who is an intelligent, comical, and caring person who goes above and beyond for her friends. I am very thankful for my friends at MIT, Gino Occhialini and Elaine Reichart, who in addition to being incredibly talented, hardworking chemists, are caring friends that have been a consistent source of support for me. Will Rafey has also lent a compassionate and understanding ear to me since my second year of graduate school, providing me with a logical and insightful outlook which helped me gain perspective in times of hardship. My friends from high school, Claire Foster and Amani Dharani, have also helped keep me grounded throughout graduate school, extracting me from my phase of borderline-workaholism to remind me there was a world outside of graduate school with people who cared about me. I am grateful for my friends from Occidental college, including Natalie

Dwulet, Nick Foy, Scott Niman, and Molly Brown, who have also been encouraging and understanding friends during graduate school. I am also thankful for Jeff Cannon, my undergraduate mentor from Occidental, who has always believed in me (even when I didn't believe in myself) and continued to mentor me intermittently throughout graduate school.

Finally, I would like to thank my family for their relentless support and love. My mother always answered the phone when I needed someone to talk to and has been a consistent voice of reason in my life. My father has been equally supportive and has provided me with a seemingly endless supply of affection and confidence. My siblings, Julia and Brian, always offer different perspectives—Julia with her optimism, and Brian with his wily spirit and sense of irony. Mom, Dad, Julia, and Brian: I love you all so much.

List of Abbreviations

Å	Angstrom, 10^{-10} m
Ac	Acetyl
anti	L., against, opposite
aq.	Aqueous
alk	Alkyl
Ar	Aryl
$BAr^F{}_4$	Tetrakis[(3,5-trifluoromethyl)phenyl]borate
Bn	Benzyl
Boc	*Tert*-butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
˚C	Degree Celsius
c	Concentration
cal	Calorie
cat	Catalyst
Cbz	Benzyloxycarbonyl
Cis	L., on the same side
conv.	Conversion
δ	Chemical shift in parts per million
d	Day(s); doublet (spectral)
D	Deuterium, after solvent = solvent-d_n
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane

DIPEA	Diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
dr, d.r.	Diastereomeric ratio
ds	Diastereospecificity (i.e. stereospecificity for reaction of a chiral compound to another chiral compound)
E	Energy
E	Ger., entgegen
ee	Enantiomeric excess
EI	Electron ionization
Ent	Enantiomeric
Eq	Equation
Equiv.	Equivalent
e.r.	Enantiomeric ratio
es	Enantiospecificity
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FT	fourier transform
G	Gram
GC	Gas chromatography
Gem	Geminal
h	Hour(s)

HBD	Hydrogen-bond donor
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Iso
^{i}Am	Isoamyl, isopentyl
^{i}Bu	Isobutyl
^{i}Pr	Isopropyl
*i*PrOH	Isopropanol
IR	Infrared
J	Coupling constant
K	Kelvin
KIE	Kinetic isotope effect
L	Liter(s)
M	Micro
m	*Meta*
m	Meter; milli; multiplet (spectral)
M	Molar
m-CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl
Mes	Mesityl
MeOH	Methanol
Mg	Milligram(s)
min	Minute(s)
mol	Mole

Ms	Methanesulfonyl
MS	Mass spectrometry
m/z	mass to charge ratio
N	Normal
NaHMDS	Sodium hexamethyldisilazide
^{n}Bu	*n*-butyl
NMR	Nuclear magnetic resonance
Nu	Nucleophile
O	*Ortho*
Obs	Observed
OTf	Triflate, trifluoromethanesulfonate
p	*Para*
PG	Protecting group
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
p-TsOH	*Para*-toluenesulfonic acid
py, pyr	Pyridine
q	Quartet (spectral)
R	Rectus
rac	Racemic
Rt	Room temperature
S	Sinister
SAM	*S*-Adenosyl methionine
S_N1	Unimolecular nucleophilic substitution

S_N2	Bimolecular nucleophilic substitution
Syn	D., with, together
T	*Tert*, tertiary
T	Time; triplet (spectral)
t_r	Retention time
T	Temperature
TBME	*Tert*-butyl methyl ether
Trt	Trityl, triphenylmethyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
Trans	L., on the opposite side
Ts	*Para*-toluenesulfonyl
UV	Ultraviolet
Z	Ger., zusammen

Chapter 1

Organocatalytic Strategies for the Enantioselective Synthesis of Stereogenic-at-P(V) Compounds

1.1 Introduction

Asymmetric organocatalysis, or the use of chiral small molecules to catalyze the production of enantiomerically enriched compounds, has been established as a broadly useful approach for developing efficient, enantioselective reactions.[1] Organocatalysts function via an assortment of mechanisms including covalent catalysis, base catalysis, Brønsted acid catalysis, hydrogen-bond-donor catalysis, and phase-transfer catalysis. The initial fundamental reports of

[1] (a) Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis. In *Asymmetric Organocatalysis*; John Wiley & Sons, Ltd, 2005; pp 1–8. (b) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms. *Chem. Rev.* **2020**, *120* (20), 11479–11615. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107* (12), 5471–5569. (d) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107* (12), 5713–5743. (e) Jacobsen, E. N.; MacMillan, D. W. C. Organocatalysis. *Proceedings of the National Academy of Sciences* **2010**, *107* (48), 20618–20619. (f) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51* (2), 534–547. (g) Han, B.; He, X.-H.; Liu, Y.-Q.; He, G.; Peng, C.; Li, J.-L. Asymmetric Organocatalysis: An Enabling Technology for Medicinal Chemistry. *Chem. Soc. Rev.* **2021**, *50* (3), 1522–1586. (h) Parella, R.; Jakkampudi, S.; Zhao, J. C.-G. Recent Applications of Asymmetric Organocatalytic Methods in Total Synthesis. *ChemistrySelect* **2021**, *6* (9), 2252–2280.

organocatalytic reactions in the early-to-mid-twentieth century interrogated whether small organic molecules could mimic the catalytic activity of enzymes and involved the use of chiral-pool compounds such as amino acids or natural cinchona alkaloids as catalysts to facilitate asymmetric organic transformations.[1a] Further critical innovations made in the early 2000s pursuing the broader synthetic potential of this catalytic approach have led to the development of an extensive variety of organocatalysts which have found widespread use in organic synthesis.[1]

The initial conceptualization of organocatalysis as a biomimetic approach presents a promising strategy for developing enantioselective phosphorylation reactions. Phosphoryl transfer reactions represent one of the most important biochemical processes.[2] Phosphoryl transfer enzymes are a well-studied class of proteins that catalyze phosphoryl transfer reactions through two general mechanisms, including ternary complex mechanisms and covalent mechanisms.[3] In a ternary complex mechanism, an enzyme catalyzes the direct transfer of a phosphoryl group to an incoming nucleophile through non-covalent interactions such as hydrogen bonding.[3a,4] A covalent mechanism involves phosphorylation of the enzyme to form a reactive phosphoenzyme intermediate, such as a phosphohistidine, that subsequently transfers the phosphoryl group to the nucleophile.[5]

---

[2] (a) Sefton, B. M.; Shenolikar, S. Overview of Protein Phosphorylation. *Current Protocols in Molecular Biology* **1996**, *33* (1), 18.1.1-18.1.5. (b) Hengge, A. C. Phosphoryl Transfer Reactions. In *eLS*; John Wiley & Sons, Ltd, 2015; pp 1–7.

[3] (a) Wang, Z.; Cole, P. A. Catalytic Mechanisms and Regulation of Protein Kinases. *Methods Enzymol* **2014**, *548*, 1–21. (b) Thompson, P. R.; Cole, P. A. Probing the Mechanism of Enzymatic Phosphoryl Transfer with a Chemical Trick. *Proceedings of the National Academy of Sciences* **2001**, *98* (15), 8170–8171.

[4] Zhao, L.; Liao, H.; Tsai, M.-D. The Catalytic Role of Aspartate in a Short Strong Hydrogen Bond of the Asp274–His32 Catalytic Dyad in Phosphatidylinositol-Specific Phospholipase C Can Be Substituted by a Chloride Ion*. *Journal of Biological Chemistry* **2004**, *279* (31), 31995–32000.

[5] (a) Admiraal, S. J.; Herschlag, D. Catalysis of Phosphoryl Transfer from ATP by Amine Nucleophiles. *J. Am. Chem. Soc.* **1999**, *121* (25), 5837–5845. (b) Admiraal, S. J.; Schneider, B.; Meyer, P.; Janin, J.; Véron, M.; Deville-Bonne, D.; Herschlag, D. Nucleophilic Activation by Positioning in Phosphoryl Transfer Catalyzed by Nucleoside Diphosphate Kinase,. *Biochemistry* **1999**, *38* (15), 4701–4711. (c) Post, R. L.; Kume, S. Evidence for an Aspartyl Phosphate Residue at the Active Site of Sodium and Potassium Ion Transport Adenosine Triphosphatase. *Journal of Biological Chemistry* **1973**, *248* (20), 6993–7000. (d)

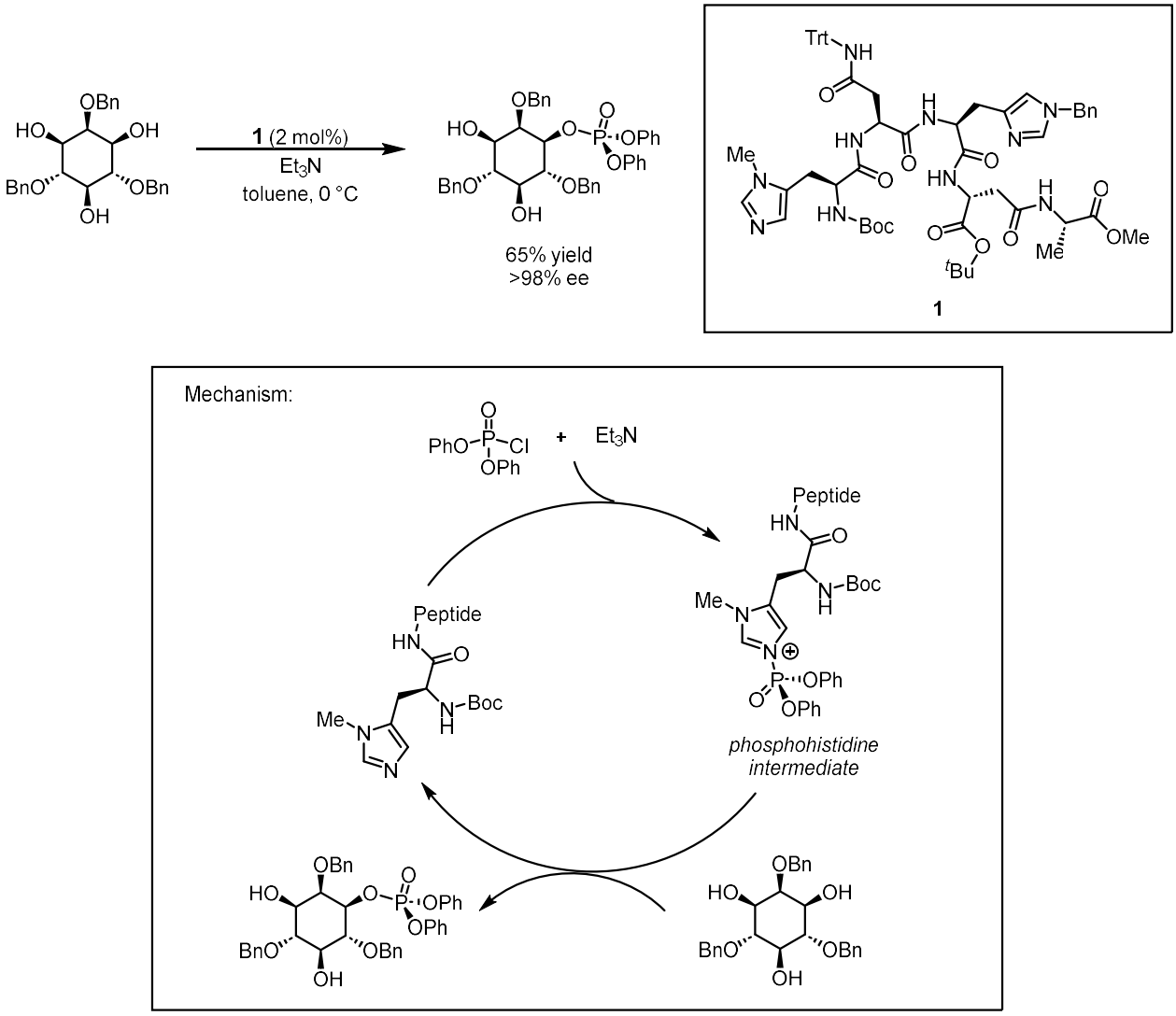


Figure 1.1 Asymmetric phosphorylation of *myo*-inositol derivative with a peptide-based catalyst.

The catalytic activation modes demonstrated by phosphoryl transfer enzymes have inspired the design of organocatalysts to facilitate asymmetric phosphorylation reactions in organic synthesis. For example, the Miller lab reported the development of a peptide-based "kinase mimic" (**1**) which catalyzed the enantioselective phosphorylation of a *myo*-inositol

Ferreira-Cerca, S.; Sagar, V.; Schäfer, T.; Diop, M.; Wesseling, A.-M.; Lu, H.; Chai, E.; Hurt, E.; LaRonde-LeBlanc, N. ATPase-Dependent Role of the Atypical Kinase Rio2 on the Evolving Pre-40S Ribosomal Subunit. *Nat Struct Mol Biol* **2012**, *19* (12), 1316–1323.

derivative with diphenyl phosphoryl chloride via a covalent mechanism, involving the formation of a phosphohistidine intermediate (Fig. 1.1).[6] Additionally, Dirocco and coworkers reported the design of a chiral bisimidazole which is proposed to mimic the catalytic functions of phospholipase C,[4] facilitating diastereoselective substitution at P(V) centers via general base activation of the nucleophile concomitant with covalent activation of the phosphorus electrophile. [4,7]

In recent years, organocatalytic strategies for activating P(V) compounds have been applied for exerting enantiocontrol in the construction of P(V) stereocenters, which remains a significant challenge in organic synthesis.[8] These strategies include covalent catalysis, hydrogen-bond-donor catalysis, and general base catalysis. This chapter will discuss each of these activation modes and detail the organocatalytic methods that exploit each of these tactics for the enantioselective construction of P(V) stereocenters.

1.2 Conceptual Approaches

Enantioselectivity in the construction of P(V) stereocenters in a catalytic manner can be induced through three general mechanisms (Fig. 1.2). A kinetic resolution[9] would require a catalyst that differentiates between two enantiomers of a stereogenic-at-P(V) substrate, such that only one enantiomer undergoes a stereospecific reaction to form a chiral product. Alternatively, a dynamic kinetic resolution would involve a catalyst that differentiates between two enantiomers

[6] Sculimbrene, B. R.; Miller, S. J. Discovery of a Catalytic Asymmetric Phosphorylation through Selection of a Minimal Kinase Mimic: A Concise Total Synthesis of d-Myo-Inositol-1-Phosphate. *J. Am. Chem. Soc.* **2001**, *123* (41), 10125–10126.

[7] DiRocco, D. A.; Ji, Y.; Sherer, E. C.; Klapars, A.; Reibarkh, M.; Dropinski, J.; Mathew, R.; Maligres, P.; Hyde, A. M.; Limanto, J.; Brunskill, A.; Ruck, R. T.; Campeau, L.-C.; Davies, I. W. A Multifunctional Catalyst That Stereoselectively Assembles Prodrugs. *Science* **2017**, *356* (6336), 426–430.

[8] Ye, X.; Peng, L.; Bao, X.; Tan, C.-H.; Wang, H. Recent Developments in Highly Efficient Construction of P-Stereogenic Centers. *Green Synthesis and Catalysis* **2021**, *2* (1), 6–18.

[9] Pellissier, H. Catalytic Non-Enzymatic Kinetic Resolution. *Advanced Synthesis & Catalysis* **2011**, *353* (10), 1613–1666.

of a stereogenic-at-P(V) substrate that readily epimerizes under the reaction conditions, such that both epimers of the substrate are catalytically converted to a single enantiomer of product.[10] Finally, an enantioselective desymmetrization reaction would consist of a catalyst that interacts with a prochiral P(V) substrate, influencing which of the substrate's two enantiotropic substituents is either displaced or functionalized.[11]

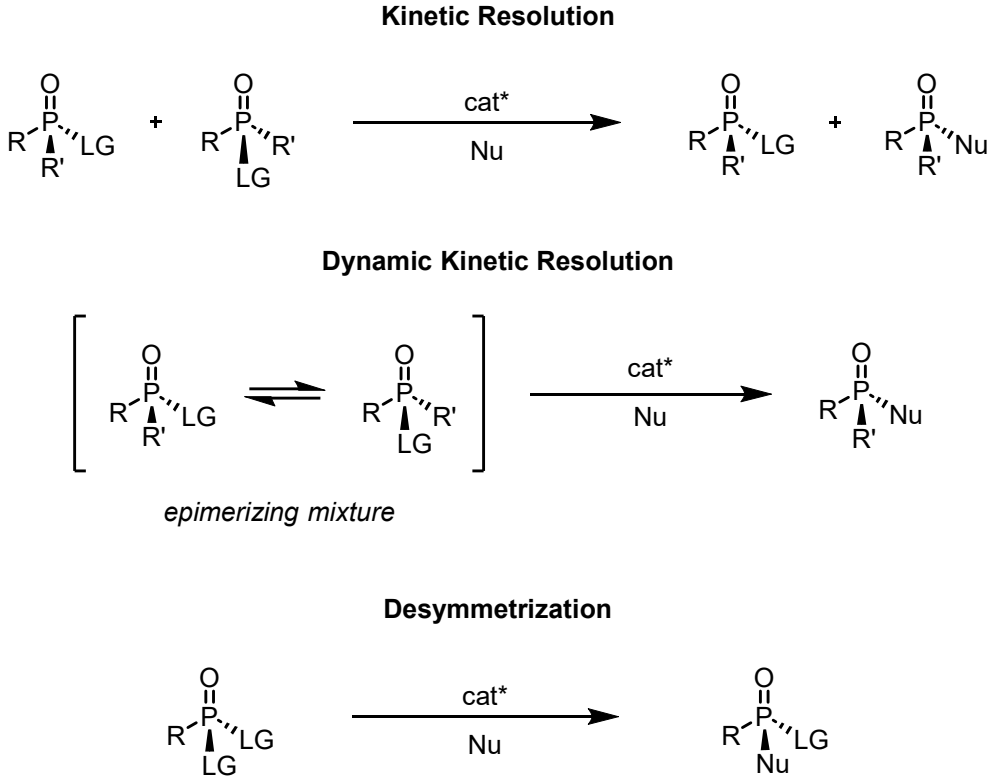


Figure 1.2 Possible mechanisms for inducing enantioselectivity in the synthesis of stereogenic-at-P(V) compounds exemplified via nucleophilic substitution reactions at P(V).

[10] (a) Steinreiber, J.; Faber, K.; Griengl, H. De-Racemization of Enantiomers versus de-Epimerization of Diastereomers--Classification of Dynamic Kinetic Asymmetric Transformations (DYKAT). *Chemistry* **2008**, *14* (27), 8060–8072. (b) Pellissier, H. Organocatalytic Dynamic Kinetic Resolution: An Update. *European Journal of Organic Chemistry* **2022**, *2022* (7), e202101561.

[11] Borissov, A.; Davies, T. Q.; Ellis, S. R.; Fleming, T. A.; Richardson, M. S. W.; Dixon, D. J. Organocatalytic Enantioselective Desymmetrisation. *Chem. Soc. Rev.* **2016**, *45* (20), 5474–5540.

There are many catalytic activation modes which can induce enantioselectivity via these three general mechanisms. However, the modes relevant to this chapter include covalent catalysis, hydrogen-bond-donor catalysis, and general base catalysis (Figure 1.3). Covalent catalysis generally refers to reactions in which a catalyst undergoes a reaction with a substrate to form a covalently bound intermediate, activating the substrate to undergo a subsequent reaction to turn over the catalyst and form the corresponding product.[12] Hydrogen-bond-donor catalysis describes reactions in which a mildly acidic catalyst engages in hydrogen-bonding interactions with a substrate, inducing an organic transformation.[1d] General base catalysis refers to the use of a mildly basic catalyst which serves as a hydrogen-bond acceptor with a weakly acidic substrate such as an alcohol, activating the substrate to undergo a reaction by increasing its nucleophilicity or basicity in the transition state.[13] In this chapter, the primary organocatalytic activation modes that will be discussed include covalent catalysis and hydrogen-bond-donor catalysis, while general base catalysis is invoked to occur concurrently with these modalities.

[12] Holland, M. C.; Gilmour, R. Deconstructing Covalent Organocatalysis. *Angewandte Chemie International Edition* **2015**, *54* (13), 3862–3871.

[13] Narlikar, G. J.; Herschlag, D. MECHANISTIC ASPECTS OF ENZYMATIC CATALYSIS: Lessons from Comparison of RNA and Protein Enzymes. *Annual Review of Biochemistry* **1997**, *66*, 19–59.

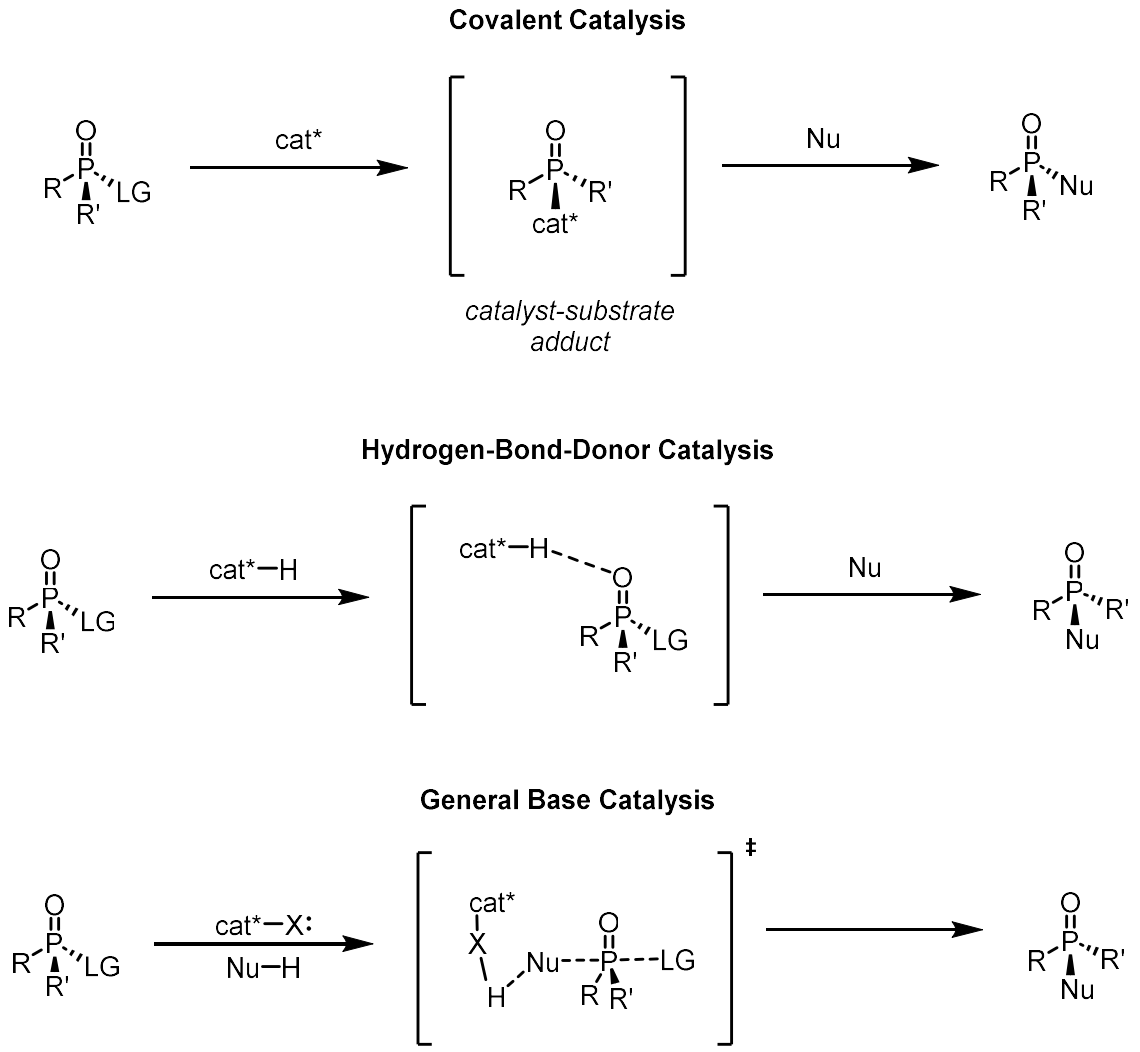


Figure 1.3 Organocatalytic activation modes for exerting enantiocontrol in the construction of P(V) stereocenters exemplified via nucleophilic substitution reactions at P(V).

1.3 Covalent Catalysis

Covalent catalysis is one of the most widely used organocatalytic strategies for enantioselectively constructing *P*-stereogenic centers. The first report of an organocatalytic enantioselective synthesis of stereogenic-at-phosphorus compounds was published by Hayakawa and coworkers in 2003, reporting the dynamic kinetic resolution of racemic

phosphorochloridites with alcohols. In this reaction, catalytic amounts of a chiral amine (**5**) facilitated enantioselective P–O bond formation to furnish trialkyl phosphites (Fig 1.4).[14] In the proposed mechanism for this reaction, phosphochloridite **2** reacts with amine catalyst **5** to form a diastereomeric mixture of phosphorylated ammonium intermediates (**6a** and **6b**), which can epimerize via reaction with free amine catalyst. It is hypothesized that one of the two epimeric catalyst-substrate covalent adducts then selectively undergoes irreversible substitution with an alcohol to form the trialkyl phosphite product (**3**). The trialkyl phosphite can then undergo stereospecific oxidation in a separate step to form the corresponding chiral phosphate (**4**).

[14] Hayakawa, Y.; Hyodo, M.; Kimura, K.; Kataoka, M. The First Asymmetric Synthesis of Trialkyl Phosphates on the Basis of Dynamic Kinetic Resolution in the Phosphite Method Using a Chiral Source in a Catalytic Manner. *Chem. Commun.* **2003**, No. 14, 1704–1705.

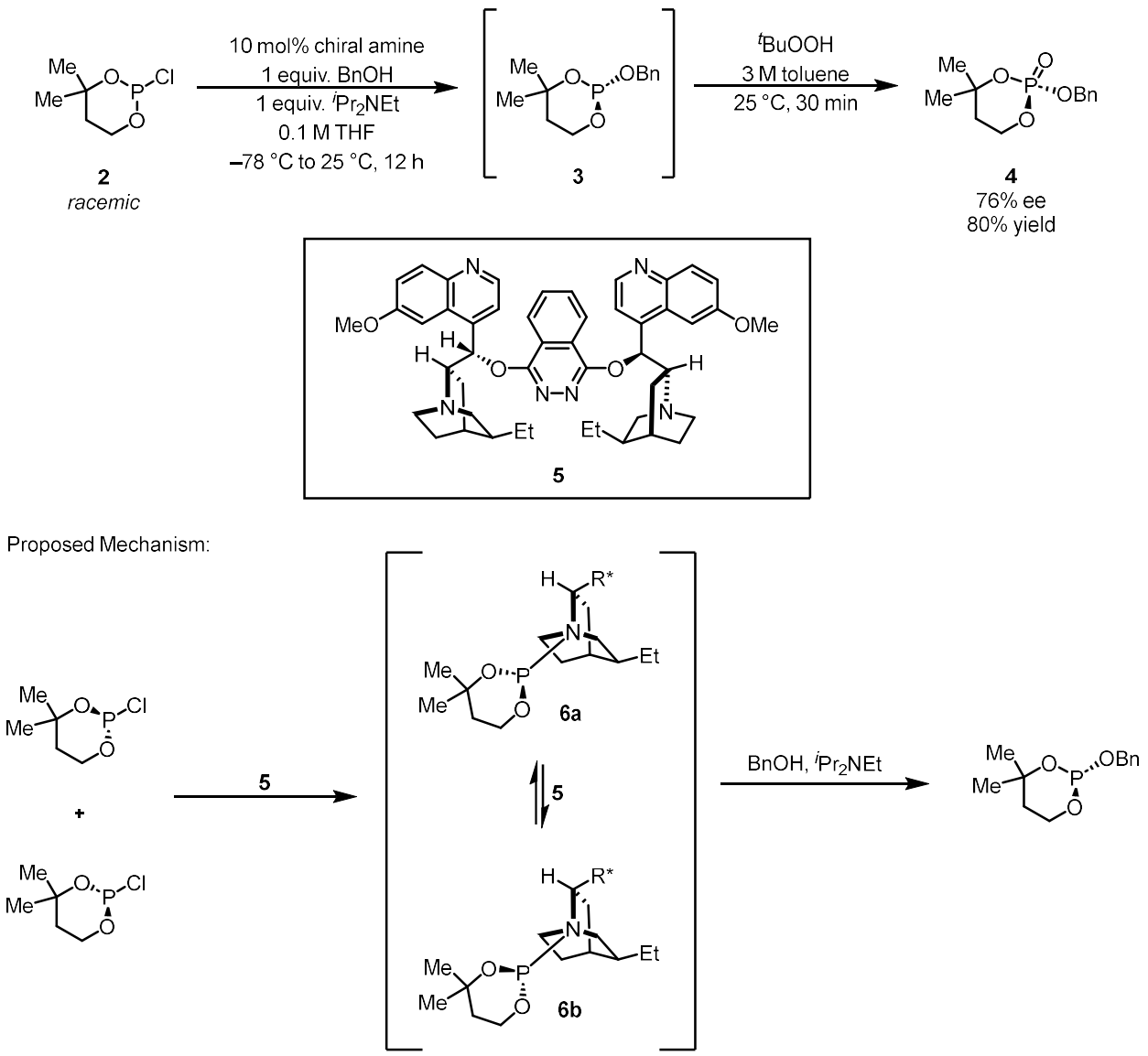
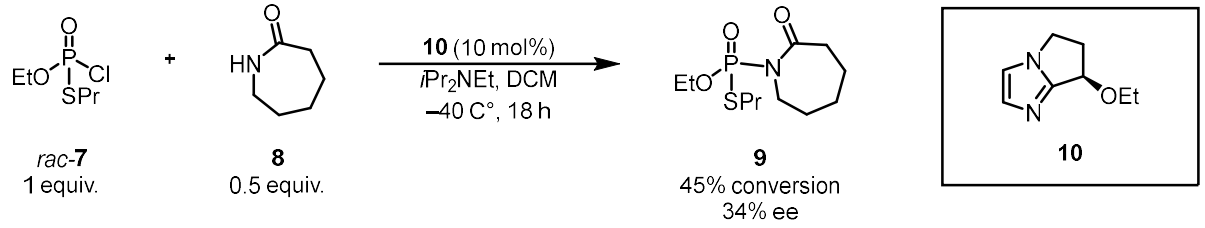


Figure 1.4 Enantioselective synthesis of trialkyl phosphates via chiral amine-catalyzed dynamic kinetic resolution.

Zhang and coworkers used a similar catalytic tactic for a more direct construction of P(V) centers in their report of the enantioselective synthesis of phosphoramidates from racemic phosphoryl chlorides using a chiral imidazole catalyst (**10**) (Fig 1.5).[15] In this reaction, it is

[15] Liu, S.; Zhang, Z.; Xie, F.; Butt, N. A.; Sun, L.; Zhang, W. First Catalytic Enantioselective Synthesis of P-Stereogenic Phosphoramides via Kinetic Resolution Promoted by a Chiral Bicyclic Imidazole Nucleophilic Catalyst. *Tetrahedron: Asymmetry* **2012**, *23* (5), 329–332.

proposed that **10** reacts with the phosphoryl chloride (**7**) to diastereoselectively form a phosphorylated imidazolium adduct (**11a** or **11b**). It is then proposed that amide **8** engages in rate-determining stereospecific nucleophilic substitution with the electrophilic imidazolium adduct to generate the phosphoramidate product (**9**). In this mechanistic proposal, it is hypothesized that the reaction proceeds via a kinetic resolution of the two enantiomers of phosphoryl chloride **7**. It is important to note that little experimental support is provided by the authors for this mechanism, and considering the preceding work by Hayakawa, this reaction may alternatively proceed via a dynamic kinetic resolution.



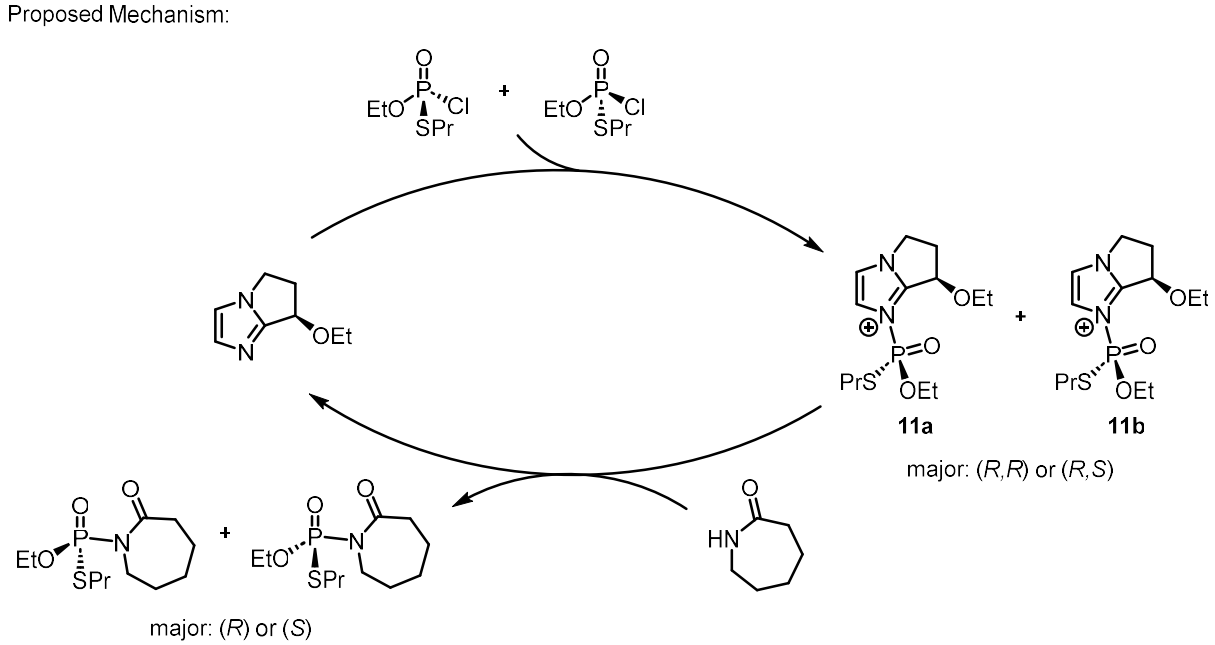


Figure 1.5 Enantioselective synthesis of phosphoramidates via chiral imidazole catalyst.

Building off Zhang and coworkers' advance using a chiral imidazole catalyst, Wang and coworkers reported the enantioselective desymmetrization of phenyl phosphonic dichloride (**12**) with amino alcohols (**13**) catalyzed by chiral imidazole **15** to furnish chiral oxazaphospholidines (**14**) (Fig 1.6).[16] In this reaction, it was observed that the identity of the stoichiometric base used in addition to the catalyst significantly impacted the reaction rate, as well as the magnitude and direction of enantioselectivity. Furthermore, spectroscopic studies analyzing a mixture of chiral imidazole **15** and phosphonic dichloride **12** by ^{31}P NMR showed the diastereoselective formation of a covalent adduct (**16a** or **16b**) in 72% de and 45% yield. Given these experimental observations, this reaction is proposed to proceed via a reversible diastereoselective reaction between catalyst **15** and **12** to preferentially form either **16a** or **16b** (Fig. 1.6). The stoichiometric 2-methylimidazole additive then acts as a general base to activate the amine (**13**) as a nucleophile, facilitating nucleophilic substitution with the major diastereomer of phosphonylated imidazolium adduct **16**, generating a chlorophosphonamidate intermediate (**17a** or **17b**). The chlorophosphonamidate then undergoes nucleophilic substitution with the pendant alcohol to displace the second chloride, furnishing the oxazaphospholidine product (**14**). Notably, the observed enantiomeric excess of the oxazaphospholidine is the result of both the enantioselectivity of the amine substitution step and the enantiospecificity of the intramolecular alcohol substitution step, and it is unclear to what extent the enantiospecificity of alcohol substitution affects the enantioenrichment of the products.

[16] Wang, L.; Du, Z.; Wu, Q.; Jin, R.; Bian, Z.; Kang, C.; Guo, H.; Ma, X.; Gao, L. Organocatalytic Enantioselective Synthesis of P-Stereogenic Chiral Oxazaphospholidines. *European Journal of Organic Chemistry* **2016**, *2016* (11), 2024–2028.

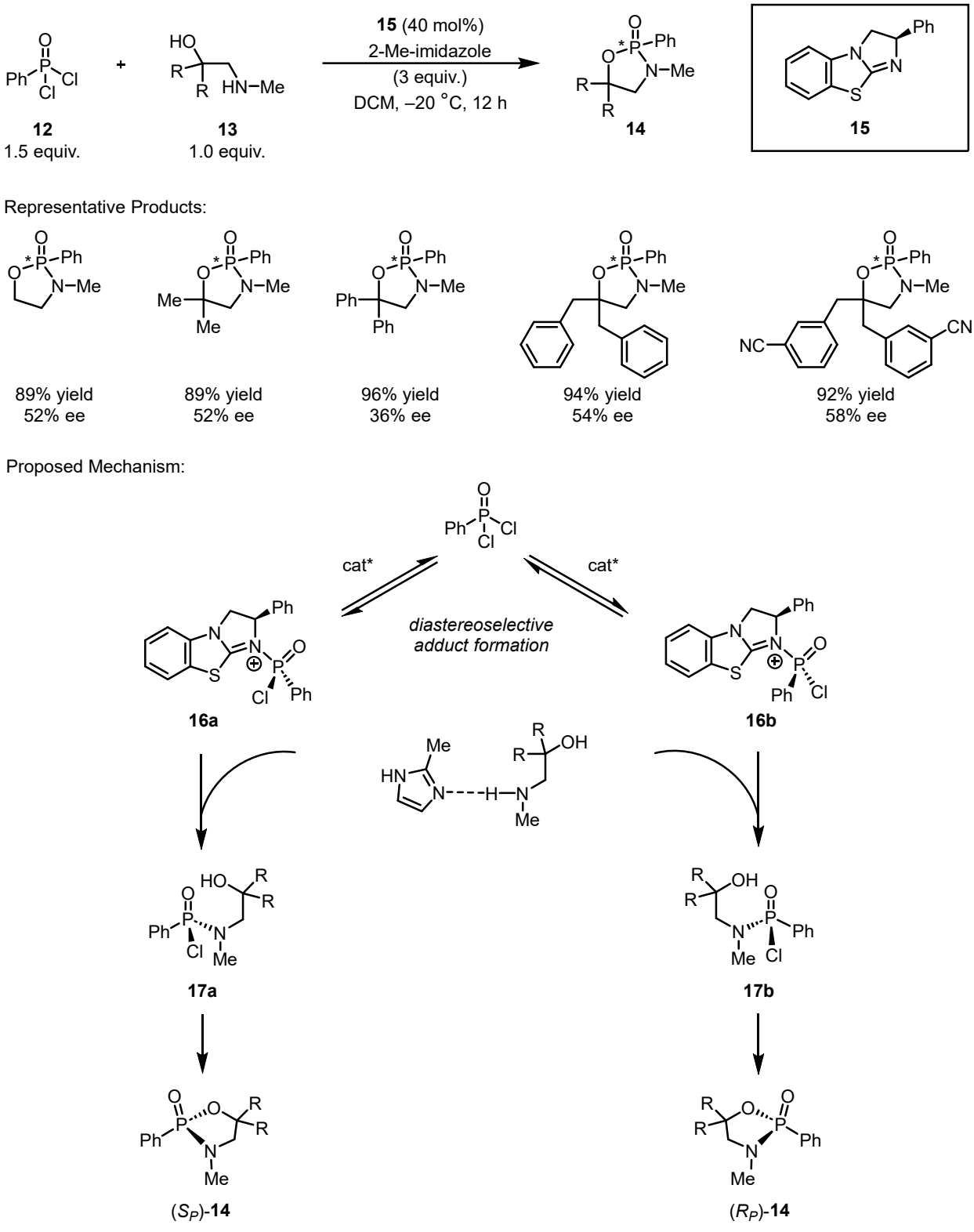
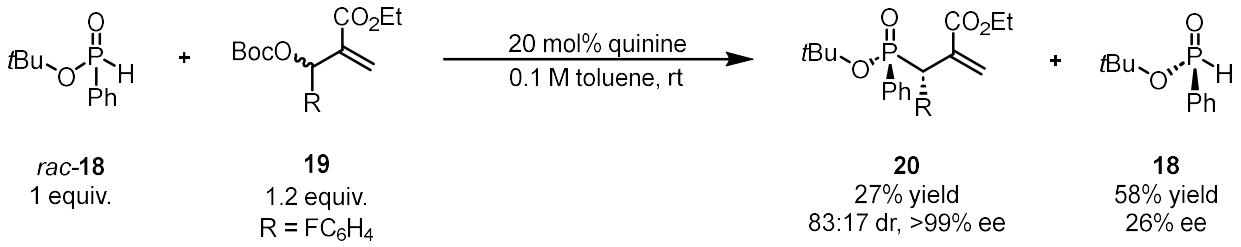


Figure 1.6 Enantioselective desymmetrization of phosphonic dichlorides via chiral imidazole catalyzed dynamic kinetic resolution.

Alternative approaches for the enantioselective synthesis of P(V) stereocenters proceed via the formation covalent adducts between organocatalysts and allylic carbonates, activating these electrophiles to undergo nucleophilic attack with phosphorus-based nucleophiles. Xie and coworkers reported the kinetic resolution of racemic secondary phosphine oxide **18** via a quinine-catalyzed P–C bond-forming reaction with allylic carbonate **19** (Fig 1.7).[17] In this reaction, it is proposed that quinine reacts with **19** via an addition-elimination process to form an allyl-ammonium intermediate. Phosphine oxide **18** is then deprotonated *in situ* by *tert*-butoxide to form the phosphinate anion, and a critical hydrogen-bonding interaction between quinine's hydroxyl group and the anionic phosphinate is proposed to stabilize a highly organized transition state in which the R_P enantiomer of the phosphinate preferentially reacts with the allylated catalyst adduct to displace quinine in an enantioselective S_N2' process (**21**). This kinetic resolution process produced the corresponding allylated phosphine oxide **20** in 27% yield and >99% ee, with 58% of S_P-**18** recovered in 26% ee. Similarly, Li and coworkers reported the hydroquinidine-catalyzed kinetic resolution of chiral phosphamides with allylic carbonates (Fig 1.8).[18] The proposed mechanism for this reaction is analogous to the process hypothesized by Xie and coworkers: hydroquinidine reacts with the allylic carbonate (**23**) to form an allylated ammonium intermediate. This intermediate then selectively reacts with one of the epimers of racemic phosphamide **22** in a transition state stabilized by a network of hydrogen-bonding interactions, producing allyl phosphamide **24** in 49% yield, 90% ee, and 3.5:1 dr, with phosphamide **22** recovered in 51% yield and 60% ee.

[17] Xie, P.; Guo, L.; Xu, L.; Loh, T.-P. Asymmetric P−C Bond Formation: Diastereoselective Synthesis of Adjacent P,C-Stereogenic Allylic Phosphorus Compounds. *Chemistry – An Asian Journal* **2016**, *11* (9), 1353–1356.

[18] Yang, G.-H.; Zheng, H.; Li, X.; Cheng, J.-P. Asymmetric Synthesis of Axially Chiral Phosphamides via Atroposelective N-Allylic Alkylation. *ACS Catal.* **2020**, *10* (3), 2324–2333.



Proposed Transition State:

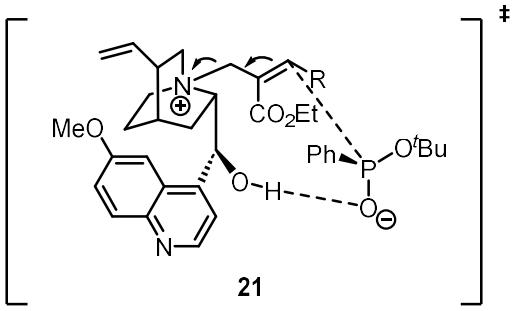


Figure 1.7 Kinetic resolution of secondary phosphine oxides via enantioselective quinine-catalyzed reaction with allylic carbonates.

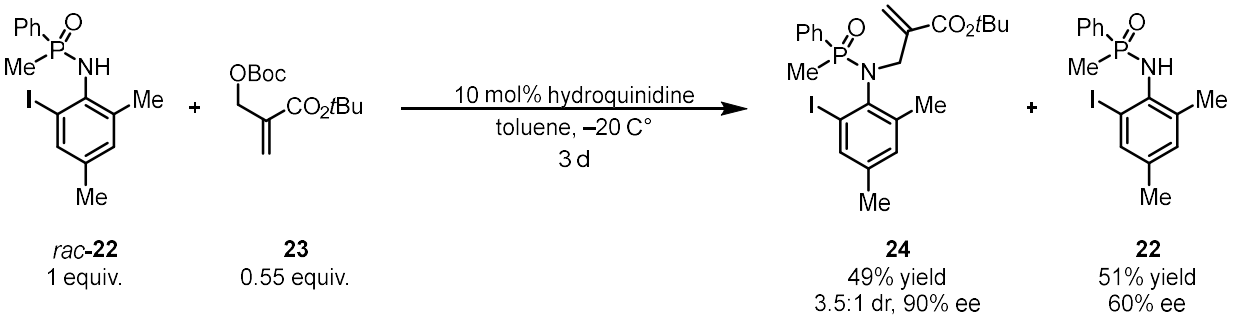


Figure 1.8 Kinetic resolution of racemic phosphamide via asymmetric hydroquinidine-catalyzed C–N bond formation.

1.4 Hydrogen-Bond-Donor Catalysis

Hydrogen-bond-donor catalysis has proven one of the most versatile strategies for exerting enantiocontrol in organic transformations.[1d] In this catalytic approach, weakly acidic small molecules activate substrates through hydrogen-bonding interactions, which often occur cooperatively with other non-covalent stabilizing interactions such as cation-π interactions or general base activation.[19] The versatility of hydrogen-bond-donor catalysis has enabled the development of enantioselective syntheses of stereogenic-at-P(V) compounds through a variety of distinct methodologies. The first application of a hydrogen-bond-donor catalyst to the enantioselective construction of P(V) stereocenters was published by Tan and coworkers in 2009, who reported an asymmetric phospha-Mannich reaction catalyzed by a chiral guanidinium salt (Fig 1.9).[20] In this reaction, guanidinium **28** catalyzes the kinetic resolution of racemic secondary phosphine oxide **25** by selectively facilitating nucleophilic addition of one enantiomer of **25** to imine **26**, resulting in the recovery of starting material **25** in 32% yield and 87% ee, and affording phospha-Mannich product **27** in 52% yield, 1.6:1 dr, and 50% ee. The specific role of the guanidinium catalyst is not proposed in this report. It is plausible that the guanidinium associates with the deprotonated phosphinate anion formed upon reaction of **25** with potassium carbonate and/or engages in hydrogen-bonding with imine **26**.

---

[19] (a) Knowles, R. R.; Lin, S.; Jacobsen, E. N. Enantioselective Thiourea-Catalyzed Cationic Polycyclizations. *J. Am. Chem. Soc.* **2010**, *132* (14), 5030–5032. (b) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. Macrocyclic Bis-Thioureas Catalyze Stereospecific Glycosylation Reactions. *Science* **2017**, *355* (6321), 162–166. (c) Formica, M.; Rozsar, D.; Su, G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Superbase Catalysis: Applications in Organic Synthesis. *Acc. Chem. Res.* **2020**, *53* (10), 2235–2247. (d) Strassfeld, D. A.; Jacobsen, E. N. The Aryl-Pyrrolidine- Tert - Leucine Motif as a New Privileged Chiral Scaffold: The Role of Noncovalent Stabilizing Interactions. In *Supramolecular Catalysis*; John Wiley & Sons, Ltd, 2022; pp 361–385.

[20] Fu, X.; Loh, W.-T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. Chiral Guanidinium Salt Catalyzed Enantioselective Phospha-Mannich Reactions. *Angewandte Chemie International Edition* **2009**, *48* (40), 7387–7390.

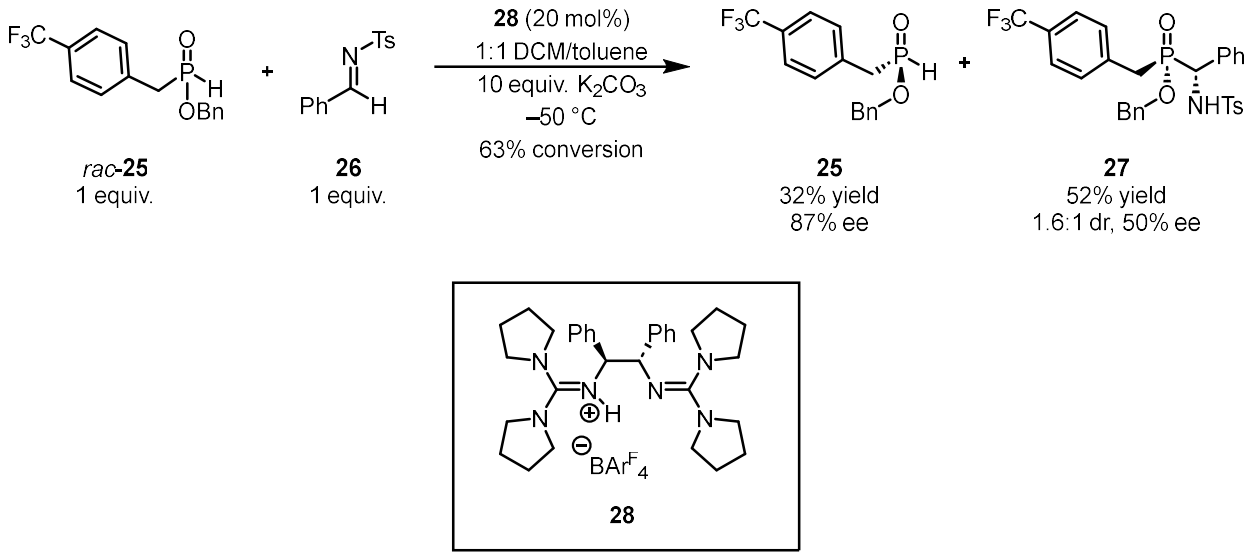


Figure 1.9 Kinetic resolution of secondary phosphine oxide via chiral guanidinium-catalyzed phospha-Mannich reaction.

Johnston and coworkers reported the application of a cationic hydrogen-bond donor (**31**·HTf_2) for the asymmetric intramolecular addition of phosphoramidic acids to iodonium intermediates (Fig 1.10).[21] In this reaction, it was observed that in the presence of catalytic free base **31**, phosphoramidic acid **29** underwent reaction with *N*-iodosuccinimide to produce phosphoramidate **30** in 86% yield, >20:1 dr, and 83% ee. A significant increase in enantioselectivity was observed when a StilPBAM-triflimidic acid complex (**31**·$HNTf_2$) was used, generating **30** in 85% yield, >20:1 dr, and 96% ee. These data indicate that the ammonium proton on the catalyst plays an important role in selectivity. Additionally, it was observed that using a less basic analog of **31**·HTf_2 lacking the pyrrolidine moieties resulted in a significant decrease in selectivity, affording phosphoramidate **30** in 4:1 dr and 46% ee. These observations are

[21] Toda, Y.; Pink, M.; Johnston, J. N. Brønsted Acid Catalyzed Phosphoramidic Acid Additions to Alkenes: Diastereo- and Enantioselective Halogenative Cyclizations for the Synthesis of C- and P-Chiral Phosphoramidates. *J. Am. Chem. Soc.* **2014**, *136* (42), 14734–14737.

consistent with a mechanism in which the catalyst induces enantioselectivity via cooperative action of the basic nitrogens and the ammonium proton. While no specific interactions between the catalyst and the substrate are proposed, it is possible that **31**·HTf_2 reacts with *N*-iodosuccinimide to form an iodonium imidate,[22] engages in hydrogen-bonding interactions with the corresponding iodonium intermediate resulting from iodination of **29**, and/or activates the phosphoramidic acid via general base catalysis. Investigation of the scope of this reaction revealed that disubstituted and tetrasubstituted alkenes underwent highly enantioselective cyclization to afford the corresponding cyclic phosphoramidate products, while monosubstituted alkenes reacted with moderative levels of enantioselectivity.

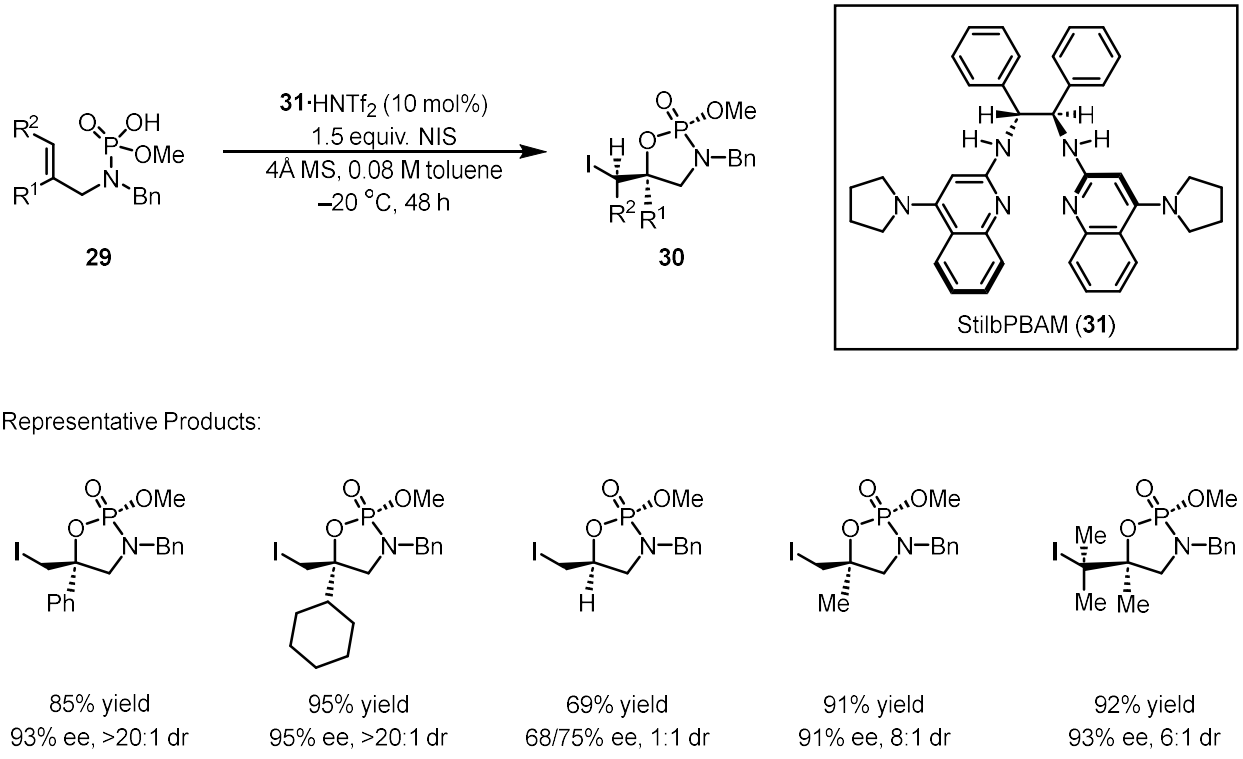


Figure 1.10 Asymmetric addition of phosphoramidic acids to iodonium intermediates in a hydrogen-bond-donor catalyzed cyclization reaction.

[22] Veitch, G. E.; Jacobsen, E. N. Tertiary Aminourea-Catalyzed Enantioselective Iodolactonization. *Angew Chem Int Ed Engl* **2010**, *49* (40), 7332–7335.

Dixon and coworkers reported the use of a hydrogen-bond-donor catalyst (**35**) for the desymmetrization of phosphonate esters via an enantioselective nucleophilic substitution reaction (Fig 1.11).[23] In this report, bifunctional urea iminophosphorane **35** catalyzes the enantioselective nucleophilic substitution of diaryl phosphonate esters (**32**) with *ortho*-substituted phenols (**33**). In the proposed mechanism for this reaction, the catalyst performs electrophilic activation of phosphonate ester **32** and nucleophilic activation of the phenol (**33**). It is hypothesized that the two N–H bonds of urea **35** engage in hydrogen-bonding interactions with the phosphonate's P=O bond. Simultaneously, the catalyst's iminophosphorane group activates **33** as a nucleophile through general base catalysis. Additionally, π- π stacking interactions are proposed to occur between the anthracenyl group on the catalyst and the aryloxy leaving group. The confluence of these interactions is posited to catalyze enantiodetermining nucleophilic addition of the phenol to the phosphonate ester in transition state **36** to form pentacoordinate intermediate **37**, followed by elimination of the aryloxy leaving group (**38**) to generate the enantioenriched product (**34**). While the scope of nucleophiles that can be used in this approach is limited to *ortho*-substituted phenols, a variety of phosphonate esters underwent enantioselective substitution with high levels of enantioselectivity, including both aryl and alkyl-substituted substrates. Furthermore, it was discovered that the products readily underwent stereospecific substitution with a variety of nucleophiles to displace the second leaving group, affording a variety of phenoxy-substituted derivatives.

[23] Formica, M.; Rogova, T.; Shi, H.; Sahara, N.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Dixon, D. J. Catalytic Enantioselective Nucleophilic Desymmetrisation of Phosphonate Esters. ChemRxiv July 22, 2021.

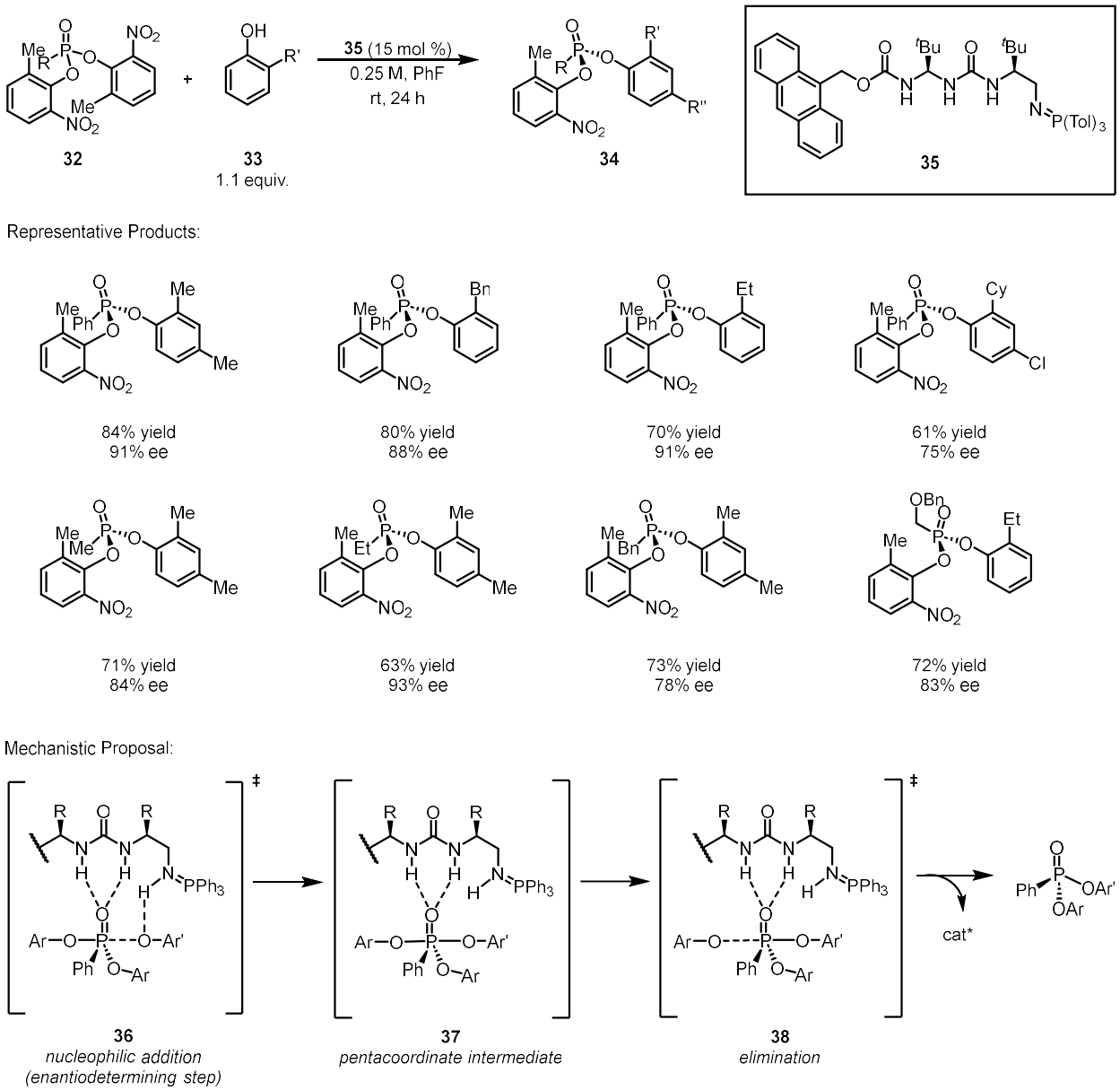


Figure 1.11 Enantioselective desymmetrization of phosphonate esters via a hydrogen-bond-donor catalyzed nucleophilic substitution reaction.

1.5 Conclusion and Outlook

The enantioselective synthesis of stereogenic-at-P(V) compounds remains a frontier in organic chemistry. Asymmetric organocatalysis is a versatile approach for the synthesis of these

products that leverages the catalytic design principles of phosphoryl transfer enzymes, such as covalent activation and hydrogen-bonding, to exert enantiocontrol in the reactions of P(V)-based substrates and intermediates. While existing organocatalytic enantioselective syntheses of stereogenic-at-P(V) compounds represent critical developments in this research area, the collective scope of products that can be accessed via these methods remains relatively narrow. The innovations discussed herein lay a foundation for the design and development of asymmetric organocatalytic syntheses of *P*-stereogenic compounds, and future work may build off these preceding innovations to establish catalytic methods for the synthesis of P(V) stereocenters bearing a vast range of possible substitution patterns and structural frameworks.

Chapter 2

Enantioselective Synthesis of Stereogenic-at-P(V) Building Blocks via Hydrogen-Bond-Donor Catalyzed Desymmetrization of Phosphonic Dichlorides

2.1 Introduction

Phosphorus(V) stereocenters are present in a wide assortment of important molecules, including several recently developed pharmaceuticals (Fig. 2.1).[1] The absolute stereochemistry at phosphorus is often directly associated with the biological activity of those molecules.[2]

[1] Parts of this chapter have been adapted from Forbes, K. C.; Jacobsen, E. N. Enantioselective Hydrogen-Bond-Donor Catalysis to Access Diverse Stereogenic-at-P(V) Compounds. *Science* **2022**, *376* (6598), 1230–1236.

[2] (a) Lee, W. A.; He, G.-X.; Eisenberg, E.; Cihlar, T.; Swaminathan, S.; Mulato, A.; Cundy, K. C. Selective Intracellular Activation of a Novel Prodrug of the Human Immunodeficiency Virus Reverse Transcriptase Inhibitor Tenofovir Leads to Preferential Distribution and Accumulation in Lymphatic Tissue. *Antimicrob Agents Chemother* **2005**, *49* (5), 1898–1906. (b) Pikul, S.; McDow Dunham, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Mieling, G. E. Design and Synthesis of Phosphinamide-Based Hydroxamic Acids as Inhibitors of Matrix Metalloproteinases. *J. Med. Chem.* **1999**, *42* (1), 87–94. (c) Sørensen, M. D.; Blaehr, L. K. A.; Christensen, M. K.; Høyer, T.; Latini, S.; Hjarnaa, P.-J. V.; Björkling, F. Cyclic Phosphinamides and Phosphonamides, Novel Series of Potent Matrix Metalloproteinase Inhibitors with Antitumour Activity. *Bioorg Med Chem* **2003**, *11* (24), 5461–5484. (d) Nocentini, A.; Gratteri, P.; Supuran, C. T. Phosphorus versus Sulfur: Discovery of Benzenephosphonamidates as Versatile Sulfonamide-Mimic Chemotypes Acting as Carbonic Anhydrase Inhibitors. *Chemistry* **2019**, *25* (5), 1188–1192. (e) Nocentini, A.; Alterio, V.; Bua, S.; Micheli, L.; Esposito, D.; Buonanno, M.; Bartolucci, G.; Osman, S. M.; ALOthman, Z. A.; Cirilli, R.; Pierini, M.; Monti, S. M.; Di Cesare Mannelli, L.; Gratteri, P.; Ghelardini, C.; De Simone, G.; Supuran, C. T. Phenyl(Thio)Phosphon(amid)Ate Benzenesulfonamides as Potent and Selective Inhibitors of Human Carbonic Anhydrases II and VII Counteract Allodynia in a Mouse Model of Oxaliplatin-Induced Neuropathy. *J. Med. Chem.* **2020**, *63* (10), 5185–5200. (f) Babbs, A.; Berg, A.; Chatzopoulou, M.; Davies, K. E.; Davies, S. G.; Edwards, B.; Elsey, D. J.; Emer, E.; Figuccia, A. L. A.; Fletcher, A. M.; Guiraud, S.; Harriman, S.; Moir, L.; Robinson, N.; Rowley, J. A.; Russell, A. J.; Squire, S. E.; Thomson, J. E.; Tinsley, J. M.; Wilson,

Stereogenic-at-phosphorus compounds also serve as broadly useful ligands and catalysts in asymmetric organic synthesis.[3] Though a variety of natural products bearing *P*-stereogenic centers have been identified,[4] these molecules are not practical synthetic building blocks due to their sparsity. Thus, whereas the synthesis of compounds bearing *C*-stereogenic centers has historically drawn heavily on nature's chiral pool, access to *P*-stereogenic molecules relies entirely on *de novo* synthesis. Nucleophilic substitution at stereogenic P(V) centers can occur stereospecifically, thereby providing a powerful strategy for the synthesis of complex, optically active compounds from simple P(V) building blocks bearing one or more leaving groups attached to phosphorus.[3b,5]

F. X.; Wynne, G. M. Synthesis of SMT022357 Enantiomers and in Vivo Evaluation in a Duchenne Muscular Dystrophy Mouse Model. *Tetrahedron* **2020**, *76* (2), 130819.

[3] (a) Imamoto, T. Synthesis and Applications of High-Performance P-Chiral Phosphine Ligands. *Proc Jpn Acad Ser B Phys Biol Sci* **2021**, *97* (9), 520–542. (b) Dutartre, M.; Bayardon, J.; Jugé, S. Applications and Stereoselective Syntheses of P-Chirogenic Phosphorus Compounds. *Chem Soc Rev* **2016**, *45* (20), 5771–5794.

[4] Kolodiazhnyi, O. I. Phosphorus Compounds of Natural Origin: Prebiotic, Stereochemistry, Application. *Symmetry* **2021**, *13* (5), 889.

[5] (a) Kolodiazhnyi, O. I.; Kolodiazhna, A. Nucleophilic Substitution at Phosphorus: Stereochemistry and Mechanisms. *Tetrahedron: Asymmetry* **2017**, *28* (12), 1651–1674. (b) Kolodiazhnyi, O. I. Recent Developments in the Asymmetric Synthesis of P-Chiral Phosphorus Compounds. *Tetrahedron: Asymmetry* **2012**, *23* (1), 1–46. (c) Ye, X.; Peng, L.; Bao, X.; Tan, C.-H.; Wang, H. Recent Developments in Highly Efficient Construction of P-Stereogenic Centers. *Green Synthesis and Catalysis* **2021**, *2* (1), 6–18.

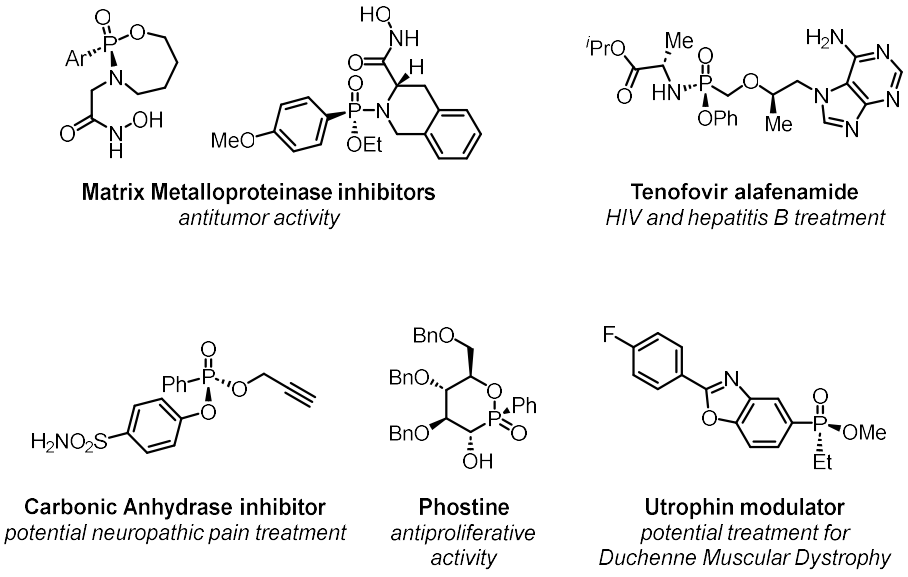


Figure 2.1 Exemplary bioactive molecules bearing *P*-stereogenic centers.

Effective methods for accessing stereogenic-at-phosphorus targets have relied primarily on the use of covalently attached chiral auxiliaries to achieve diastereocontrol, and a variety of chelating auxiliaries have been developed successfully for this purpose (Fig. 2.2).[6] Their

[6] (a) Kato, T.; Kobayashi, K.; Masuda, S.; Segi, M.; Nakajima, T.; Suga, S. Asymmetric Synthesis of Phosphine Oxides with the Arbuzov Reaction. *Chem. Lett.* **1987**, *16* (10), 1915–1918. (b) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. Efficient Asymmetric Synthesis of Optically Pure Tertiary Mono and Diphosphine Ligands. *Tetrahedron Letters* **1990**, *31* (44), 6357–6360. (c) Koizumi, T.; Yanada(nee Ishizaka), R.; Takagi, H.; Hirai, H.; Yoshii, E. Grignard Reaction 0f 2-Phenyl-Tetrahydropyrrolo-1,5,2-Oxazaphospholes, Observation of the Stereospecific Inversion of Configuration. *Tetrahedron Letters* **1981**, *22* (6), 571–572. (d) Corey, E. J.; Chen, Z.; Tanoury, G. J. A New and Highly Enantioselective Synthetic Route to P-Chiral Phosphines and Diphosphines. *J. Am. Chem. Soc.* **1993**, *115* (23), 11000–11001. (e) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. Efficient Asymmetric Synthesis of P-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-Oxide Agents. *J. Am. Chem. Soc.* **2013**, *135* (7), 2474–2477. (f) Knouse, K. W.; deGruyter, J. N.; Schmidt, M. A.; Zheng, B.; Vantourout, J. C.; Kingston, C.; Mercer, S. E.; Mcdonald, I. M.; Olson, R. E.; Zhu, Y.; Hang, C.; Zhu, J.; Yuan, C.; Wang, Q.; Park, P.; Eastgate, M. D.; Baran, P. S. Unlocking P(V): Reagents for Chiral Phosphorothioate Synthesis. *Science* **2018**, *361* (6408), 1234–1238. (g) Xu, D.; Rivas-Bascón, N.; Padial, N. M.; Knouse, K. W.; Zheng, B.; Vantourout, J. C.; Schmidt, M. A.; Eastgate, M. D.; Baran, P. S. Enantiodivergent Formation of C–P Bonds: Synthesis of P-Chiral Phosphines and Methylphosphonate Oligonucleotides. *J. Am. Chem. Soc.* **2020**, *142* (12), 5785–5792. (h) Kuwabara, K.; Maekawa, Y.; Minoura, M.; Maruyama, T.; Murai, T. Chemoselective and Stereoselective Alcoholysis of Binaphthyl Phosphonothioates: Straightforward Access to Both Stereoisomers of Biologically Relevant P-Stereogenic Phosphonothioates. *J. Org. Chem.* **2020**, *85* (22), 14446–14455. (i) Mondal, A.; Thiel, N. O.; Dorel, R.; Feringa, B. L. P-Chirogenic Phosphorus Compounds by Stereoselective Pd-Catalysed Arylation of Phosphoramidites. *Nat Catal* **2022**, *5* (1), 10–19.

applicability depends on stereospecific displacement of the auxiliary to forge P(V) stereocenters with absolute stereocontrol. Among noteworthy recent advances using the chiral auxiliary approach, Baran and co-workers reported the development of highly reactive oxathiaphospholane-sulfide building blocks.[6f,6g] The propensity of the P–S bonds in these building blocks to undergo substitution by both alcohols and organometallic reagents was demonstrated and enables the synthesis of a variety of stereogenic-at-P(V) compounds, ranging from oligonucleotides to chiral phosphine oxides.

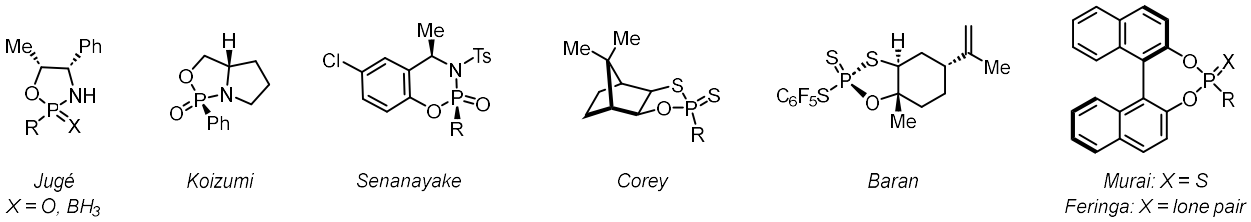


Figure 2.2 Chiral-auxiliary based stereogenic-at-P(V) building blocks.

Despite important advances in the stereoselective synthesis of chiral P(V) compounds by the chiral auxiliary approach, there is both practical and fundamental motivation for developing asymmetric catalytic strategies toward these targets. In that vein, there have been several recent breakthroughs (Fig. 2.3). Dirocco and coworkers developed a chiral bisimidazole catalyzed synthesis of phosphoramidate prodrugs through the diastereoselective addition of nucleosides to chlorophosphoramidates, proceeding via a cooperative mechanism of covalent activation of P(V) and general-base activation of the alcohol nucleophile (Fig. 2.3a).[7] An alternative approach was demonstrated by Miller and co-workers in the catalytic, stereodivergent synthesis of *P*-stereogenic oligonucleotides from phosphoramidites via chiral phosphoric acid catalysis (Fig. 2.3b).[8] Finally,

[7] DiRocco, D. A.; Ji, Y.; Sherer, E. C.; Klapars, A.; Reibarkh, M.; Dropinski, J.; Mathew, R.; Maligres, P.; Hyde, A. M.; Limanto, J.; Brunskill, A.; Ruck, R. T.; Campeau, L.-C.; Davies, I. W. A Multifunctional Catalyst That Stereoselectively Assembles Prodrugs. *Science* **2017**, *356* (6336), 426–430.

[8] Featherston, A. L.; Kwon, Y.; Pompeo, M. M.; Engl, O. D.; Leahy, D. K.; Miller, S. J. Catalytic Asymmetric and Stereodivergent Oligonucleotide Synthesis. *Science* **2021**, *371* (6530), 702–707.

in work that appeared as this study was being completed, Dixon and co-workers reported a catalytic, enantioselective desymmetrization of diaryl phosphonate esters by substitution with *ortho*-substituted phenols.[9] Although high levels of stereoselectivity were achieved in these catalytic, nucleophilic substitution reactions, each is limited to a narrow class of nucleophiles that are not further displaced. We conceived that the catalytic, enantioselective installation of a nucleophile that could further serve as a leaving group for stereospecific substitution at P(V) could provide a generalizable strategy for the synthesis of chiral P(V) targets with the broad synthetic scope of state-of-the-art auxiliary approaches while avoiding the need for the stoichiometric use of chiral control elements.

[9] Formica, M.; Rogova, T.; Shi, H.; Sahara, N.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Dixon, D. J. Catalytic Enantioselective Nucleophilic Desymmetrisation of Phosphonate Esters. ChemRxiv [Preprint] July 22, 2021.

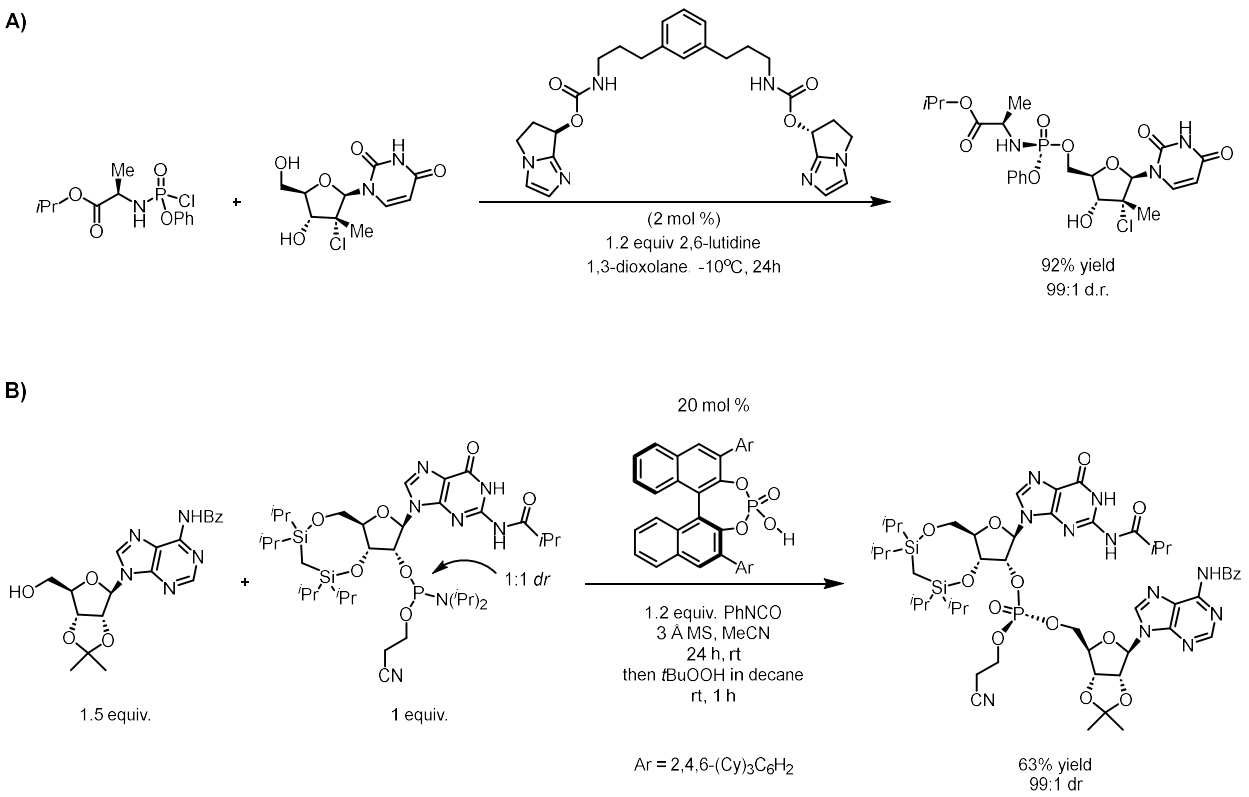


Figure 2.3 Synthetic approaches to stereogenic-at-P(V) targets using stereoselective catalysis. (A) Diastereoselective synthesis of phosphoramidate prodrugs via chiral imidazole-catalyed dynamic kinetic resolution of chlorophosphoramidates. (B) Diastereoselective synthesis of oligonucleotides via chiral phosphoric acid-catalyzed dynamic kinetic resolution of phosphoramidites.

We selected chlorophosphonamidates as potential targets of an enantioselective catalytic approach (Fig. 2.4). The chloride and amino groups on P(V) possess orthogonal reactivity that might permit sequential and stereospecific displacement *en route* to chiral P(V) targets bearing a broad range of substitution patterns. Given that P–Cl bonds in particular are susceptible to

substitution by a wide variety of nucleophiles,[10] chlorophosphonamidates would be highly versatile precursors to a multitude of P(V) frameworks.

We recognized that a most concise enantioselective synthesis of chlorophosphonamidates would be realized via a catalytic desymmetrization reaction of phosphonic dichlorides with amines. Dual-hydrogen-bond-donor catalysts have been applied broadly and successfully to promote stereoselective nucleophilic substitution reactions via chloride-abstraction pathways,[11] and we hypothesized that this reactivity principle could serve to activate one of the two enantiotopic chlorides of a phosphonic dichloride electrophile toward displacement by an amine.

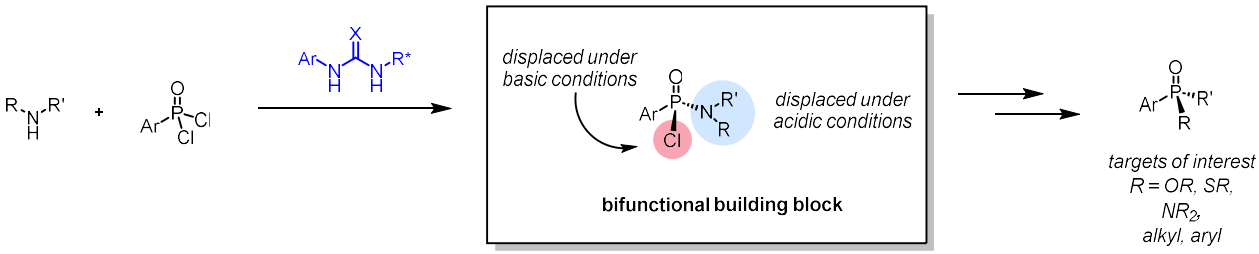


Figure 2.4 Hydrogen-bond-donor catalyzed synthesis of chlorophosphonamidate building blocks.

[10] (a) Kimura, T.; Murai, T. P-Chiral Phosphinoselenoic Chlorides and Optically Active P-Chiral Phosphinoselenoic Amides: Synthesis and Stereospecific Interconversion with Extrusion and Addition Reactions of the Selenium Atom. *Chem. Lett.* **2004**, *33* (7), 878–879. (b) Bauduin, C.; Moulin, D.; Kaloun, E. B.; Darcel, C.; Jugé, S. Highly Enantiomerically Enriched Chlorophosphine Boranes: Synthesis and Applications as P-Chirogenic Electrophilic Blocks. *J Org Chem* **2003**, *68* (11), 4293–4301. (c) Kimura, T.; Murai, T. Enantiomerically Pure P-Chiral Phosphinoselenoic Chlorides: Inversion of Configuration at the P-Chirogenic Center in the Synthesis and Reaction of These Substances. *Chem. Commun.* **2005**, No. 32, 4077–4079.

[11] (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107* (12), 5713–5743. (b) Kutateladze, D. A.; Strassfeld, D. A.; Jacobsen, E. N. Enantioselective Tail-to-Head Cyclizations Catalyzed by Dual-Hydrogen-Bond Donors. *J. Am. Chem. Soc.* **2020**, *142* (15), 6951–6956. (c) Bendelsmith, A. J.; Kim, S. C.; Wasa, M.; Roche, S. P.; Jacobsen, E. N. Enantioselective Synthesis of α-Allyl Amino Esters via Hydrogen-Bond-Donor Catalysis. *J. Am. Chem. Soc.* **2019**, *141* (29), 11414–11419. (d) Ford, D. D.; Lehnherr, D.; Kennedy, C. R.; Jacobsen, E. N. Anion-Abstraction Catalysis: The Cooperative Mechanism of α-Chloroether Activation by Dual Hydrogen-Bond Donors. *ACS Catal.* **2016**, *6* (7), 4616–4620.

2.2 Reaction Development

Phenyl phosphonic dichloride **2a** was selected as a model substrate in reactions with various amine nucleophiles and potential chiral catalysts (Fig. 2.5, 2.6). We found that chlorophosphonamidate **3** is stable in solution, however loss of enantioenrichment is observed when 3 is stored at room temperature for extended periods of time (Table S2.8). For ease of isolation and analysis, the chlorophosphonamidate products **3** were quenched with sodium methoxide at low temperature to produce the corresponding phosphonamidate **4a**. After systematic evaluation of a series of chiral dual H-bond-donor catalysts and amine nucleophiles, the sulfinamido urea **1a**[12] was found to promote the nucleophilic substitution by diisoamylamine in 95% enantiomeric excess (ee) and quantitative yield (Fig 2.5). Multiple equivalents of amine were required to attain full conversion of **2a**, as the amine functions both as a nucleophile and as a stoichiometric Brønsted base to trap the HCl byproduct produced in the reaction.

[12] (a) Tan, K. L.; Jacobsen, E. N. Indium-Mediated Asymmetric Allylation of Acylhydrazones Using a Chiral Urea Catalyst. *Angew Chem Int Ed Engl* **2007**, *46* (8), 1315–1317. (b) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Asymmetric Cooperative Catalysis of Strong Brønsted Acid-Promoted Reactions Using Chiral Ureas. *Science* **2010**, *327* (5968), 986–990.

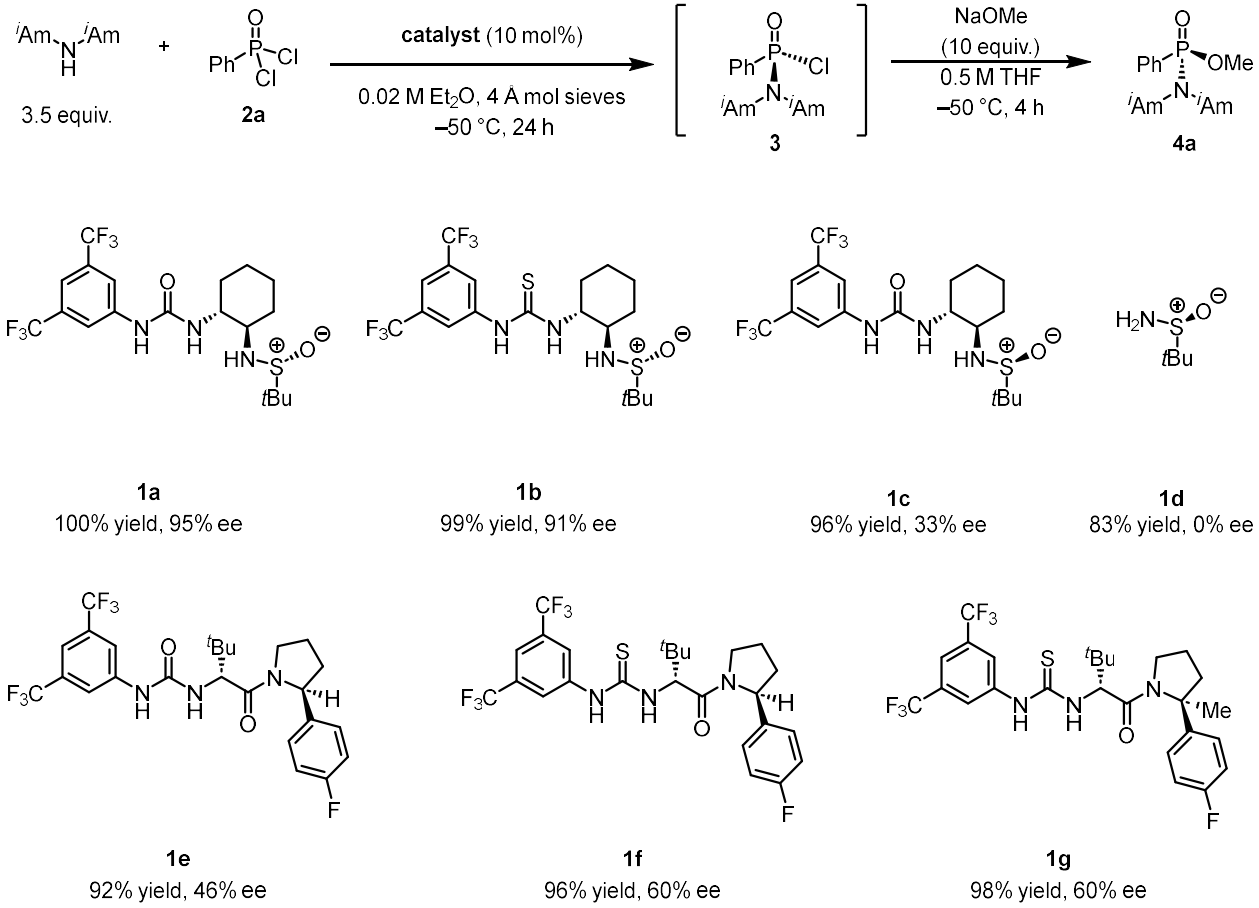


Figure 2.5 Catalyst optimization for enantioselective reaction of diisoamylamine with phenyl phosphonic dichloride. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

Examination of the role of catalyst structure revealed the importance of both the H-bond donor and the sulfinamide group in promoting high enantioselectivity. Whereas sulfinamido urea **1a** and its thiourea analog **1b** proved similarly effective as catalysts, the sulfinamide **1d** lacking the H-bond-donor motif induced little acceleration above the uncatalyzed rate (83% vs. 64% yield after 24 h) and afforded only racemic product. The sulfinamido urea **1c** epimeric to **1a** also induced severely diminished enantioselectivity, an observed “mismatch” effect that is consistent

with previous applications of this catalyst.[12] Arylpyrrolidino (thio)ureas such as **1e–g**, which have proven useful in a wide range of asymmetric anion-binding pathways[13] but lack the sulfinamide moiety, were catalytically active but generally poorly effective with respect to enantiocontrol. The enantioselectivity of the substitution was also closely tied to the identity of the amine, with diisoamylamine undergoing reaction with distinctly superior results relative to any of the other nucleophiles examined (Fig. 2.6). Beyond a beneficial effect of distal alkyl branching, it is difficult to discern any straightforward correlation between the steric or electronic properties of the amine and enantioselectivity in the substitution reaction. It is likely that the properties of the dialkylammonium chloride byproducts play a critical and complex role in influencing the observed enantioselectivity, as soluble tetraalkylammonium chloride salts are potent inhibitors of anion-binding H-bond-donor catalysts and were also shown to promote a racemic reaction between **2a** and diisoamylamine (Table S2.5, Table S2.7). Epimerization of chlorophosphonamidate **3** was not observed under the catalytic conditions, even in the presence of added tetrabutylammonium chloride (Scheme S2.1).

[13] Strassfeld, D. A.; Jacobsen, E. N. The Aryl-Pyrrolidine- Tert -Leucine Motif as a New Privileged Chiral Scaffold: The Role of Noncovalent Stabilizing Interactions. In *Supramolecular Catalysis*; John Wiley & Sons, Ltd, 2022; pp 361–385.

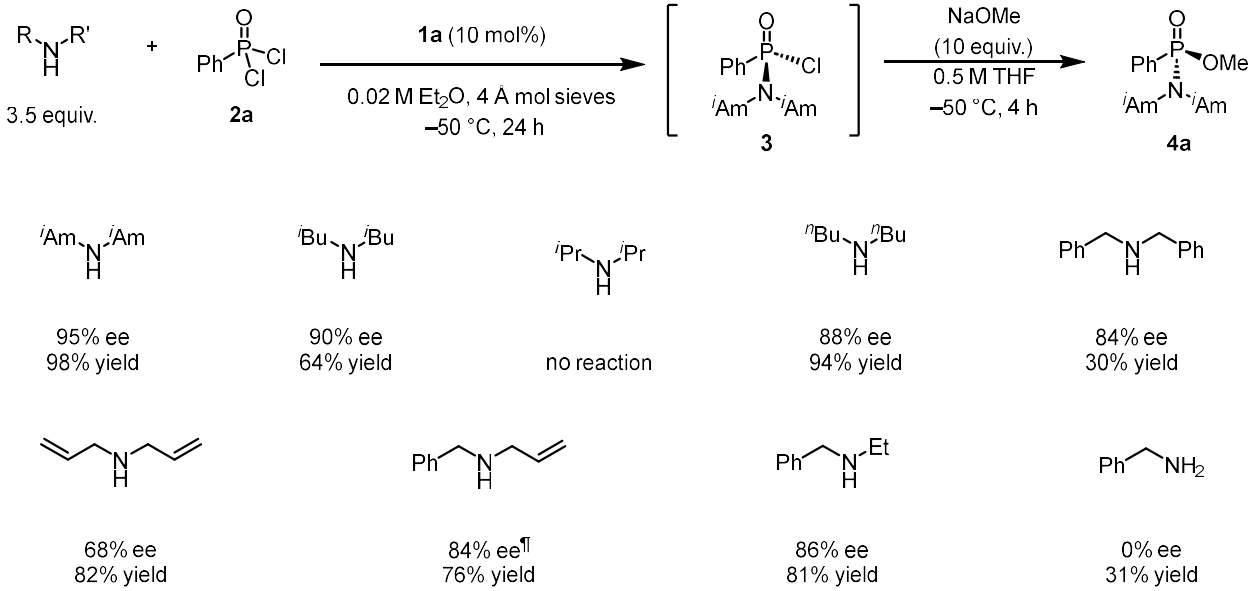


Figure 2.6 Optimization of amine structure for enantioselective substitution reaction with phenyl phosphonic dichloride. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard. *Reaction performed at –40 °C for 48 h.

High levels of enantioselectivity were achieved in the reaction of a variety of aryl phosphonic dichlorides with diisoamylamine (Fig 2.7). Substrates bearing arenes with either electron-withdrawing or electron-donating substituents underwent substitution with consistently high levels of enantioselectivity (**4b–g**). However, alkyl phosphonic dichlorides do not undergo high enantioselectivity in this reaction, as hexylphosphonic dichloride yielded the corresponding phosphonamidate **4h** with 26% ee under these conditions.

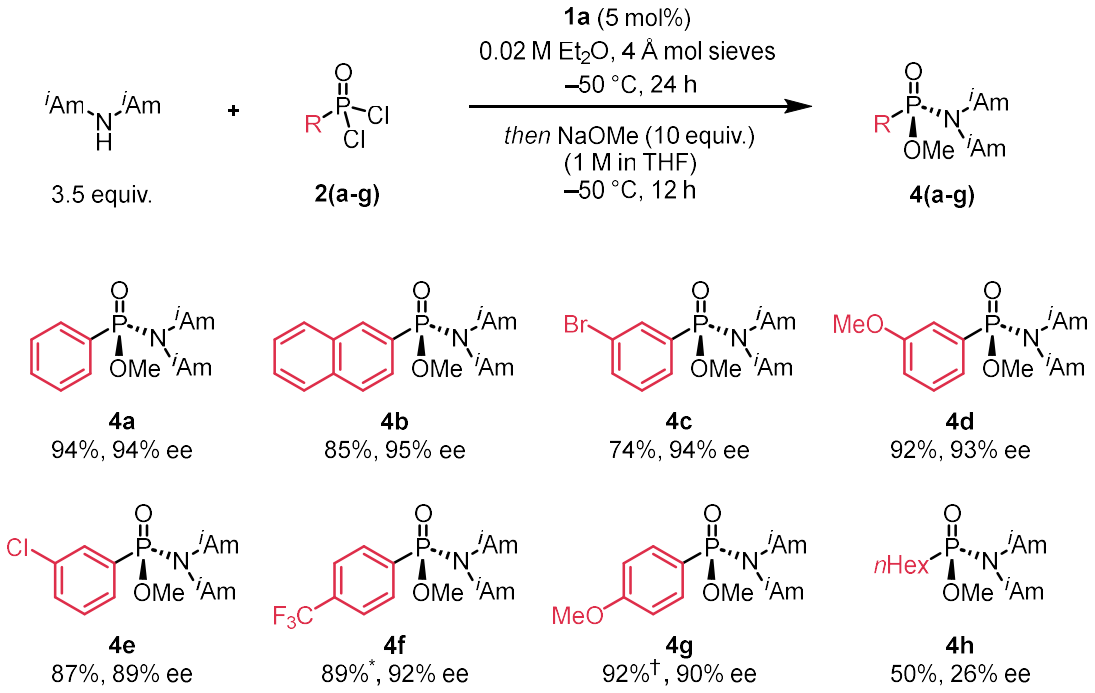


Figure 2.7 Substrate scope of addition of diisoamylamine to aryl phosphonyl dichlorides catalyzed by **1a**. Reactions were carried out on 0.2 mmol scale. Yield values correspond to chromatographically purified, isolated products. The absolute stereochemistry of the products was assigned based on the x-ray crystal structure of **10**. *Reaction was carried out at –78 °C with 20 mol% catalyst. †Reaction was carried out at –40 °C with 4.5 equivalents of diisoamylamine.

The products of the enantioselective reactions feature two chemically distinct leaving groups on phosphorus that could be selectively and stereospecifically displaced to afford access to multiple classes of chiral P(V) compounds. We first explored the scope of nucleophiles capable of enantiospecific displacement of the remaining chloride (Fig. 2.8). Reaction of **3** with alkoxides, phenoxides, thiolates, carbamides, and Grignard reagents afforded the desired products with high levels of enantiospecificity (es) in all cases (**5a–h**). The substitution reactions could be performed with or without isolation of **3** from the prior enantioselective catalytic step.

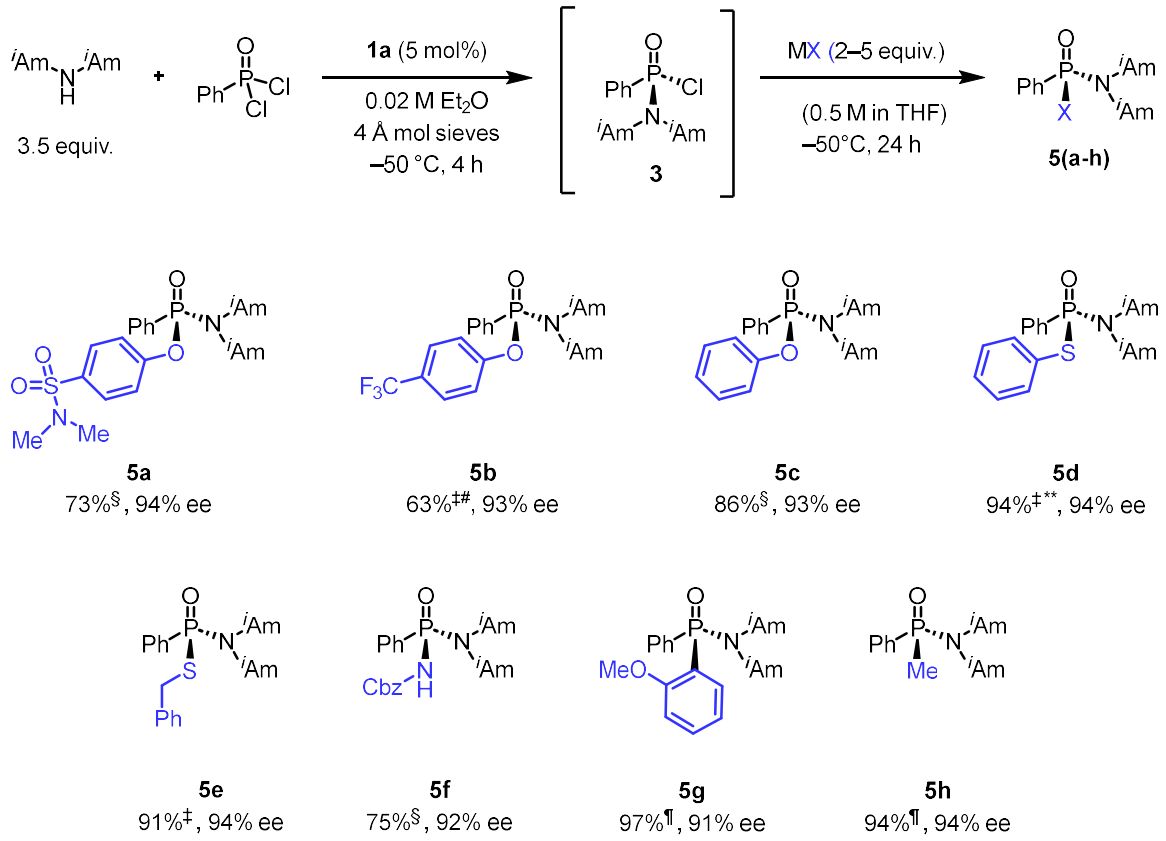
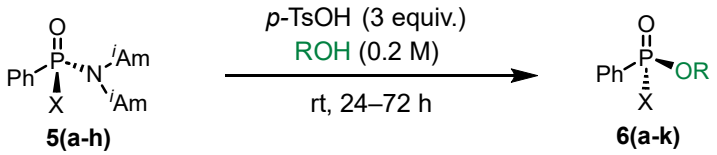


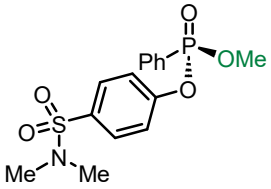
Figure 2.8 Scope of nucleophiles for enantiospecific substitution with **3**. Reactions were carried out on 0.2 mmol scale. Yield values correspond to chromatographically purified, isolated products. The absolute stereochemistry of the products was assigned based on the x-ray crystal structure of **10**. ‡Reaction was carried out using two-pot procedure involving isolation of **3** and subsequent reaction with 2 equivalents of nucleophile. §Reaction was carried out using one-pot procedure without isolation of **3** with 5 equivalents of nucleophile. ¶Reaction was carried out using two-pot procedure involving isolation of **3** and subsequent reaction with 5 equivalents of nucleophile. #Reaction was carried out on 0.9 mmol scale. **Reaction was carried out on 1.0 mmol scale.

The products of the chloride-displacement reactions could be further elaborated to afford alkoxy-substituted P(V) compounds via an acid-mediated stereoinvertive displacement of the diisoamylamino group (Fig. 2.9). Substitution of **5a–h** with methanol yielded a variety of

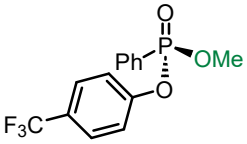
enantioenriched phosphonates, phosphinates, and phosphonamidates (**6a–h**) with nearly complete enantiospecificity observed in every case. The slightly diminished stereospecificity observed with **5g** and **5h** is consistent with prior observations.[6a,6c] Substitution with other primary alcohols proceeded with varied but generally high levels of enantiospecificity (**6i**–**k**).



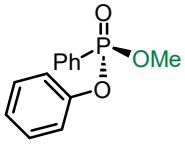
5(a-h) **6(a-k)**



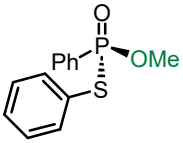
6a (from **5a**)
93%, 93% ee
99% es



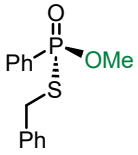
6b (from **5b**)
74%††, 93% ee
100% es



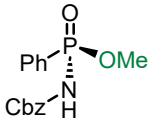
6c (from **5c**)
92%‡‡, 93% ee
100% es



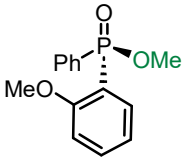
6d (from **5d**)
82%#§§, 93% ee
99% es



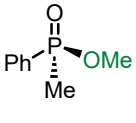
6e (from **5e**)
79%, 92% ee
98% es



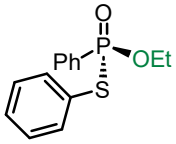
6f (from **5f**)
86%, 92% ee
100% es



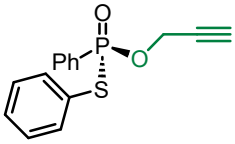
6g (from **5g**)
70%, 87% ee
96% es



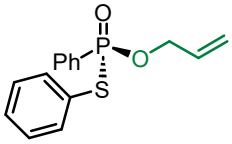
6h (from **5h**)
48%##, 89% ee
95% es



6i (from **5d**)
58%, 92% ee
99% es



6j (from **5d**)
49%, 81% ee
86% es



6k (from **5d**)
55%, 91% ee
97% es

Figure 2.9 Enantiospecific displacement of the diisoamylamino group with alcohols. Reactions were run on 0.1 mmol scale. Yield values correspond to chromatographically purified, isolated products. ††Reaction was carried out on 0.57 mmol scale. ‡‡Reaction was carried out on 0.24 mmol scale. §§ Reaction was run at 0.3 M concentration instead of 0.2 M. ##H_3PO_3 was used instead of *para*-tolylsulfonic acid.

2.3 Synthetic Applications of Chlorophosphonamidates as Chiral Building Blocks

2.3.1 Phosphonylation of Alcohols

The phosphonate thioester product **6d** possesses a thiophenoxy group, which is a further readily displaceable substituent. Previous reports have demonstrated the propensity of P–S bonds to undergo stereospecific displacement by alcohols.[6f,6g] Therefore, we hypothesized that compound **6d** could be a useful synthetic building block for further elaboration to chiral P(V) compounds bearing complex alcohol substituents. In the presence of $MgCl_2$ and diisopropylethylamine, we found that phosphonate thioester **6d** underwent reaction with functionally complex alcohols to furnish the corresponding phosphonylated biomolecules with high levels of stereospecificity (**7a–c**, Fig. 2.10). These substitutions are performed under Brønsted-acid–free conditions using little-or-no excess of the alcohol reagent, highlighting the utility of **6d** for the phosphonylation of precious or acid-sensitive alcohols that are incompatible with the two previous elaboration procedures.

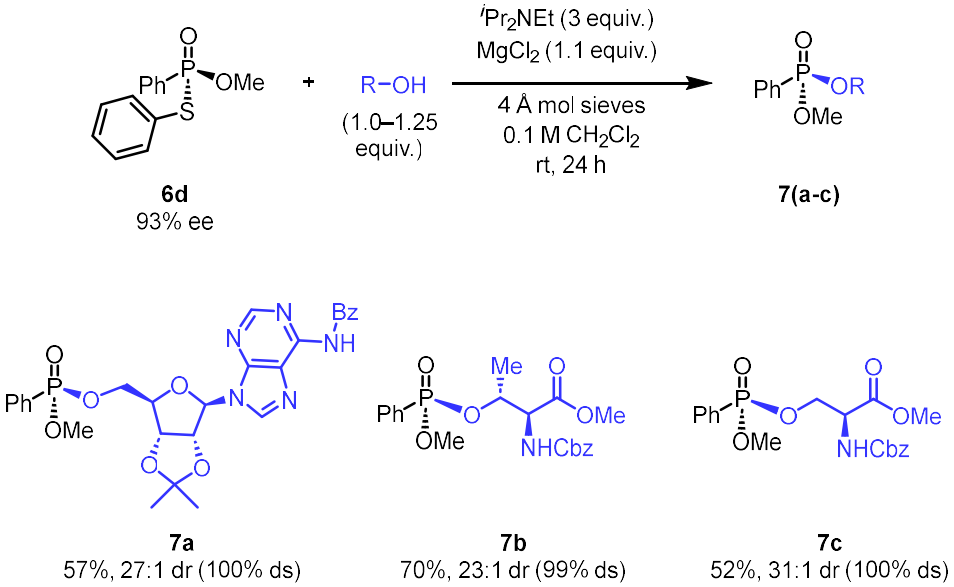


Figure 2.10 Stereospecific phosphonylation of precious alcohols with **6d**. Reactions were carried out on 0.1 mmol scale. Yield values correspond to chromatographically purified, isolated products.

2.3.2 Synthesis of Phosphinate Esters

Phosphonate ester product **6b** possesses an electron-deficient group, which is a further readily displaceable substituent that can undergo displacement with Grignard reagents.[6i] We hypothesized that **6b** could also serve as a chiral building block for elaboration to other chiral P(V) compounds. We found that phosphonate **6b** underwent efficient substitution with Grignard reagents with displacement of the electron-deficient aryloxide to yield highly enantioenriched phosphinate esters, known precursors to chiral phosphine oxides (Fig. 2.11).[6g]

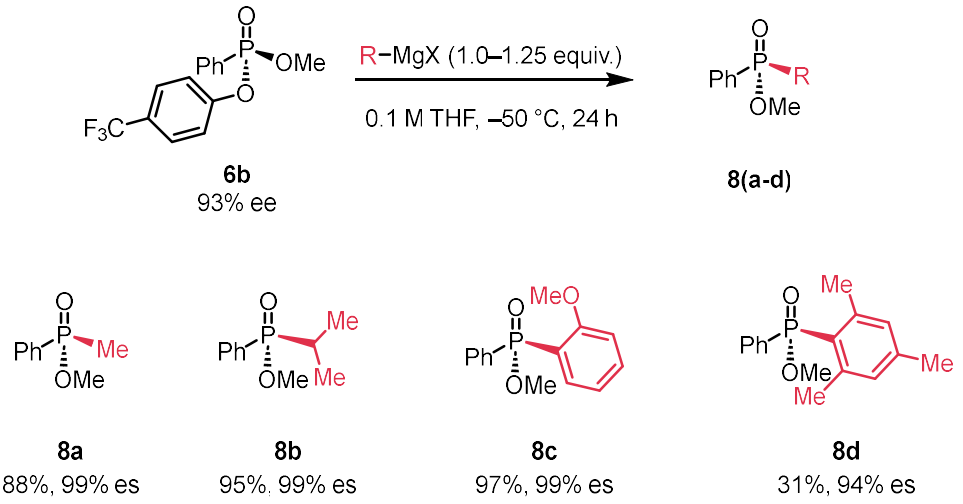


Figure 2.11 Stereospecific reaction of Grignard reagents with **6b** for the synthesis of enantioenriched phosphinate esters. Absolute stereochemistry of **8a** was determined by comparison of optical rotation to literature value; others assigned by analogy. Reactions run on 0.05–0.1 mmol scale. Yield values correspond to chromatographically purified, isolated products.

2.3.3 Enantioselective Synthesis of (+)-SMT022332

We hypothesized that our developed three-step route to highly enantioenriched phosphinate esters could be applied to the synthesis of (+)-SMT022332, a utrophin modulator

developed as a potential treatment for Duchenne Muscular Dystrophy.[14] An analogue of (+)-SMT022332 was previously accessed in 83% ee and 5% overall yield from phosphonic dichloride **9** using a chiral auxiliary-based approach (Fig 2.12).[2f]

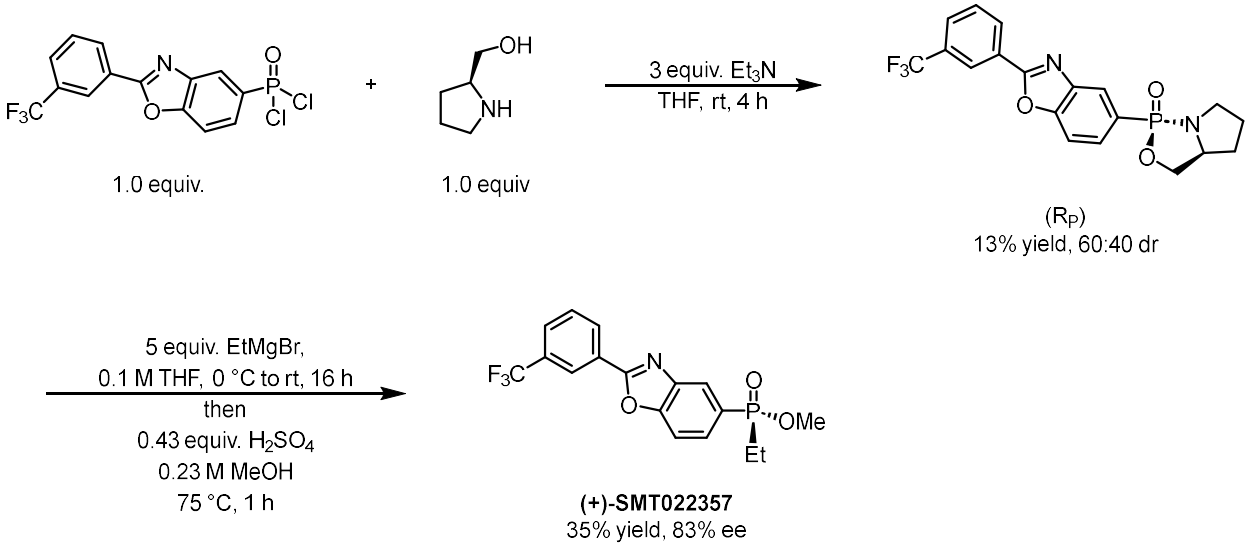


Figure 2.12 Stereospecific synthesis of (+)-SMT022357 using prolinol auxiliary.

Subjection of phosphonic dichloride **9** to the standard reaction conditions for the enantioselective substitution initially yielded phosphonamidate **10** in 38% yield and 95% ee with 10 mol% **1a**. Increasing the loading of diisoamylamine to 5 equivalents, increasing the reaction temperature to –40 °C, and increasing the reaction duration resulted in an increase in yield of

[14] (a) Wilkinson, I. V. L.; Perkins, K. J.; Dugdale, H.; Moir, L.; Vuorinen, A.; Chatzopoulou, M.; Squire, S. E.; Monecke, S.; Lomow, A.; Geese, M.; Charles, P. D.; Burch, P.; Tinsley, J. M.; Wynne, G. M.; Davies, S. G.; Wilson, F. X.; Rastinejad, F.; Mohammed, S.; Davies, K. E.; Russell, A. J. Chemical Proteomics and Phenotypic Profiling Identifies the Aryl Hydrocarbon Receptor as a Molecular Target of the Utrophin Modulator Ezutromid. *Angew Chem Int Ed Engl* **2020**, *59* (6), 2420–2428. (b) Babbs, A.; Berg, A.; Chatzopoulou, M.; Davies, K. E.; Davies, S. G.; Edwards, B.; Elsey, D. J.; Emer, E.; Guiraud, S.; Harriman, S.; Lecci, C.; Moir, L.; Peters, D.; Robinson, N.; Rowley, J. A.; Russell, A. J.; Squire, S. E.; Tinsley, J. M.; Wilson, F. X.; Wynne, G. M. 2-Arylbenzo[d]Oxazole Phosphinate Esters as Second-Generation Modulators of Utrophin for the Treatment of Duchenne Muscular Dystrophy. *J Med Chem* **2020**, *63* (14), 7880–7891. (c) Chatzopoulou, M.; Emer, E.; Lecci, C.; Rowley, J. A.; Casagrande, A.-S.; Moir, L.; Squire, S. E.; Davies, S. G.; Harriman, S.; Wynne, G. M.; Wilson, F. X.; Davies, K. E.; Russell, A. J. Decreasing HepG2 Cytotoxicity by Lowering the Lipophilicity of Benzo[d]Oxazolephosphinate Ester Utrophin Modulators. *ACS Med Chem Lett* **2020**, *11* (12), 2421–2427.

phosphonamidate **10** to 68% (Fig 2.13). Phosphonamidate **10** was characterized crystallographically, allowing confirmation of absolute configuration (Fig. 2.14). Subsequent methanolysis of **10** afforded **11** in 65% yield and 94% ee. Reaction of phosphonate **11** with ethylmagnesium chloride to displace the phenol furnished (+)-SMT022332 (**12**) in 94% ee and 43% overall yield over 3 steps.

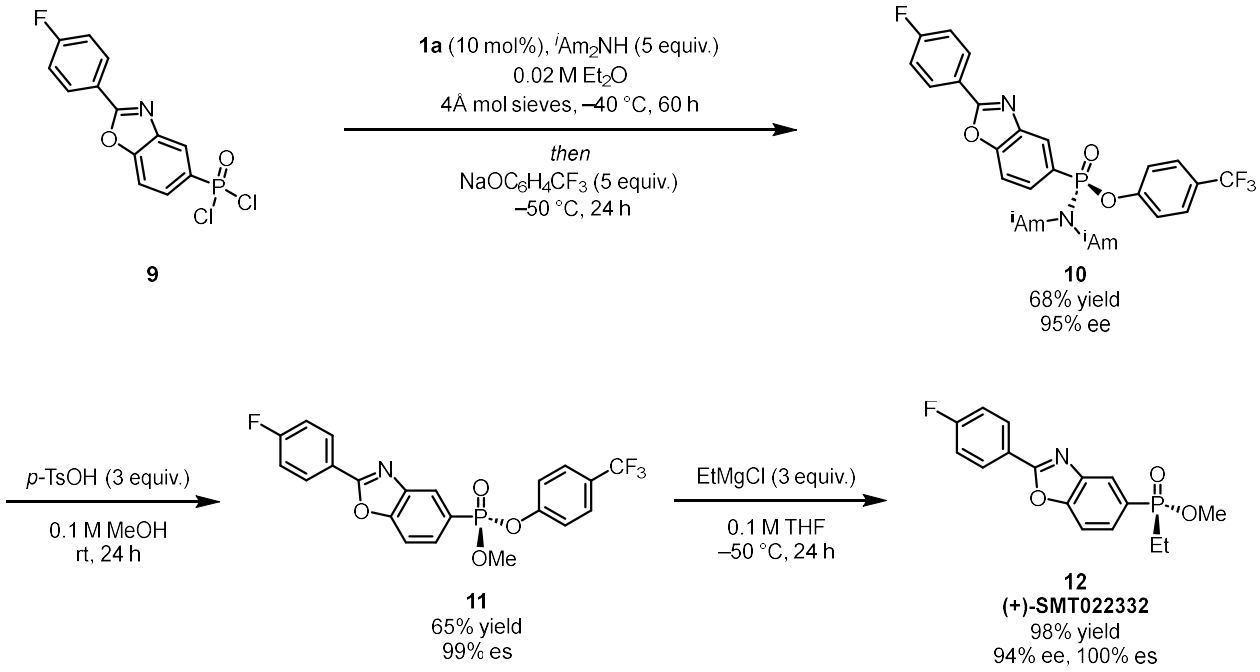


Figure 2.13 Application of method to the enantioselective synthesis of (+)-SMT022332. Yield values refer to isolated yields. Absolute stereochemistry of **10** assigned by the depicted X-ray crystal structure, and of **12** by comparison of the optical rotation to the literature value.

Figure 2.14 X-ray crystal structure of phosphonamidate **10**.

2.3.4 Enantioselective Formal Synthesis of Matrix Metalloproteinase Inhibitor

In addition to serving as versatile synthetic building blocks, phosphonamidates are often synthetic targets themselves,[2b,2c,2d,2e,15] and general access to these compounds by the catalytic procedure would be desirable. However, the structural requirements on the amine for achieving high enantioselectivity in catalytic reaction impose restrictions to the N-substituents that can be introduced directly (Fig. 2.6). We therefore sought to identify amine derivatives that participate successfully in the enantioselective reaction while bearing orthogonally cleavable *N*-protecting groups that might provide centralized access to a variety of substituted phosphonamidates (Fig. 2.15). High enantioselectivity was obtained using *N*-allyl benzylamine in the substitution reaction under modified conditions. The benzyl group and the allyl group on the chlorophosphonamidate products can each be cleaved successively, enabling their sequential replacement.[16]

---

[15] (a) Kasper, M.-A.; Glanz, M.; Stengl, A.; Penkert, M.; Klenk, S.; Sauer, T.; Schumacher, D.; Helma, J.; Krause, E.; Cardoso, M. C.; Leonhardt, H.; Hackenberger, C. P. R. Cysteine-Selective Phosphonamidate Electrophiles for Modular Protein Bioconjugations. *Angew Chem Int Ed Engl* **2019**, *58* (34), 11625–11630. (b) Lentini, N. A.; Foust, B. J.; Hsiao, C.-H. C.; Wiemer, A. J.; Wiemer, D. F. Phosphonamidate Prodrugs of a Butyrophilin Ligand Display Plasma Stability and Potent Vγ9 Vδ2 T Cell Stimulation. *J Med Chem* **2018**, *61* (19), 8658–8669. (c) Van Overtveldt, M.; Heugebaert, T. S. A.; Verstraeten, I.; Geelen, D.; Stevens, C. V. Phosphonamide Pyrabactin Analogues as Abscisic Acid Agonists. *Org Biomol Chem* **2015**, *13* (18), 5260–5264. (d) Slusarczyk, M.; Serpi, M.; Pertusati, F. Phosphoramidates and Phosphonamidates (ProTides) with Antiviral Activity. *Antivir Chem Chemother* **2018**, *26*, 2040206618775243. (e) Buti, M.; Riveiro-Barciela, M.; Esteban, R. Tenofovir Alafenamide Fumarate: A New Tenofovir Prodrug for the Treatment of Chronic Hepatitis B Infection. *J Infect Dis* **2017**, *216* (suppl_8), S792–S796.

[16] (a) Xu, Y.; Su, Q.; Dong, W.; Peng, Z.; An, D. The Chan-Evans-Lam N-Arylation of Phosphonic/Phosphinic Amides. *Tetrahedron* **2017**, *73* (31), 4602–4609. (b) Zhao, Z.; Zhu, Q.; Che, S.; Luo, Z.; Lian, Y. Palladium/Nickel-Mediated Cross Coupling Reaction between Phosphorylamides and Alkenes toward Enephosphorylamides. *Synthetic Communications* **2020**, *50* (15), 2338–2346. (c) Zhu, Q.; Che, S.; Luo, Z.; Zhao, Z. Ligand-Free Copper-Catalyzed Denitrogenative Arylation of Phosphorylamides with Arylhydrazines. *Synthetic Communications* **2020**, *50* (7), 947–957. (d) Zhong, L.; Su, Q.; Xiao, J.; Peng, Z.; Dong, W.; Zhang, Y.; An, D. Ligand-Free Copper-Catalyzed Arylation of Phosphonamides and Phosphinamides with Aryl Siloxanes. *Asian Journal of Organic Chemistry* **2017**, *6* (8), 1072–1079. (e) Xiao, J.; Li, P.; Zhang, Y.; Xie, D.; Peng, Z.; An, D.; Dong, W. Cobalt-Catalyzed Oxidative Arylmethylation of Phosphorylamides. *Tetrahedron* **2018**, *74* (35), 4558–4568.

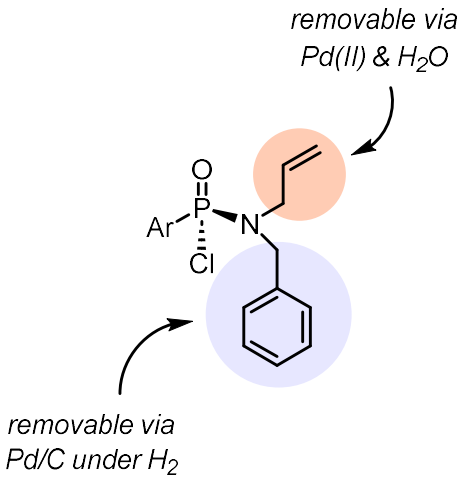


Figure 2.15 *N*-protected chlorophosphonamidate building block.

This strategy was exploited in the synthesis of phosphonamidate **17**, a matrix metalloproteinase (MMP) inhibitor with demonstrated anticancer activity (Fig. 2.16).[2c] Phosphonic dichloride **2h** effectively underwent the catalytic reaction with *N*-allylbenzylamine to produce, after quenching with allyl alkoxide, phosphonamidate **13** in 89% ee and 88% yield. Phosphonamidate **13** was elaborated over three steps to afford cyclic phosphonamidate **16** in 90% ee, completing the enantioselective formal synthesis of MMP inhibitor **17**. We anticipate that *N*-allyl benzylamine's versatility as a masked "–NH_2" equivalent may enable access to a wide variety of phosphonamidate targets.

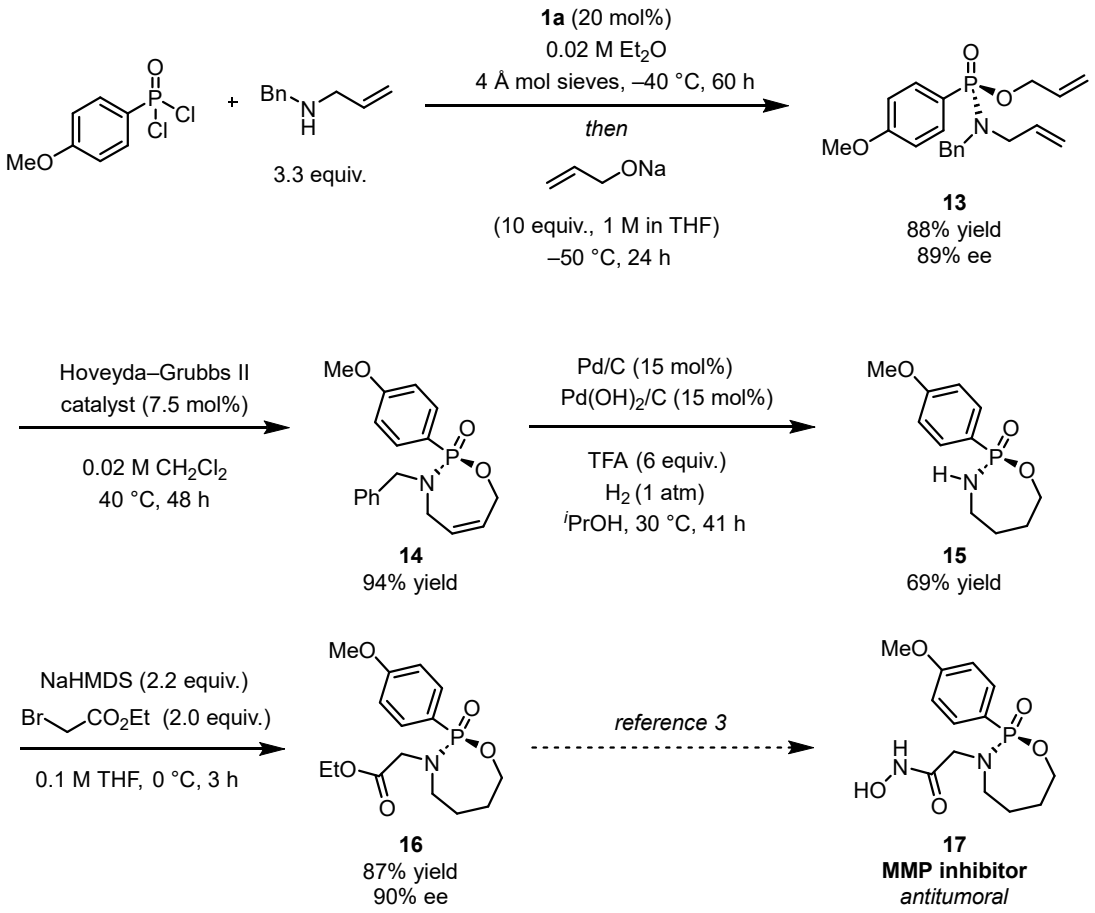


Figure 2.16 Formal synthesis of matrix metalloproteinase inhibitor **17**. Yield values correspond to chromatographically purified, isolated products.

We also discovered that higher levels of enantioselectivity could be achieved with phenyl phosphonic dichloride (**2a**) and *N*-allyl benzylamine using thiourea **1b** as a catalyst in place of **1a**. Employing catalyst **1b**, phosphonamidate 18 was observed in 88% ee in comparison to 84% ee with catalyst **1a** (Figure 2.6, 2.17).

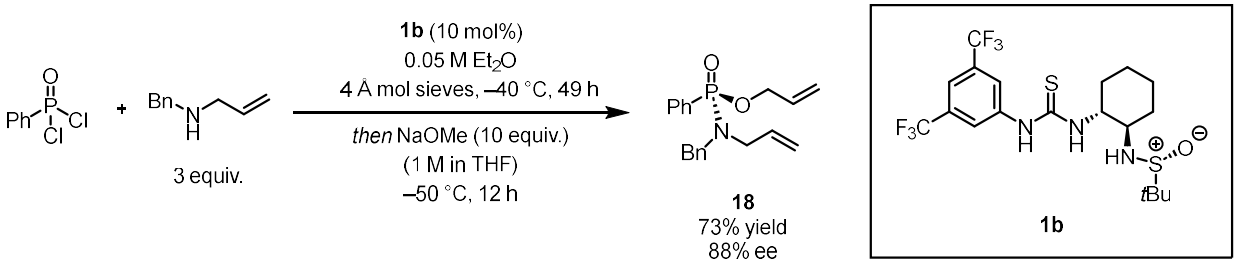


Figure 2.17 Enantioselective desymmetrization of **2a** with *N*-allylbenzylamine catalyzed by **1b.** Reaction was carried out on 0.06 mmol scale. Yield value corresponds to chromatographically purified, isolated product.

2.4 Conclusion

In conclusion, we report an enantioselective hydrogen-bond-donor-catalyzed desymmetrization of phosphonic dichlorides to produce chlorophosphonamidates, and the development of these products as versatile chiral P(V) building blocks. We demonstrate that chlorophosphonamidates possess two leaving groups that can be displaced sequentially and stereospecifically to access a wide variety of stereogenic-at-P(V) compounds featuring diverse substitution patterns. This methodology was successfully applied to the enantioselective synthesis of bioactive targets bearing *P*-stereogenic centers, including a utrophin modulator and a matrix metalloproteinase inhibitor. We expect the versatile enantioenriched chlorophosphonamidate intermediates accessed via synthetic strategies outlined herein to enable the facile synthesis of both known and new stereogenic-at-P(V) compounds of interest.

2.5 Experimental

2.5.1 General Considerations

All reactions were performed in standard, oven-dried glassware fitted capped with rubber septa under a N_2 atmosphere unless otherwise described. Concentration of solutions was carried out under reduced pressure using house vacuum (40 torr) at 35 °C unless otherwise described. Concentrations refer to solution volumes at room temperature (~22 °C). High-vacuum was achieved using a vacuum pump at 400 mTorr. Flash column chromatography was performed using a Biotage Isolera One system. Thin layer chromatography was used for product detection using Silica Gel 60 F254 plates, with visualization effected via exposure to UV Light (λ_{ex} = 254 nm) or staining and heating with $KMnO_4$.

2.5.2 Materials and Instrumentation

Materials and Reagents

Catalyst **1a** ((R)-N-[(1R,2R)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl]-tert-butyl-sulfinamide ; CAS = 934762-68-2) and phenyl phosphonic dichloride **2a** (CAS = 824-72-6) were purchased from Sigma-Aldrich and used as received. Diisoamylamine (CAS = 544-00-3) and 4-methoxyphenyl phosphonic dichloride **4g** (CAS = 37632-18-1) were purchased from TCI America and used as received. All other reagents and solvents were purchased from commercial suppliers including Sigma-Aldrich, TCI, Alfa Aesar, Acros Organics, Matrix Scientific, Cambridge Isotope Laboratories, or Strem and used as received. Anhydrous solvents (diethyl ether, toluene, tetrahydrofuran (THF), dichloromethane (DCM), and dimethylformamide (DMF)) were dried using activated alumina columns. Deuterated solvents were purchased from Cambridge Isotope Laboratories.

Special Note:

Aryl phosphonic dichlorides (**2a-g**) are hydrolytically sensitive and undergo decomposition when exposed to air. These reagents should be stored under an anhydrous/inert atmosphere. Optimal results were achieved by using phosphonyl dichlorides immediately after preparation or freshly distilled under inert atmosphere. Similarly, aryl chlorophosphonamidate **3** and its analogues are susceptible to decomposition and/or racemization upon attempted purification. These intermediates are best used immediately via in situ addition of a nucleophile or via filtration and partial concentration according to the procedures reported herein. Alternatively, the aryl chlorophosphonamidate intermediates may be stored as crude mixtures at –78 °C.

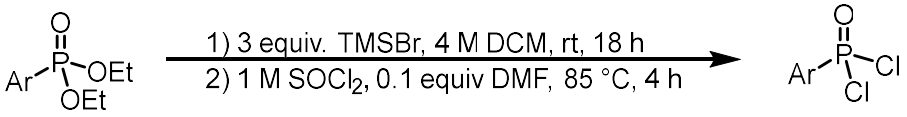
Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE NEO 400 or Bruker AVANCE NEO 400B spectrometer. Proton NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced using the NMR solvent ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Proton-decoupled ^{13}C NMR spectra are reported in ppm downfield from tetramethylsilane, and are referenced using the NMR solvent ($CDCl_3$: 77.16 ppm, C_6D_6: 128.06 ppm). Proton-decoupled ^{31}P NMR spectra are reported in ppm downfield from 85% H_3PO_4. ^{19}F NMR spectra are reported in ppm downfield from chlorotrifluoromethane. Splitting patterns for peaks on NMR spectra are represented as: (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, m = multiplet). Coupling constants are measured in Hertz (Hz). High-resolution Mass Spectrometry (HRMS) data were acquired by the Harvard FAS Division of Science Small Molecule Mass Spectrometry facility. Gas chromatography (GC) analysis was performed on an Agilent 7890A series GC system outfitted with a commercially available Cyclodex B (60 m) column. Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1200 series quaternary HPLC system with commercially

available CHIRALCEL and CHIRALPAK analytical columns (4.6 x 250 mm). Optical rotations ([α]) were obtained using a Jasco DIP 370 digital polarimeter at 589 nm using sodium D line at 22 °C in a 1 mL cell with a 0.5 dm path length.

2.5.3 General Procedures

General procedure for synthesis of non-commercial phosphonic dichlorides:

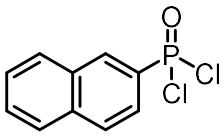


Conditions were adapted from a reported procedure for synthesis of phosphonic dichlorides.[17] An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with the aryl phosphonate ester (0.4 mmol, 1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with DCM (0.1 mL) and allowed to stir at room temperature for ~1 minute. Bromotrimethylsilane (158 µL, 1.2 mmol, 3 equiv.) was then added to the stirring solution via syringe through the septum. The resulting solution was then subjected to stirring 18 hours at room temperature. After subjection to stirring for 18 hours, the solution was concentrated under reduced pressure in the same vial, then subjected to high vacuum to remove the remaining bromotrimethylsilane and solvent. The vial was then capped with a new septum, sealed with electrical tape, and evacuated/backfilled three times with N_2. $SOCl_2$ (0.4 mL) and DMF (3 µL, 0.04 mmol, 0.1 equiv.) were then added to the vial via a syringe through the septum. The top of the vial was then sealed tightly with electrical tape. The solution was then subjected to stirring at 85 °C for 4 hours. Afterwards, the solution was cooled to room temperature. Without exposing the mixture to the atmosphere, the $SOCl_2$, HCl, and other volatiles were removed via a

[17] Schull, T. L.; Brandow, S. L.; Dressick, W. J. Synthesis of Symmetrical Triarylphosphines from Aryl Fluorides and Red Phosphorus: Scope and Limitations. *Tetrahedron Letters* **2001**, *42* (32), 5373–5376.

syringe needle inserted through the septum cap positioned above the solution and attached to a high-vacuum line. The resulting crude phosphonic dichloride was used immediately without further purification.

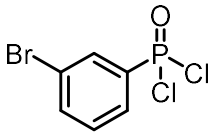
Naphthalen-2-ylphosphonic dichloride (2b)



2b

Following **General Procedure A**, phosphonic dichloride **2b** was prepared from diethyl naphthalen-2-ylphosphonate (106 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2b** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or detectable byproducts. ^{1}H NMR (400 MHz, C_6D_6) δ 8.39 (d, *J* = 18.5 Hz, 1H), 7.55 (ddd, *J* = 15.4, 8.6, 1.7 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.02 (m, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 135.34 (d, *J* = 3.5 Hz), 132.99 (d, *J* = 13.1 Hz), 132.06 (d, *J* = 59.4 Hz), 131.19 (d, *J* = 75.2 Hz), 129.41, 129.34, 129.32, 129.16, 127.38 (d, *J* = 1.8 Hz), 123.94 (d, *J* = 14.9 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.31.

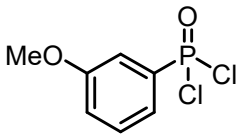
(3-bromophenyl)phosphonic dichloride (2c)



2c

Following **General Procedure A**, phosphonic dichloride **2c** was prepared from diethyl (3-bromophenyl)phosphonate (118 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2c** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.89 (dt, *J* = 18.0, 1.7 Hz, 1H), 7.41 (dd, *J* = 17.3, 7.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.56 (q, *J* = 7.6 Hz, 1H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 137.03 (d, *J* = 3.7 Hz), 136.52 (d, *J* = 153.5 Hz), 132.58 (d, *J* = 14.9 Hz), 130.44 (d, *J* = 19.6 Hz), 128.51 (d, *J* = 13.0 Hz), 123.06 (d, *J* = 24.0 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 30.18.

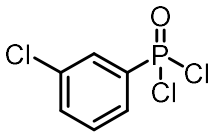
(3-methoxyphenyl)phosphonic dichloride (2d)



2d

Following **General Procedure A**, phosphonic dichloride **2d** was prepared from diethyl (3-methoxyphenyl)phosphonate (98 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2d** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 – 7.24 (m, 2H), 6.85 (q, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 3.10 (s, 3H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 159.61 (d, *J* = 23.2 Hz), 135.81 (d, *J* = 153.2 Hz), 130.19 (d, *J* = 22.1 Hz), 122.28 (d, *J* = 13.4 Hz), 120.75 (d, *J* = 4.0 Hz), 114.39 (d, *J* = 15.6 Hz), 54.71 ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.57.

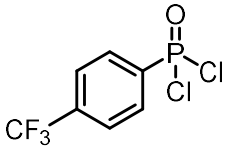
(3-chlorophenyl)phosphonic dichloride (2e)



2e

Following **General Procedure A**, phosphonic dichloride **2e** was prepared from diethyl (3-chlorophenyl)phosphonate (100 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2e** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.71 (dt, *J* = 18.4, 1.8 Hz, 1H), 7.36 (ddt, *J* = 17.3, 7.7, 1.3 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.60 (q, *J* = 7.7 Hz, 1H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 136.33 (d, *J* = 154.6 Hz), 135.14 (d, *J* = 24.8 Hz), 134.05 (d, *J* = 3.7 Hz), 130.23 (d, *J* = 20.0 Hz), 129.78 (d, *J* = 15.2 Hz), 128.10 (d, *J* = 12.7 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 30.53.

(4-(trifluoromethyl)phenyl)phosphonic dichloride (2f)



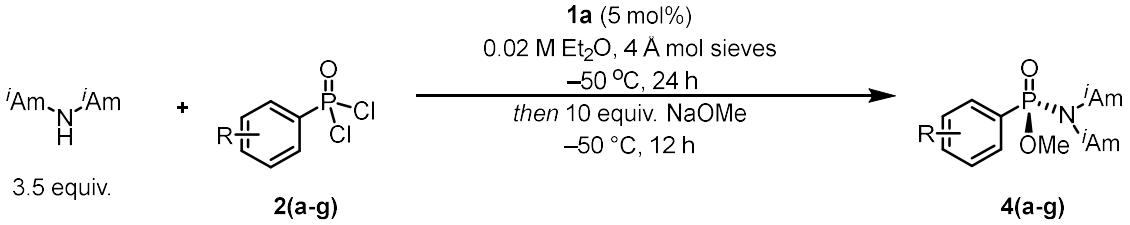
2f

Following **General Procedure A**, phosphonic dichloride **2f** was prepared from diethyl (4-(trifluoromethyl)phenyl)phosphonate (113 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2f** by ^{1}H and ^{31}P, ^{19}F, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (dd, *J* = 17.4, 8.0 Hz, 2H), 7.03 (dd, *J* = 8.2, 5.4 Hz, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 137.87 (d, *J* = 154.5 Hz), 134.91 (qd, *J* = 33.0, 4.3 Hz), 130.55

(d, *J* = 14.4 Hz), 125.59 (dq, *J* = 18.9, 3.7 Hz), 123.21 (dd, *J* = 273.2, 1.8 Hz) ; ^{19}F NMR (376 MHz, C_6D_6) δ -63.43 ; ^{31}P NMR (162 MHz, C_6D_6) δ 30.34.

General procedures for enantioselective, catalytic substitution of phosphonic dichlorides with amines:

General Procedure A: General procedure for the enantioselective substitution by amine followed by direct substitution by sodium methoxide *in situ.*



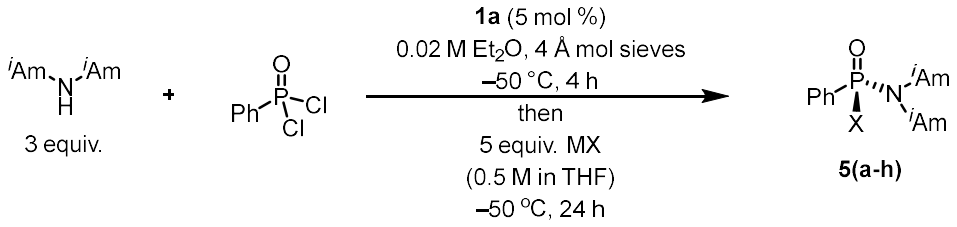
**Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves.*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. The aryl phosphonic dichloride (0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and the mixture was allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added

dropwise via a syringe through the septum over a 2-minute period to the stirring mixture, and stirring was continued at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above at –50 °C. The resulting reaction mixture was then subjected to stirring for 12 hours at –50 °C, and then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General Procedure B: General procedure for the enantioselective substitution by amine followed by direct substitution by a second nucleophile *in situ*



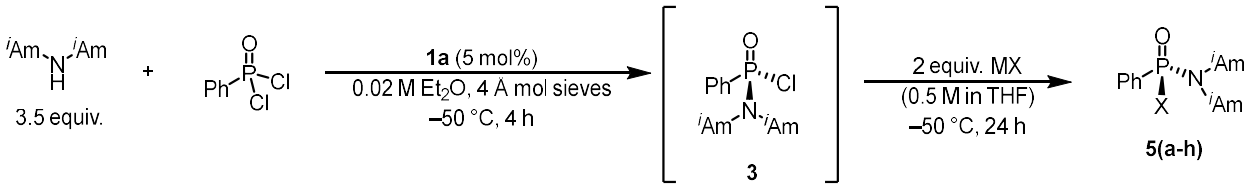
**Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves.*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. Phenyl phosphonic dichloride (28 µL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 to 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 120 mg of sodium

hydride (3 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and the resulting mixture was subjected to stirring at room temperature for 1 minute. The nucleophile (5 equiv., 1 mmol) dissolved in THF (0.5 mL) was then added dropwise over 2 min. via a syringe to the stirring sodium hydride mixture, and stirring was continued at room temperature for 30 minutes after addition. The resultant mixture was then added in a single portion directly to the catalytic reaction mixture generated as described above at –50 °C. The resultant mixture was then subjected to stirring for 24 hours at –50 °C. The mixture was then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General Procedure C: General procedure for the enantioselective substitution by amine followed by filtration and substitution by a second nucleophile in a separate step.



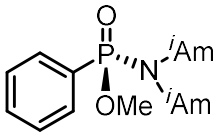
**Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves.*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. A solution of phenyl phoshonic dichloride (28 µL, 0.2 mmol, 1 equiv.) in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 hours. The mixture was

filtered at room temperature through ~10 grams of dry silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained (**Note: this product undergoes racemization when concentrated above room temperature**). The crude toluene solution of product **3** was then diluted with THF (1.5 mL) and transferred to an oven-dried 2-dram vial equipped with a magnetic stir bar and a septum cap. The vial was sealed with parafilm and put under N_2 atmosphere and allowed to stir at –50 °C for 20 minutes.

A separate oven-dried 2-dram vial equipped with a magnetic stir bar was charged with sodium hydride (48 mg,1.2 mmol, 6 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. THF (0.5 mL) was then added, and the resulting mixture was subjected to stirring at room temperature for ~1 minute. The nucleophile (2 equiv., 0.4 mmol) dissolved in THF (0.1 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period. The mixture was then allowed to stir at room temperature for 30 minutes to ensure full deprotonation of the nucleophile. The resultant mixture was then added directly to the stirred solution of chlorophosphonamidate produced as described above at –50 °C and stirring was continued at –50 °C for 24 hours. The mixture was then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

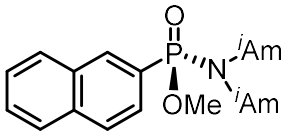
Methyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (4a)



4a

Following **General Procedure A**, phosphonamidate **4a** (59 mg, 94% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (ddd, *J* = 12.7, 8.2, 1.5 Hz, 2H), 7.53 – 7.35 (m, 3H), 3.72 (d, *J* = 11.0 Hz, 3H), 3.11 – 2.76 (m, 4H), 1.48 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.42 – 1.26 (m, 4H), 0.84 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.42 (d, *J* = 2.9 Hz), 131.41 (d, *J* = 9.4 Hz), 131.23 (d, *J* = 174.9 Hz), 128.30 (d, *J* = 14.1 Hz), 50.84 (d, *J* = 5.9 Hz), 43.26 (d, *J* = 4.6 Hz), 37.60 (d, *J* = 2.0 Hz), 26.01, 22.55 (d, *J* = 4.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.89 ; HRMS (ESI) m/z calcd for $C_{17}H_{31}NO_2P$ $(M+H)^+$: 312.2087; found: 312.2088. Phosphonamidate **4a** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 20.3 min, t_R(major) = 17.7 min).

Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(naphthalen-2-yl)phosphonamidate (4b)

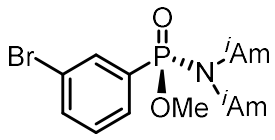


4b

Following **General Procedure A**, phosphonamidate **4b** (62 mg, 85% yield, 95% ee) was produced as a colorless oil from **2b** (0.2 mmol). The product was purified using flash chromatography on silica gel (0 to 100% EtOAc in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 14.6 Hz, 1H), 7.89 (dt, *J* = 12.1, 7.5 Hz, 2H), 7.73 (ddd, *J* = 10.3, 8.4, 1.5 Hz, 2H), 7.56 (pd, *J* = 7.0, 1.6 Hz, 2H), 3.77 (d, *J* = 11.1 Hz, 3H), 3.28 – 2.69 (m, 4H), 1.49 (dq, *J* = 13.5, 6.8 Hz, 2H), 1.44 – 1.28 (m, 4H), 0.84 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.57 (d, *J* = 2.6 Hz), 133.08 (d, *J* = 9.1 Hz), 132.53 (d, *J* = 15.4 Hz), 128.82, 128.41 (d, *J* = 174.9 Hz), 128.10 (d, *J* = 13.7 Hz), 127.76, 126.75, 126.66, 126.63 (d, *J* = 1.2 Hz), 50.98 (d, *J* = 5.9 Hz),

43.37 (d, *J* = 4.6 Hz), 37.67 (d, *J* = 2.0 Hz), 26.03, 22.56 (d, *J* = 4.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.91 ; HRMS (ESI) m/z calcd for $C_{21}H_{33}NO_2P$ $(M+H)^+$: 362.2243; found: 362.2245. Phosphonamidate **4b** was determined to be 95% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 23.2 min, t_R(major) = 20.8 min).

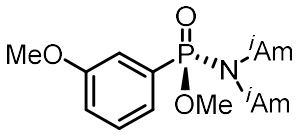
Methyl (*R*)-*P*-(3-bromophenyl)-*N*,*N*-diisopentylphosphonamidate (4c)



4c

Following **General Procedure A**, phosphonamidate **4c** (57.5 mg, 74% yield, 94% ee) was produced as a colorless oil from phosphonic dichloride **2c** (0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 12.9, 1.7 Hz, 1H), 7.69 – 7.55 (m, 2H), 7.31 (td, *J* = 7.8, 4.4 Hz, 1H), 3.73 (d, *J* = 11.2 Hz, 3H), 3.00 (ddd, *J* = 10.4, 8.9, 7.1 Hz, 4H), 1.49 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.34 (ttt, *J* = 12.7, 6.0, 3.4 Hz, 4H), 0.86 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.41 (d, *J* = 2.9 Hz), 134.19 (d, *J* = 10.1 Hz), 134.08 (d, *J* = 173.0 Hz), 130.02 (d, *J* = 15.0 Hz), 129.80 (d, *J* = 8.9 Hz), 122.75 (d, *J* = 18.6 Hz), 50.96 (d, *J* = 6.1 Hz), 43.25 (d, *J* = 4.7 Hz), 37.59 (d, *J* = 1.9 Hz), 26.00, 22.54 (d, *J* = 3.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.33 ; HRMS (ESI) m/z calcd for $C_{17}H_{30}BrNO_2P$ $(M+H)^+$: 390.1192; found: 390.1193. Phosphonamidate **4c** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 19.9 min, t_R(major) = 16.1 min).

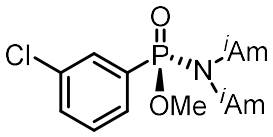
Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(3-methoxyphenyl)phosphonamidate (4d)



4d

Following **General Procedure A**, phosphonamidate **4d** (63 mg, 92% yield, 94% ee) was produced as a colorless oil from **2d** (0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 3H), 7.01 (ddd, *J* = 8.7, 2.3, 0.9 Hz, 1H), 3.83 (s, 3H), 3.72 (d, *J* = 11.1 Hz, 3H), 3.35 – 2.74 (m, 4H), 1.49 (dq, *J* = 13.1, 6.6 Hz, 4H), 1.41 – 1.28 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40 (d, *J* = 17.8 Hz), 132.55 (d, *J* = 173.9 Hz), 129.53 (d, *J* = 16.5 Hz), 123.65 (d, *J* = 9.0 Hz), 117.68 (d, *J* = 3.0 Hz), 116.20 (d, *J* = 10.7 Hz), 55.40, 50.92 (d, *J* = 6.0 Hz), 43.27 (d, *J* = 4.7 Hz), 37.59 (d, *J* = 1.9 Hz), 26.02, 22.57 (d, *J* = 4.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.72; HRMS (ESI) m/z calcd for $C_{18}H_{33}NO_3P$ $(M+H)^+$: 342.2193; found: 342.2193. Phosphonamidate **4d** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 29.7 min, t_R(major) = 23.5 min).

Methyl (*R*)-*P*-(3-chlorophenyl)-*N*,*N*-diisopentylphosphonamidate (4b)

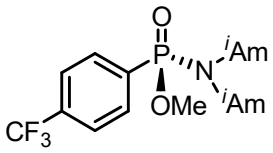


4e

Following **General Procedure A**, phosphonamidate **4e** (63 mg, 87% yield, 89% ee) was produced as a colorless oil from phosphonic dichloride **2e** (0.2 mmol). Product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 13.0, 1.8 Hz, 1H), 7.61 (ddt, *J* = 12.4, 7.5, 1.3 Hz, 1H), 7.45 (ddt, *J* =

8.1, 2.2, 1.1 Hz, 1H), 7.37 (td, *J* = 7.7, 4.3 Hz, 1H), 3.73 (d, *J* = 11.1 Hz, 3H), 3.00 (dddd, *J* = 10.8, 8.7, 6.7, 1.5 Hz, 4H), 1.49 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.34 (dddd, *J* = 19.2, 12.8, 8.7, 6.1 Hz, 4H), 0.86 (d, *J* = 6.6 Hz, 12H); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.66 (d, *J* = 7.1 Hz), 133.71 (d, *J* = 162.1 Hz), 131.50 (d, *J* = 2.9 Hz), 131.33 (d, *J* = 10.0 Hz), 129.78 (d, *J* = 15.4 Hz), 129.37 (d, *J* = 8.9 Hz), 50.95 (d, *J* = 6.0 Hz), 43.25 (d, *J* = 4.7 Hz), 37.59 (d, *J* = 1.9 Hz), 26.00, 22.54 (d, *J* = 3.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.63 ; HRMS (ESI) m/z calcd for $C_{17}H_{30}ClNO_2P$ $(M+H)^+$: 346.1697; found: 346.1698. Phosphonamidate **4e** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 19.2 min, t_R(major) = 15.2 min).

Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(4-(trifluoromethyl)phenyl)phosphonamidate (4f)



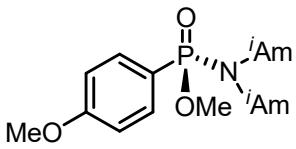
4f

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (20 mg, 0.04 mmol, 0.2 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –78 °C and subjected to stirring at that temperature for 20 minutes. Phosphonic dichloride **2f** (0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction was subjected to stirring at –78 °C for 18 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 80 mg of sodium hydride (2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and

allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and the solution was subjected to stirring at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly to the catalytic reaction at –78 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –50 °C, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 50% Et_2O in DCM) to afford the product. Phosphonamidate **4f** (76 mg, 89% yield, 92% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 12.3, 7.9 Hz, 2H), 7.69 (dd, *J* = 8.1, 3.2 Hz, 2H), 3.74 (d, *J* = 11.1 Hz, 3H), 3.18 – 2.80 (m, 4H), 1.56 – 1.23 (m, 6H), 0.85 (dd, *J* = 6.6, 1.0 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.86 (d, *J* = 173.0 Hz), 133.13 (qd, *J* = 32.6, 3.2 Hz), 131.77 (d, *J* = 9.5 Hz), 125.14 (dq, *J* = 14.2, 3.7 Hz), 123.70 (q, *J* = 818.0 Hz), 50.94 (d, *J* = 5.9 Hz), 43.24 (d, *J* = 4.7 Hz), 37.57 (d, *J* = 1.8 Hz), 25.99, 22.50 (d, *J* = 3.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.33 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.13 ; HRMS (ESI) m/z calcd for $C_{18}H_{30}F_3NO_2P$ $(M+H)^+$: 380.1961; found: 380.1960. Phosphonamidate **4f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 15.5 min, t_R(major) = 18.0 min).

Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(4-methoxyphenyl)phosphonamidate (4g)



4g

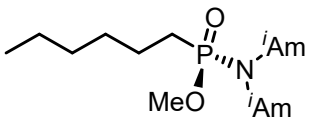
An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5

equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –40 °C and subjected to stirring at that temperature for 20 minutes. 4-methoxyphenyl phosphonic dichloride (32 µL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction was subjected to stirring at –40 °C for 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and the solution was subjected to stirring at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly to the catalytic reaction at –40 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –40 °C, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 100% Et_2O in DCM) to afford the product. Phosphonamidate **4g** (63 mg, 92% yield, 90% ee) was afforded as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.51 (m, 2H), 6.93 (dd, *J* = 8.8, 3.0 Hz, 2H), 3.84 (s, 3H), 3.69 (d, *J* = 11.0 Hz, 3H), 3.09 – 2.89 (m, 4H), 1.54 – 1.41 (m, 2H), 1.34 (ddt, *J* = 16.2, 12.9, 6.3 Hz, 4H), 0.85 (d, *J* = 6.5 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.08 (d, *J* = 3.2 Hz), 133.35 (d, *J* = 10.8 Hz), 122.53 (d, *J* = 181.8 Hz), 113.80 (d, *J* = 15.2 Hz), 55.28, 50.80 (d, *J* = 6.0 Hz), 43.29 (d, *J* = 4.7 Hz), 37.64 (d, *J* = 2.0 Hz), 26.03, 22.58 (d, *J* = 4.8 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.71 ; HRMS (ESI) m/z calcd for $C_{18}H_{33}NO_3P$ $(M+H)^+$: 342.2193; found: 342.2193. Phosphonamidate **4g** was determined to be 90% ee by chiral HPLC analysis (Chiralcel OD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 26.2 min, t_R(major) = 18.2 min).

Methyl (*R*)-*P*-hexyl-*N*,*N*-diisopentylphosphonamidate (4h)



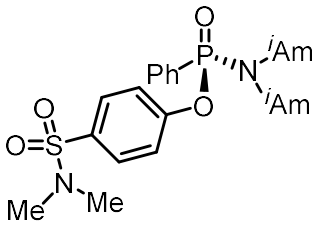
4h

Following **General Procedure A**, phosphonamidate **4h** (32.1 mg, 50% yield, 26% ee) was produced as a colorless oil from hexylphosphonic dichloride (34 µL, 0.2 mmol). Product **4h** was purified by flash chromatography on silica gel (0 to 60% Et_2O in Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, *J* = 10.9 Hz, 3H), 2.97 (td, *J* = 10.1, 6.5 Hz, 4H), 1.75 – 1.48 (m, 6H), 1.45 – 1.31 (m, 6H), 1.35 – 1.19 (m, 4H), 0.91 (d, *J* = 6.6 Hz, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 49.72 (d, *J* = 6.9 Hz), 42.96 (d, *J* = 4.3 Hz), 37.88 (d, *J* = 1.7 Hz), 31.40, 30.55 (d, *J* = 17.2 Hz), 26.53 (d, *J* = 131.1 Hz), 26.15, 22.64, 22.46, 22.35 (d, *J* = 4.1 Hz), 14.04; ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.97; HRMS (ESI) m/z calcd for $C_{17}H_{39}N_1O_2P_1$ $(M+H)^+$: 320.2713; found: 320.2712.

Phosphonamidate **4h** was determined to be 26% ee by chiral GC analysis (Cyclodex B 60 m x 0.25 mm x 0.25 µm, 1.0 °C/min, 100 °C to 200 °C, 7 psi), t_R(minor) = 33.1 min, t_R(major) = 31.4 min.

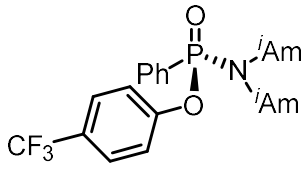
4-(*N*,*N*-dimethylsulfamoyl)phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (5a)



5a

Following **General Procedure C**, phosphonamidate **5a** (70 mg, 73% yield, 94% ee) was produced as a white solid from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and 4-hydroxy-*N*,*N*-dimethylbenzenesulfonamide (81 mg, 0.4 mmol, 2 equiv.). *NOTE: after addition of phenoxide solution, reaction was subjected to stirring at –30 °C instead of –50 °C.* The product was purified via flash chromatography on silica gel (0 to 100% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 2H), 7.78 – 7.66 (m, 2H), 7.62 – 7.53 (m, 1H), 7.49 (tdd, *J* = 7.0, 3.1, 1.8 Hz, 2H), 7.46 – 7.39 (m, 2H), 3.24 – 2.94 (m, 4H), 2.69 (s, 6H), 1.44 (h, *J* = 6.6 Hz, 2H), 1.37 – 1.17 (m, 4H), 0.81 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.94 (d, *J* = 7.6 Hz), 132.22 (d, *J* = 3.3 Hz), 131.50 (d, *J* = 9.9 Hz), 131.04 (d, *J* = 1.7 Hz), 129.68, 128.64 (d, *J* = 14.8 Hz), 128.46 (d, *J* = 164.2 Hz), 120.81 (d, *J* = 5.3 Hz), 43.16 (d, *J* = 4.5 Hz), 37.94, 37.27 (d, *J* = 2.2 Hz), 25.92, 22.50 (d, *J* = 7.7 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.44 ; HRMS (ESI) m/z calcd for $C_{24}H_{38}N_2O_4P$ $(M+H)^+$: 481.2284; found: 481.2282. Phosphonamidate **5a** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 46.9 min, t_R(major) = 41.8 min).

4-(trifluoromethyl)phenyl (R)-N,N-diisopentyl-P-phenylphosphonamidate (5b)



5b

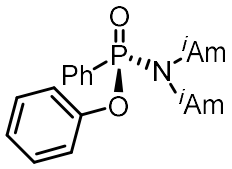
Following **General Procedure B** on 0.9 mmol scale, an oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (23 mg, 0.045 mmol), 4 Å mol sieves (800 mg), and diisoamylamine (0.65 mL, 3.15 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (45 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for

20 minutes. Phenyl phosphonic dichloride (126 μL, 0.9 mmol, 1 equiv.) dissolved in toluene (1 mL) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 4 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (0.54 g, 15 equiv, 13.5 mmol, 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (9 mL) and allowed to stir at room temperature for 1 minute. 4-(trifluoromethyl)phenol (729 mg, 4.5 mmol, 5 equiv.) dissolved in THF (1 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 5-minute period, and stirring was continued at room temperature for 30 minutes. The resultant 4-(trifluoromethyl)phenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 4 hours. The reaction was then subjected to stirring for 24 hours at –50 °C, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (0 to 40% Et_2O in Hexanes) to afford the product. Phosphonamidate **5b** (251 mg, 63% yield, 93% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.73 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.48 (ddd, *J* = 8.5, 6.5, 4.2 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.06 (dddd, *J* = 11.4, 8.9, 6.4, 2.0 Hz, 4H), 1.49 – 1.36 (m, 2H), 1.34 – 1.11 (m, 4H), 0.80 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.98 (d, *J* = 7.6 Hz), 132.07 (d, *J* = 3.1 Hz), 131.53 (d, *J* = 9.6 Hz), 130.41 (d, *J* = 179.1 Hz), 128.56 (d, *J* = 14.8 Hz), 126.95 (q, *J* = 3.8 Hz), 126.47 (q, *J* = 32.9 Hz), 124.02 (q, *J* = 271.7 Hz), 120.78 (d, *J* = 5.1 Hz), 43.10 (d, *J* = 4.6 Hz), 37.23 (d, *J* = 2.1 Hz), 25.91, 22.47 (d, *J* = 8.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.16 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.04 ; HRMS (ESI) m/z calcd for $C_{23}H_{32}F_3NO_2P$ $(M+H)^+$: 442.2117; found: 442.2117. Phosphonamidate **5b** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 27.4 min, t_R(major) = 32.8 min).

Following **General Procedure C**, phosphonamidate **5b** was produced as a colorless oil (52.3 mg, 59% yield, 93% ee) from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (24 mg, 3 mmol, 6 equiv., 60% in mineral oil), and 4-(trifluoromethyl)phenol (65 mg, 0.4 mmol, 2 equiv.).

Phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (5c)

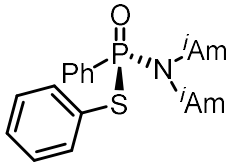


5c

Following **General Procedure C**, phosphonamidate **5c** (64 mg, 86% yield, 93% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and phenol (38 mg, 0.4 mmol, 2 equiv.). The product was purified via flash chromatography on silica gel (0 to 50% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.61 – 7.38 (m, 3H), 7.38 – 7.20 (m, 4H), 7.16 – 7.03 (m, 1H), 3.05 (dddd, *J* = 10.9, 8.7, 6.5, 1.5 Hz, 4H), 1.54 – 1.34 (m, 2H), 1.34 – 1.00 (m, 4H), 0.79 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.23 (d, *J* = 8.2 Hz), 131.70 (d, *J* = 3.0 Hz), 131.58 (d, *J* = 9.5 Hz), 131.15 (d, *J* = 179.2 Hz), 129.53, 128.39 (d, *J* = 14.5 Hz), 124.21, 120.54 (d, *J* = 5.0 Hz), 43.11 (d, *J* = 4.4 Hz), 37.20 (d, *J* = 2.1 Hz), 25.95, 22.51 (d, *J* = 7.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.20 ; HRMS (ESI) m/z calcd for $C_{22}H_{33}NO_2P$ $(M+H)^+$: 374.2243; found: 374.2242. Phosphonamidate **5c** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 26.6 min, t_R(major) = 21.1 min).

Following **General Procedure B** on 0.6 mmol scale, Phosphonamidate **5c** was produced as a colorless oil (211 mg, 94% yield, 93% ee) from phenyl phosphonic dichloride (84 µL, 0.6 mmol), diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.), sodium hydride (72 mg, 9 mmol, 6 equiv., 60% in mineral oil), and phenol (282 mg, 3 mmol, 5 equiv.).

***S*-phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidothioate (5d)**



5d

Following **General Procedure B** on 1 mmol scale, An oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (24 mg, 0.05 mmol), 4 Å mol sieves (800 mg), and diisoamylamine (0.72 mL, 3.5 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (50 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for 20 minutes at that temperature. Phenyl phosphonic dichloride (140 µL, 1 mmol, 1 equiv.) dissolved in toluene (1 mL) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 4 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (0.6 g, 15 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (10 mL) and allowed to stir at room temperature for 1 minute. Thiophenol (509 µL, 5 mmol, 5 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute

period, and stirring was continued at room temperature for 30 minutes. The resultant thiophenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 24 hours at –50 °C, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (0 to 40% Et_2O in Hexanes) to afford the product. Phosphonamidothioate **5d** (366 mg, 90% yield, 94% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.74 (m, 2H), 7.55 (ddt, *J* = 6.8, 3.0, 1.5 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.42 (tdd, *J* = 6.7, 3.8, 1.5 Hz, 2H), 7.25 – 7.19 (m, 3H), 3.25 – 2.80 (m, 4H), 1.53 – 1.29 (m, 4H), 1.18 (ddt, *J* = 12.7, 10.2, 6.3 Hz, 2H), 0.80 (dd, *J* = 6.6, 2.2 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.62 (d, *J* = 4.3 Hz), 133.03 (d, *J* = 136.0 Hz), 131.98 (d, *J* = 3.1 Hz), 131.80 (d, *J* = 10.0 Hz), 128.99 (d, *J* = 1.4 Hz), 128.34 (d, *J* = 14.1 Hz), 128.34 (d, *J* = 5.3 Hz), 128.19 (d, *J* = 2.1 Hz), 43.77 (d, *J* = 3.6 Hz), 37.53 (d, *J* = 2.6 Hz), 26.00, 22.51 (d, *J* = 8.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.82 ; HRMS (ESI) m/z calcd for $C_{22}H_{33}NOPS$ $(M+H)^+$: 390.2015; found: 390.2013. Phosphonamidothioate **5d** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 11.6 min, t_R(major) = 22.2 min).

Gram-scale synthesis of 5d*:*

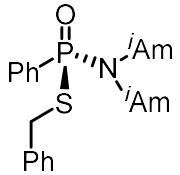
An oven-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (71 mg, 0.15 mmol), 4 Å mol sieves (2.6 g), and diisoamylamine (1.85 mL, 9 mmol, 3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (125 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for 20 minutes at that temperature. Phenyl phosphonic dichloride (0.42 mL, 3 mmol, 1 equiv.) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 12 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (1.8 g, 45 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with

parafilm, and put under N_2 atmosphere. The vial was then charged with THF (30 mL) and allowed to stir at room temperature for 1 minute. Thiophenol (1.6 mL, 5 mmol, 5 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 5-minute period, and stirring was continued at room temperature for 30 minutes. The resultant thiophenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –50 °C then warmed to room temperature while subjected to stirring. The reaction as then filtered through a fritted funnel packed with ~2 inches of silica gel to remove the solids, which was then washed with diethyl ether (250 mL). The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 25% EtOAc in Hexanes) to afford the product. Phosphonamidothioate **5d** (1.1095 g, 95% yield, 92% ee) was afforded as a colorless oil. Phosphonamidothioate **5d** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 11.6 min, t_R(major) = 21 min).

Following **General Procedure C**, phosphonamidothioate **5d** was produced as a colorless oil (48 mg, 62% yield, 93% ee) from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (24 mg, 3 mmol, 6 equiv., 60% in mineral oil), and thiophenol (41 µL, 0.4 mmol, 2 equiv.).

_S_-benzyl (_R_)-_N_,_N_-diisopentyl-_P_-phenylphosphonamidothioate (5e)

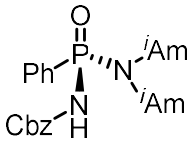


5e

Following **General Procedure B**, phosphonamidothioate **5e** (73 mg, 91% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (120 mg, 3 mmol, 15 equiv., 60% in mineral oil), and benzyl mercaptan (117 µL, 1 mmol, 5 equiv.). The product was purified via flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.81 (m, 2H), 7.55 – 7.38 (m, 3H), 7.29 – 7.13 (m, 5H), 4.14 – 3.77 (m, 2H), 3.08 – 2.89 (m, 4H), 1.51 – 1.19 (m, 6H), 0.80 (dd, *J* = 6.5, 4.7 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.83, 133.24 (d, *J* = 135.6 Hz), 131.99 (d, *J* = 10.6 Hz), 131.91 (d, *J* = 2.8 Hz), 129.01, 128.48, 128.37 (d, *J* = 14.1 Hz), 127.17, 43.79 (d, *J* = 3.8 Hz), 37.70 (d, *J* = 2.7 Hz), 34.48 (d, *J* = 2.5 Hz), 26.00, 22.49 (d, *J* = 7.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.57 ; HRMS (ESI) m/z calcd for $C_{23}H_{35}NOPS$ $(M+H)^+$: 404.2171; found: 404.2170. Phosphonamidothioate **5e** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK IB, 2% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 22.2 min, t_R(major) = 19.0 min).

Following **General Procedure C**, phosphonamidothioate **5e** was produced as a colorless oil (57.7 mg, 72% yield, 92% ee) from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (24 mg, 3 mmol, 6 equiv., 60% in mineral oil), and benzyl mercaptan (47 µL, 0.4 mmol, 2 equiv.).

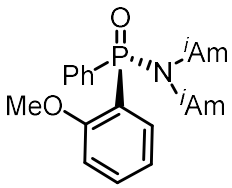
Benzyl (*R*)-((diisopentylamino)(phenyl)phosphoryl)carbamate (5f)



5f

Following **General Procedure B**, compound **5f** (64 mg, 75% yield, 92% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and benzyl carbamate (60 mg, 0.4 mmol, 2 equiv.). The product was purified via flash column chromatography (0 to 100% EtOAc in DCM). *NOTE: after addition of sodium benzyl carbamide mixture, reaction was subjected to stirring at –30 °C instead of –50 °C.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 13.5, 8.3, 1.4 Hz, 2H), 7.58 – 7.49 (m, 1H), 7.49 – 7.40 (m, 2H), 7.40 – 7.27 (m, 5H), 5.96 (s, 1H), 5.21 – 5.01 (m, 2H), 3.17 – 2.86 (m, 4H), 1.49 – 1.34 (m, 4H), 1.34 – 1.18 (m, 2H), 0.77 (t, *J* = 6.1 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.91 (d, *J* = 3.2 Hz), 135.49, 132.35 (d, *J* = 3.2 Hz), 132.02 (d, *J* = 10.3 Hz), 128.92 (d, *J* = 385.5 Hz), 128.46 (d, *J* = 7.4 Hz), 128.44 (d, *J* = 153.6 Hz), 128.42 (d, *J* = 34.3 Hz), 128.26 (d, *J* = 18.9 Hz), 67.67, 43.64 (d, *J* = 4.7 Hz), 37.35 (d, *J* = 2.6 Hz), 26.04, 22.47 (d, *J* = 10.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.96 ; HRMS (ESI) m/z calcd for $C_{24}H_{36}N_2O_3P$ $(M+H)^+$: 431.2458; found: 431.2454. Compound **5f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 22.3 min, t_R(major) = 16.5 min).

(*R*)-*N*,*N*-diisopentyl-*P*-(2-methoxyphenyl)-*P*-phenylphosphinic amide (5g)

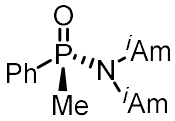


5g

Following **General Procedure C** (excluding the sodium hydride step), phosphinamidate **5g** (75 mg, 97% yield, 91% ee) was produced as a colorless oil from phenyl phosphonic dichloride (42 mg, 0.2 mmol), with the addition of 2-methoxyphenyl magnesium bromide (1 mL, 1 M solution in

THF, 5.0 equiv.) to the solution of **3** in THF at –50 °C. The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 13.5, 7.6, 1.8 Hz, 1H), 7.93 – 7.74 (m, 2H), 7.55 – 7.33 (m, 4H), 7.06 (tdd, *J* = 7.5, 2.1, 0.9 Hz, 1H), 6.91 – 6.82 (m, 1H), 3.74 (s, 3H), 3.19 – 2.80 (m, 4H), 1.53 – 1.29 (m, 6H), 0.74 (d, *J* = 6.2 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.44 (d, *J* = 3.2 Hz), 136.03 (d, *J* = 6.8 Hz), 134.07, 133.73 (d, *J* = 2.0 Hz), 132.67 (d, *J* = 10.2 Hz), 131.14 (d, *J* = 2.9 Hz), 127.77 (d, *J* = 12.9 Hz), 120.73 (d, *J* = 11.9 Hz), 120.38 (d, *J* = 123.5 Hz), 110.65 (d, *J* = 7.2 Hz), 54.95, 43.82 (d, *J* = 4.1 Hz), 37.61 (d, *J* = 3.0 Hz), 26.15, 22.53 (d, *J* = 2.7 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.34 ; HRMS (ESI) m/z calcd for $C_{23}H_{35}NO_2P$ $(M+H)^+$: 388.2400; found: 388.2397. Phosphinamidate **5g** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK AD-H, 4% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 67.4 min, t_R(major) = 42.7 min).

(*S*)-*N*,*N*-diisopentyl-*P*-methyl-*P*-phenylphosphinic amide (5h)



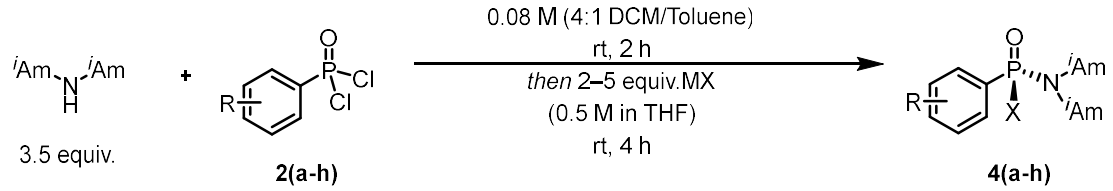
5h

Following **General Procedure C** (excluding the sodium hydride step), phosphinamidate **5h** (55 mg, 94% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), with the addition of methylmagnesium chloride (0.5 mL, 2 M solution in THF, 5 equiv.) to the solution of **3** in THF at –50 °C. The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (ddt, *J* = 11.8, 8.3, 1.8 Hz, 2H), 7.46 (dddd, *J* = 14.0, 9.0, 6.7, 2.1 Hz, 3H), 2.94 (tdd, *J* = 10.9, 5.6, 2.9 Hz, 4H), 1.70 (dd, *J* = 13.6, 3.1 Hz, 3H), 1.53 – 1.29 (m, 6H), 0.81 (dt, *J* = 6.4, 2.2 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.90 (d, *J* = 125.8 Hz), 131.46, 131.39 (d, *J* = 9.4 Hz), 128.38 (d, *J* = 12.3 Hz),

43.99 (d, *J* = 3.2 Hz), 38.06 (d, *J* = 3.2 Hz), 26.09, 22.51 (d, *J* = 7.4 Hz), 15.30 (d, *J* = 93.4 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.81 ; HRMS (ESI) m/z calcd for $C_{17}H_{31}NOP$ $(M+H)^+$: 296.2138; found: 296.2138. Phosphinamidate **5h** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 20.2 min, t_R(major) = 23.5 min).

Synthesis of racemic amine substitution products:

General Procedure D:



An oven-dried 20 mL vial equipped with a magnetic stir bar was charged with diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with DCM (2 mL), followed by 0.2 mmol of aryl phosphonic dichloride (**2a-g**) dissolved in toluene (0.5 mL), and the reaction mixture was subjected to stirring at room temperature for 2 hours, or until reaction completion. The reaction was then quenched according to one of the following procedures:

For racemic standards of **4a–g**:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 80 mg of sodium hydride (2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period, and the solution was

subjected to stirring at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above. The reaction mixture was then subjected to stirring for 4 hours at room temperature, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

For racemic standards of **5a**–**e**:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (120 mg, 3 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and allowed to stir at room temperature for 1 minute. The nucleophile (5 equiv., 1 mmol) dissolved in THF (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature for 30 minutes. The resultant mixture was then added directly as a single portion directly to the solution of chlorophosphonamidate **3** stirring in DCM. The resultant mixture was then subjected to stirring for 4 hours at room temperature. Afterwards, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

For racemic standard of **5f**:

Upon reaction completion, the mixture was filtered through ~10 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. The crude phosphonamidate in toluene (**3**) was then dissolved in THF (2 mL) and transferred to an oven-dried 2-dram vial

equipped with a magnetic stir bar and capped with a septum. The vial was sealed with parafilm and put under a N_2 atmosphere and allowed to stir at room temperature for ~1 minute.

A separate oven-dried 2-dram vial equipped with a magnetic stir bar was charged with sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. THF (0.5 mL) was then added, and the mixture was allowed to stir at room temperature for ~1 minute. Benzyl carbamate (60 mg, 0.4 mmol, 2 equiv.) dissolved in THF (0.2 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period. The mixture was then allowed to stir at room temperature for 30 minutes to ensure full deprotonation of the nucleophile. The resultant mixture was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above. The resultant mixture was subjected to stirring at room temperature for 4 hours. Upon completion, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

For racemic standards of **5g–h**:

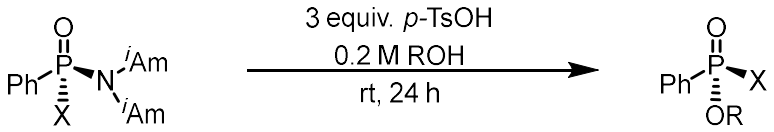
Upon reaction completion, the mixture was filtered through ~10 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. The crude product in toluene (**3**) was then dissolved in THF (2 mL) and transferred to an oven-dried 2-dram vial equipped with a magnetic stir bar and capped with a septum. The vial was sealed with parafilm and put under N_2 atmosphere and allowed to stir at room temperature for ~1 minute.

The Grignard reagent (5 equiv., 0.4 mmol) was then added in a single portion to the solution of chlorophosphonamidate **3** stirring in THF. The reaction was subsequently subjected to stirring at

room temperature for 4 hours. Upon completion, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General procedure for the displacement of the diisoamylamino group with alcohols:

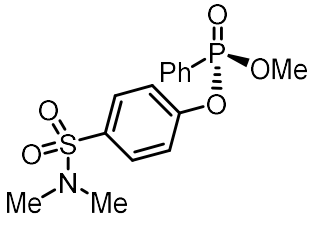
General Procedure E:



6(a-i)

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with the substrate (**5a-h**). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. A 0.6 M solution of *para*-tolylsulfonic acid monohydrate (3 equiv.) in the corresponding alcohol was then added through the septum, and the reaction was allowed to stir at room temperature for 24 hours. *Do not concentrate*. After 24 hours, the methanol solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

4-(*N*,*N*-dimethylsulfamoyl)phenyl methyl (*R*)-phenylphosphonate (6a)

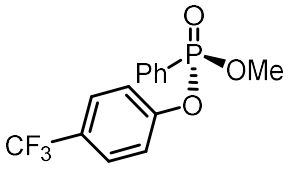


6a

Following **General Procedure E**, phosphonate **6a** (33 mg, 93% yield, 93% ee) was produced as a colorless oil from phosphonamidate **5a** (48 mg, 0.1 mmol, 94% ee), methanol (0.5 mL), and

para-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddt, *J* = 13.9, 6.9, 1.4 Hz, 2H), 7.80 – 7.67 (m, 2H), 7.67 – 7.57 (m, 1H), 7.51 (ddd, *J* = 8.6, 7.0, 4.6 Hz, 2H), 7.41 – 7.29 (m, 2H), 3.90 (d, *J* = 11.4 Hz, 3H), 2.69 (s, 6H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.97 (d, *J* = 6.8 Hz), 133.42 (d, *J* = 3.1 Hz), 132.04 (d, *J* = 10.3 Hz), 132.03, 129.74, 128.83 (d, *J* = 15.7 Hz), 126.14 (d, *J* = 191.6 Hz), 120.96 (d, *J* = 4.8 Hz), 53.34 (d, *J* = 5.9 Hz), 37.89 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.34 ; HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_5PS$ $(M+H)^+$: 356.0716; found: 356.0716. Phosphonate **6a** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 20% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 24.7 min, t_R(major) = 20.4 min).

Methyl (4-(trifluoromethyl)phenyl) (*R*)-phenylphosphonate (6b)

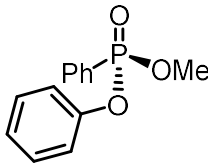


6b

Following **General Procedure E**, phosphonate **6b** (132 mg, 74% yield, 93% ee) was produced as a colorless oil from phosphonamidate **5b** (251 mg, 0.57 mmol), methanol (2.8 mL), and *para*-tolylsulfonic acid monohydrate (325 mg, 1.71 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 50% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 13.8, 8.3, 1.4 Hz, 2H), 7.67 – 7.44 (m, 5H), 7.29 (d, *J* = 8.6 Hz, 2H), 3.89 (d, *J* = 11.4 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.13 (d, *J* = 6.5 Hz), 133.29 (d, *J* = 3.1 Hz), 132.05 (d, *J* = 10.2 Hz), 128.76 (d, *J* = 15.6 Hz), 127.19 (q, *J* = 32.5 Hz), 127.11 (q, *J* = 3.8 Hz), 126.33 (d, *J* = 191.5 Hz), 123.86 (q, *J* = 271.8 Hz), 120.83 (d, *J* = 4.6 Hz), 53.26 (d, *J* = 5.8 Hz) ; ^{19}F NMR (376 MHz,

$CDCl_3$) δ -62.18 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.21 ; HRMS (ESI) m/z calcd for $C_{14}H_{13}F_3O_3P$ $(M+H)^+$: 317.0549; found: 317.0550. Phosphonate **6b** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 26.2 min, t_R(major) = 22.6 min).

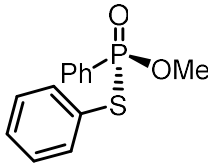
Methyl phenyl (*R*)-phenylphosphonate (6c)



6c

Following **General Procedure E**, phosphonate **6c** (55 mg, 92%; 93% ee) was produced as a colorless oil from phosphonamidate **5c** (90 mg, 0.24 mmol, 93% ee), methanol (1.2 mL), and *para*-tolylsulfonic acid monohydrate (137 mg) with a 24-hour reaction time. The product was purified via flash column chromatography (0 to 60% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.67 – 7.54 (m, 1H), 7.53 – 7.43 (m, 2H), 7.33 – 7.24 (m, 3H), 7.17 – 7.09 (m, 2H), 3.87 (d, *J* = 11.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.56 (d, *J* = 7.2 Hz), 132.92 (d, *J* = 3.1 Hz), 132.08 (d, *J* = 10.2 Hz), 129.69, 128.59 (d, *J* = 15.5 Hz), 126.98 (d, *J* = 191.1 Hz), 124.90, 120.51 (d, *J* = 4.5 Hz), 53.10 (d, *J* = 5.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.82 ; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_3P$ $(M+H)^+$: 249.0675; found: 249.0675. Phosphonate **6c** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 29.0 min, t_R(major) = 23.2 min).

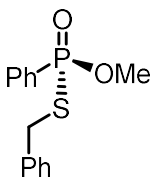
***O*-methyl *S*-phenyl (*R*)-phenylphosphonothioate (6d)**



6d

Following **General Procedure E**, phosphonothioate **6d** (197 mg, 82% yield, 93% ee) was produced as a colorless oil from phosphonamidothioate **5d** (350 mg, 0.9 mmol, 94% ee), methanol (3 mL), and *para*-tolylsulfonic acid monohydrate (513 mg, 27 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 60% Et_2O in Hexanes). *Note: this product must be stored under inert atmosphere below 0 °C, preferably at –80 °C.* ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 2H), 7.55 – 7.45 (m, 1H), 7.37 (ddd, *J* = 8.9, 7.0, 4.6 Hz, 2H), 7.29 (ddt, *J* = 7.0, 3.8, 1.4 Hz, 3H), 7.24 – 7.17 (m, 2H), 3.95 (d, *J* = 12.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.53 (d, *J* = 4.3 Hz), 132.61 (d, *J* = 3.3 Hz), 131.47 (d, *J* = 10.6 Hz), 131.00 (d, *J* = 151.1 Hz), 129.20 (d, *J* = 2.3 Hz), 129.05 (d, *J* = 2.9 Hz), 128.23 (d, *J* = 15.1 Hz), 126.48 (d, *J* = 5.7 Hz), 52.44 (d, *J* = 7.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.65 ; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_2PS$ $(M+H)^+$: 265.0447; found: 265.0448. Phosphonothioate **6d** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 26.9 min, t_R(major) = 30.7 min).

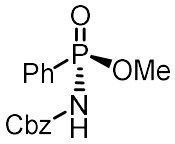
***S*-benzyl *O*-methyl (*R*)-phenylphosphonothioate (6e)**



6e

Following **General Procedure E**, phosphonothioate **6e** (21.4 mg, 79% yield, 92% ee) was produced as a colorless oil from phosphonamidothioate **5e** (39 mg, 0.1 mmol, 94% ee, prepared via **General Procedure B**), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 60% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.72 (m, 2H), 7.64 – 7.53 (m, 1H), 7.48 (ddd, *J* = 8.4, 6.8, 4.4 Hz, 2H), 7.32 – 7.09 (m, 5H), 4.11 – 3.89 (m, 2H), 3.81 (d, *J* = 12.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.23 (d, *J* = 5.1 Hz), 132.62 (d, *J* = 3.3 Hz), 132.07 (d, *J* = 151.1 Hz), 131.19 (d, *J* = 10.9 Hz), 128.74 (d, *J* = 29.5 Hz), 128.63, 128.48, 127.49, 52.23 (d, *J* = 6.9 Hz), 34.49 (d, *J* = 2.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.65 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2PS$ $(M+H)^+$: 279.0603; found: 279.0604. Phosphonothioate **6e** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AS-H, 5% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 37.2 min, t_R(major) = 43.6 min).

Benzyl (*R*)-(methoxy(phenyl)phosphoryl)carbamate (6f)

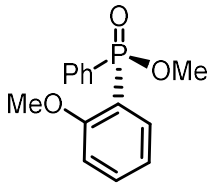


6f

Following **General Procedure E**, phosphonamidate **6f** (27 mg, 86% yield, 92% ee) was produced as a colorless solid from compound **5f** (43 mg, 0.1 mmol, 92% ee), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (ddt, *J* = 14.0, 6.8, 1.4 Hz, 2H), 7.57 (td, *J* = 7.4, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.7, 7.0, 4.4 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.23 (dd, *J* = 6.7, 3.0 Hz, 2H), 6.30 (d, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 2.3 Hz, 2H),

3.84 (d, *J* = 11.7 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.86 (d, *J* = 5.3 Hz), 135.11, 132.92 (d, *J* = 3.2 Hz), 132.06 (d, *J* = 10.7 Hz), 128.59, 128.49, 128.34, 128.21, 128.02 (d, *J* = 182.0 Hz), 67.96, 52.04 (d, *J* = 6.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.09 ; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_4P$ $(M+H)^+$: 306.0890; found: 306.0890. Phosphonamidate **6f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IB, 10% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 15.3 min, t_R(major) = 18.6 min).

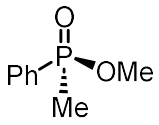
Methyl (*R*)-(2-methoxyphenyl)(phenyl)phosphinate (6g)



6g

Following **General Procedure E**, phosphinate **6g** (18 mg, 70% yield, 87% ee) was produced as a colorless oil from phosphinamidate **5g** (39 mg, 0.1 mmol), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 13.3, 7.6, 1.8 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.50 (dddd, *J* = 9.5, 6.7, 2.3, 1.1 Hz, 2H), 7.46 – 7.36 (m, 2H), 7.07 (tdd, *J* = 7.5, 2.6, 0.9 Hz, 1H), 6.87 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 3H), 3.71 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.01 (d, *J* = 3.9 Hz), 134.81 (d, *J* = 6.3 Hz), 134.46 (d, *J* = 2.0 Hz), 132.00 (d, *J* = 142.6 Hz), 131.86, 131.79, 131.76, 128.04 (d, *J* = 13.6 Hz), 120.66 (d, *J* = 12.3 Hz), 111.26 (d, *J* = 7.9 Hz), 55.53, 51.42 (d, *J* = 6.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.72 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_3P$ $(M+H)^+$: 263.0832; found: 263.0833. Phosphinate **6g** was determined to be 87% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 57.8 min, t_R(major) = 48.4 min).

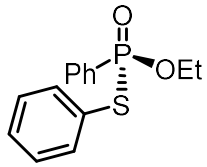
Methyl (*S*)-methyl(phenyl)phosphinate (6h)



6h

Phosphinamidate **5h** (29.5 mg, 0.1 mmol, 1 equiv.) was added to a 1-dram vial equipped with a magnetic stir bar. 25 mg of H_3PO_3 (0.3 mmol, 3 equiv.) was then dissolved in methanol (1 mL) and added to the vial, which was then capped with a septum and sealed with parafilm. The resulting solution was subjected to stirring at room temperature for 48 hours. The product was then purified via flash column chromatography on silica gel (0 to 10% MeOH in DCM). Phosphinate **6h** (8 mg, 48% yield, 89% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 2H), 7.62 – 7.52 (m, 1H), 7.55 – 7.42 (m, 2H), 3.61 (d, *J* = 11.3 Hz, 3H), 1.67 (d, *J* = 14.6 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.37 (d, *J* = 2.8 Hz), 131.33 (d, *J* = 10.2 Hz), 131.04 (d, *J* = 126.8 Hz), 128.72 (d, *J* = 12.6 Hz), 51.04 (d, *J* = 6.2 Hz), 15.53 (d, *J* = 103.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.07 ; HRMS (ESI) m/z calcd for $C_8H_{12}O_2P$ $(M+H)^+$: 171.0569; found: 171.0569. Phosphinate **6h** was determined to be 89% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 43.2 min, t_R(major) = 32.2 min).

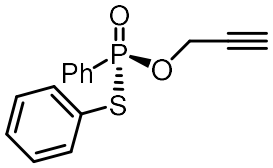
***O*-ethyl *S*-phenyl (*R*)-phenylphosphonothioate (6i)**



6i

Following **General Procedure E**, phosphonothioate **6i** (14 mg, 58% yield, 92% ee) was produced as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), ethanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 72-hour reaction time. The product was purified via flash column chromatography (slow gradient of 0 to 60% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddt, *J* = 13.6, 6.8, 1.4 Hz, 2H), 7.56 – 7.44 (m, 1H), 7.44 – 7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 7.20 (dd, *J* = 8.3, 6.3 Hz, 2H), 4.64 – 4.14 (m, 2H), 1.49 – 1.34 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.52 (d, *J* = 4.3 Hz), 132.49 (d, *J* = 3.2 Hz), 131.56 (d, *J* = 150.6 Hz), 131.46 (d, *J* = 10.7 Hz), 129.12 (d, *J* = 2.3 Hz), 128.97 (d, *J* = 2.7 Hz), 128.20 (d, *J* = 14.9 Hz), 126.68 (d, *J* = 5.6 Hz), 62.47 (d, *J* = 6.9 Hz), 16.35 (d, *J* = 6.8 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.66 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2PS$ $(M+H)^+$: 279.0603; found: 279.0604. Phosphonothioate **6i** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 11.2 min, t_R(major) = 14.6 min).

_S_-phenyl _O_-(prop-2-yn-1-yl) (_R_)-phenylphosphonothioate (6j)

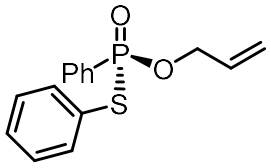


6j

Following **General Procedure E**, phosphonothioate **6j** (14 mg, 49% yield, 81% ee) was produced as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), propargyl alcohol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 48-hour reaction time. The product was purified via flash column chromatography (slow gradient of 0 to 50% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (ddt, *J* = 13.9, 6.8, 1.4 Hz, 2H), 7.58 – 7.44 (m, 1H), 7.41 – 7.27 (m, 5H), 7.22 (dd, *J* = 8.3, 6.9 Hz, 2H), 5.07 – 4.68 (m, 2H), 2.58 (t, *J* =

2.5 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.73 (d, *J* = 4.3 Hz), 132.83 (d, *J* = 3.3 Hz), 131.49 (d, *J* = 10.9 Hz), 130.68 (d, *J* = 148.8 Hz), 129.25 (d, *J* = 1.9 Hz), 129.22 (d, *J* = 2.5 Hz), 128.28 (d, *J* = 15.0 Hz), 125.91 (d, *J* = 5.7 Hz), 77.66 (d, *J* = 9.2 Hz), 76.27, 53.32 (d, *J* = 5.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.39 ; HRMS (ESI) m/z calcd for $C_{15}H_{14}O_2PS$ $(M+H)^+$: 289.0447; found: 289.0447. Phosphonothioate **6j** was determined to be 81% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 29.6 min, t_R(major) = 31.7 min).

***O*-allyl *S*-phenyl (*R*)-phenylphosphonothioate (6k)**



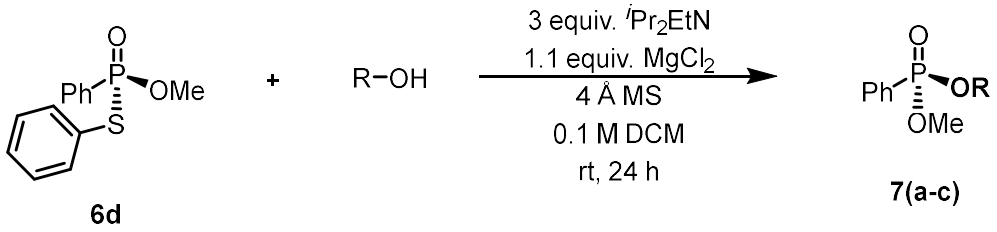
6k

Following **General Procedure E**, phosphonothioate **6k** (16 mg, 55% yield, 91% ee) was afforded as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), allyl alcohol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 48-hour reaction time. The product was purified via flash column chromatography on silica gel (slow gradient of 0 to 50% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (ddt, *J* = 13.6, 6.9, 1.3 Hz, 2H), 7.51 – 7.40 (m, 1H), 7.34 (tdd, *J* = 7.8, 5.5, 3.1 Hz, 2H), 7.30 – 7.22 (m, 3H), 7.17 (dd, *J* = 8.5, 6.6 Hz, 2H), 5.96 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.74 (ddt, *J* = 8.4, 5.5, 1.4 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.61 (d, *J* = 4.2 Hz), 132.60 (d, *J* = 3.3 Hz), 132.51 (d, *J* = 7.5 Hz), 131.47 (d, *J* = 10.6 Hz), 131.30 (d, *J* = 150.1 Hz), 129.16 (d, *J* = 2.3 Hz), 129.05 (d, *J* = 2.9 Hz), 128.24 (d, *J* = 15.0 Hz), 126.44 (d, *J* = 5.7 Hz), 118.46, 66.41 (d, *J* = 6.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.47 ; HRMS (ESI) m/z calcd for

$C_{15}H_{16}O_2PS$ $(M+H)^+$: 291.0603; found: 291.0605. Phosphonothioate **6k** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 19.9 min, t_R(major) = 22.9 min).

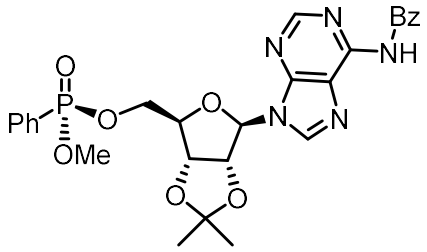
General procedure for the phosphonylation of alcohols with phosphonothioate 6d:

General Procedure F:



An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $MgCl_2$ (10 mg, 0.11 mmol, 1.1 equiv.), 4 Å mol sieves (50 mg), and the alcohol to be phosphonylated. The vial was capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with DCM (0.7 mL) followed by *N*,*N*-diisopropylethylamine (52 µL, 0.3 mmol, 3 equiv.). The solution was allowed to stir at room temperature for ~1 minute. Then phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) dissolved in DCM (0.3 mL) was added in one portion through the septum cap. The reaction was then allowed to stir at room temperature for 24 hours. *Do not concentrate*. After 24 hours, the solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

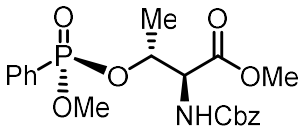
((3a*R*,4*R*,6*R*,6a*R*)-6-(6-benzamido-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl methyl (*S*)-phenylphosphonate (7a)



7a

Following **General Procedure F**, phosphonate **7a** (32.3 mg, 57% yield, 27:1 dr) was produced as a white solid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and N6-Benzoyl-2',3'-isopropylideneadenosine (41 mg, 0.1 mmol, 1 equiv.). The product was purified via flash chromatography on silica gel. First, ten column volumes of 100% ethyl acetate were passed through the column to remove thiophenol and any remaining starting materials. Then, a gradient of 0 to 10% MeOH in DCM was used to elute the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.74 (s, 1H), 8.17 (s, 1H), 8.07 – 7.99 (m, 2H), 7.77 – 7.65 (m, 2H), 7.64 – 7.59 (m, 1H), 7.58 – 7.49 (m, 3H), 7.40 (td, *J* = 7.7, 4.4 Hz, 2H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.43 (dd, *J* = 6.2, 2.5 Hz, 1H), 5.10 (dd, *J* = 6.3, 2.8 Hz, 1H), 4.55 (td, *J* = 4.4, 2.6 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.68 (d, *J* = 11.2 Hz, 3H), 1.62 (s, 3H), 1.41 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.72, 151.13, 149.59, 141.89, 133.59, 133.00 (d, *J* = 3.0 Hz), 132.89, 131.81 (d, *J* = 10.1 Hz), 128.93, 128.62 (d, *J* = 15.2 Hz), 127.88, 126.21 (d, *J* = 188.2 Hz), 123.41, 114.70, 91.54, 85.59 (d, *J* = 7.4 Hz), 84.34, 81.51, 65.23 (d, *J* = 5.2 Hz), 52.95 (d, *J* = 5.2 Hz), 27.16, 25.38 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.14. HRMS (ESI) m/z calcd for $C_{27}H_{29}N_5O_7P$ $(M+H)^+$: 566.1799; found: 566.1794. D.r. of phosphonate **7a** was determined to be 27:1 by ^{31}P NMR 162 MHz, $CDCl_3$ with a 10-second relaxation delay. (Major: δ 21.14, Minor: δ 21.29).

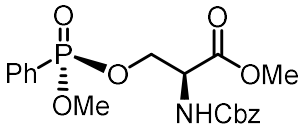
Methyl *N*-((benzyloxy)carbonyl)-*O*-((*S*)-methoxy(phenyl)phosphoryl)-*L*-threoninate (7b)



7b

Following **General Procedure F**, phosphonate **7b** (29 mg, 70% yield, 23:1 dr) was produced as a colorless liquid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and *N*-Z-L-threonine methyl ester (33 mg, 0.125 mmol, 1.25 equiv.). The product was purified via flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes with 50% DCM additive throughout). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 13.5, 8.2, 1.4 Hz, 2H), 7.50 – 7.40 (m, 1H), 7.35 (ddd, *J* = 8.4, 7.0, 4.5 Hz, 2H), 7.33 – 7.08 (m, 5H), 5.48 (d, *J* = 9.6 Hz, 1H), 5.07 – 4.94 (m, 3H), 4.32 (dt, *J* = 9.6, 2.2 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 3H), 3.31 (s, 3H), 1.38 (d, *J* = 6.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.87, 156.56, 136.05, 132.71 (d, *J* = 3.1 Hz), 131.81 (d, *J* = 10.0 Hz), 128.61, 128.58, 128.37 (d, *J* = 16.8 Hz), 128.15, 125.90 (d, *J* = 74.8 Hz), 73.85 (d, *J* = 5.6 Hz), 67.35, 58.60 (d, *J* = 6.8 Hz), 52.56 (d, *J* = 5.6 Hz), 52.43, 19.31 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.35; HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_7P$ $(M+H)^+$: 422.1363; found: 422.1362. Phosphonate **7b** was determined to be 23:1 d.r. by ^{31}P NMR 162 MHz, $CDCl_3$ with a 10-second relaxation delay (Major: δ 20.34, Minor: δ 19.75).

Methyl *N*-((benzyloxy)carbonyl)-*O*-((*S*)-methoxy(phenyl)phosphoryl)-*L*-serinate (7c)



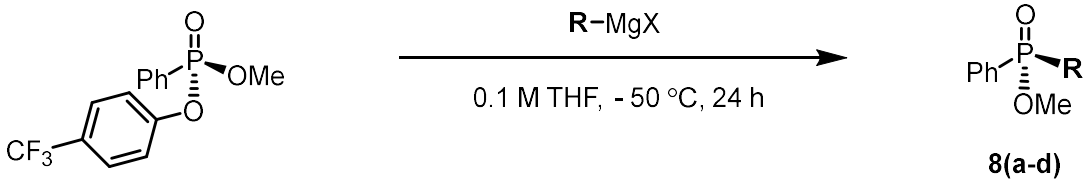
7c

Following **General Procedure F**, phosphonate **7c** (21 mg, 52% yield, 31:1 dr) was produced as a colorless liquid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and *N*-Z-L-serine

methyl ester (32 mg, 0.125 mmol, 1.25 equiv.). The product was purified via flash column chromatography on silica gel (slow gradient of 0 to 100% Et_2O in Hexanes with 50% DCM additive throughout). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (ddd, *J* = 13.5, 8.3, 1.4 Hz, 2H), 7.65 – 7.53 (m, 1H), 7.46 (ddd, *J* = 8.6, 6.9, 4.4 Hz, 2H), 7.40 – 7.28 (m, 5H), 6.01 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.57 (dd, *J* = 6.9, 3.7 Hz, 1H), 4.44 (ddd, *J* = 10.9, 8.9, 3.4 Hz, 1H), 4.33 (ddd, *J* = 10.8, 6.5, 2.9 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 3H), 3.68 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.52, 155.89, 136.15, 132.96 (d, *J* = 3.1 Hz), 131.88 (d, *J* = 10.1 Hz), 128.65 (d, *J* = 15.3 Hz), 128.55, 128.23, 128.14, 126.44 (d, *J* = 190.0 Hz), 67.18, 65.84 (d, *J* = 4.9 Hz), 54.55 (d, *J* = 6.0 Hz), 52.88 (d, *J* = 5.6 Hz), 29.72 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.42 ; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_7P$ $(M+H)^+$: 408.1207; found: 408.1204. Phosphonate **7c** was determined to be 31:1 d.r. by ^{31}P NMR (162 MHz, $CDCl_3$) with a 10-second relaxation delay (Major: δ 21.42, Minor: δ 21.09).

General procedure for the reaction of Grignard reagents with phosphonate 6b:

General Procedure G:

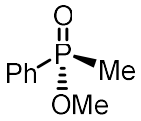


6b **8(a-d)**

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with phosphonate **6b** (1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (0.1 M) and allowed to stir at room temperature for ~1 minute. The solution was then cooled and subjected to stirring at –50 °C for 20 minutes. Next, the Grignard reagent was added through the septum cap, and the reaction mixture was then allowed to stir at –50 °C for 24 hours. After 24 hours had elapsed, isopropanol (50 µL) was added

to the solution at –50 °C to quench any remaining Grignard reagent. The resultant solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

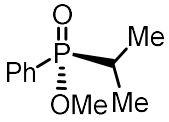
Methyl (*R*)-methyl(phenyl)phosphinate (8a)



8a

Following **General Procedure G**, phosphinate **8a** (15 mg, 88% yield, 92% ee) was produced as a colorless oil from phosphonate **6b** (32 mg, 0.1 mmol, 93% ee) and methylmagnesium chloride (50 µL, 0.1 mmol, 1 equiv., 2 M solution in THF). The product was purified using flash column chromatography on silica gel (0 to 10% MeOH in DCM). Phosphinate **8a** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 34.8 min, t_R(major) = 45.0 min). $[\alpha]^{22}$= +87.5 (c = 4 mg/mL, C_6H_6). Absolute stereochemistry was assigned by comparison to literature value.[6a]

Isopropyl (*R*)-methyl(phenyl)phosphinate (8b)

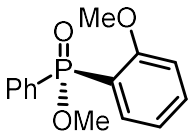


8b

Following **General Procedure G**, phosphinate **8b** (9.4 mg, 95% yield, 91% ee) was produced as a colorless oil from phosphonate **6b** (16 mg, 0.05 mmol, 92% ee) and isopropylmagnesium chloride lithium chloride complex (120 µL, 0.06 mmol, 1.2 equiv., 0.5 M solution in THF). The product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.96 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.46 (tdd, *J* = 7.1, 4.2, 1.9 Hz, 2H), 4.74 (dhept, *J* = 7.7, 6.2 Hz, 1H), 3.72 (d, *J* = 11.2 Hz, 3H), 1.39 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.35 (d, *J* = 3.1 Hz), 131.80 (d, *J* = 9.8 Hz), 128.45 (d, *J* = 188.7 Hz), 128.45 (d, *J* = 15.0 Hz), 71.13 (d, *J* = 5.7 Hz), 52.39 (d, *J* = 5.5 Hz), 23.97 (dd, *J* = 22.9, 4.4 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.12 ; HRMS (ESI) m/z calcd for $C_{10}H_{16}O_2P$ $(M+H)^+$: 199.0882; found: 199.0882. Phosphinate **8b** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK IA, 1.0% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 28.1 min, t_R(major) = 30.3 min.

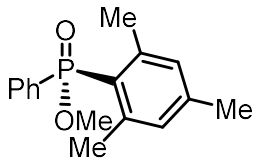
Methyl (*S*)-(2-methoxyphenyl)(phenyl)phosphinate (8c)



8c

Following **General Procedure G**, phosphinate **8c** (13.7 mg, 97% yield, 92% ee) was produced as a colorless oil from **6b** (16mg, 0.05 mmol, 93% ee). *Note: this reaction was subjected to stirring at –30 °C for 48 hours instead of –50 °C.* Product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 13.3, 7.6, 1.8 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.50 (dddd, *J* = 9.5, 6.7, 2.3, 1.1 Hz, 2H), 7.46 – 7.36 (m, 2H), 7.07 (tdd, *J* = 7.5, 2.6, 0.9 Hz, 1H), 6.87 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 3H), 3.71 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.01 (d, *J* = 3.9 Hz), 134.81 (d, *J* = 6.3 Hz), 134.46 (d, *J* = 2.0 Hz), 132.00 (d, *J* = 142.6 Hz), 131.86, 131.79, 131.76, 128.04 (d, *J* = 13.6 Hz), 120.66 (d, *J* = 12.3 Hz), 111.26 (d, *J* = 7.9 Hz), 55.53, 51.42 (d, *J* = 6.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.72 ; HRMS (CI-TOF) m/z calcd for $(M+H)^+$, found. Phosphinate **8c** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IA, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 37.2 min, t_R(major) = 40.4 min.

Methyl (*S*)-mesityl(phenyl)phosphinate (8d)



8d

Following **General Procedure G**, phosphinate **8d** (8.4 mg, 31% yield, 89% ee) was produced as a colorless oil via reaction of phosphonate **6b** (16 mg, 0.1 mmol, 93% ee) with 2-mesityl magnesium bromide (0.1 mL, 0.1 mmol, 1 equiv., 1 M in THF). *Note: this reaction was subjected to stirring at room temperature for 36 hours instead of –50 °C.* Product was purified using flash column chromatography (0 to 5% MeOH in DCM). ^{1}H NMR (300 MHz; $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.58 (m, 2H), 7.58 – 7.33 (m, 3H), 6.91 (d, *J* = 4.3 Hz, 2H), 3.74 (d, *J* = 11.3 Hz, 3H), 2.49 (d, *J* = 1.4 Hz, 6H), 2.30 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.92 (d, *J* = 11.3 Hz), 142.22 (d, *J* = 2.8 Hz), 133.24 (d, *J* = 4.8 Hz), 131.74 (d, *J* = 3.1 Hz), 130.86 (d, *J* = 13.1 Hz), 130.50 (d, *J* = 10.9 Hz), 128.46 (d, *J* = 13.4 Hz), 115.53, 50.65 (d, *J* = 5.9 Hz), 23.37 (d, *J* = 3.3 Hz), 21.11 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.42; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_2P$ $(M+H)^+$: 275.1195; found: 275.1195. Phosphinate **8d** was determined to be 89% ee by chiral HPLC analysis (CHIRALCEL OJ-H, 4% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 26.0 min, t_R(major) = 35.8 min.

General procedure used for preparation of 4 Å molecular sieves:

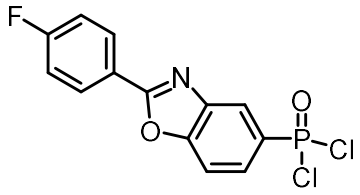
General Procedure H:

Powdered 4 Å molecular sieves (50 grams, 325 mesh, activated; CAS = 70955-01-0) were added to a 500 mL round bottom flask equipped with a large magnetic stir bar. The flask size was chosen

such that the sieves filled no more than ~1/4 of the volume of the flask. The flask was then fitted with an adapter with an inlet and placed under vacuum. The flask was then submerged in an oil bath, insulated with foil, and heated to 220 °C over a magnetic stir plate. The flask was maintained under constant vacuum for 5 days while the sieves were subjected to stirring continuously at 220 °C. Afterwards, the dried molecular sieves were stored in a sealed container under N_2.

2.5.4 Synthesis of (+)-SMT022332

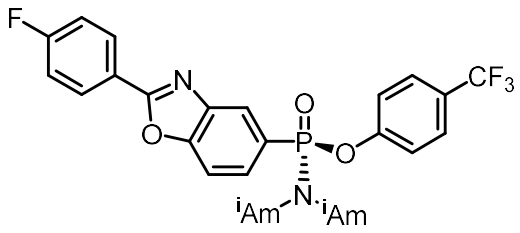
(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphonic dichloride (9)



9

Phosphonic dichloride **9** was prepared according to **General Procedure H** and used directly without further purification in the catalytic reaction. Crude phosphonic dichloride **9** was found to be pure by ^{1}H, ^{31}P, ^{19}F, and ^{13}C NMR with no significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 8.25 (dd, *J* = 18.5, 1.6 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.60 (ddd, *J* = 16.9, 8.4, 1.7 Hz, 1H), 6.92 (dd, *J* = 8.4, 4.9 Hz, 1H), 6.77 – 6.67 (m, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 165.34, 162.80 (d, *J* = 3.0 Hz), 152.80 (d, *J* = 4.3 Hz), 141.51 (d, *J* = 26.7 Hz), 130.08 (d, *J* = 158.3 Hz), 129.11 (d, *J* = 9.0 Hz), 126.09 (d, *J* = 16.3 Hz), 121.87 (d, *J* = 16.3 Hz), 121.37 (d, *J* = 3.2 Hz), 115.06 (d, *J* = 22.3 Hz), 110.07 (d, *J* = 21.7 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.00 ; ^{19}F NMR (376 MHz, C_6D_6) δ -105.73.

4-(trifluoromethyl)phenyl (*R*)-*P*-(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)-*N*,*N*-diisopentylphosphonamidate (10)



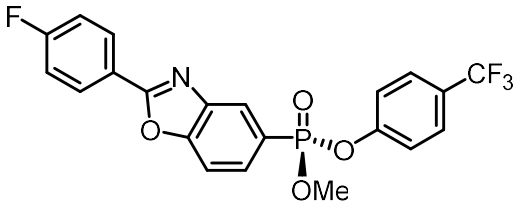
10

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (14 mg, 0.03 mmol, 0.1 equiv.), 4 Å mol sieves (300 mg), and diisoamylamine (0.31 mL, 1.5 mmol, 5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (15 mL) and the reaction mixture was cooled to –40 °C and subjected to stirring for 20 minutes at that temperature. Phosphonic dichloride **9** (0.3 mmol) was then added to the stirring reaction mixture in one portion as a stock solution in toluene (0.5 mL), and the reaction was subjected to stirring at –40 °C for 48 hours.

A separate oven-dried 20 mL vial with a magnetic stir bar was charged with sodium hydride (180 mg, 4.5 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (3 mL) and allowed to stir at room temperature for 1 minute. 4-trifluoromethylphenol (243 mg, 1.5 mmol, 5 equiv.) was dissolved in THF (0.5 mL) and then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period. Stirring was continued at room temperature for 30 minutes. The resultant mixture was then added directly to the catalytic reaction at –40 °C after it had been stirred for 48 hours. The reaction mixture was then subjected to stirring for 24 hours at –40 °C, and then concentrated under reduced pressure. Purification via flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes) afforded phosphonamidate **10** (118 mg, 68% yield, 95% ee) as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.36 – 8.18 (m, 3H), 7.88 (ddd, *J* = 12.7, 8.4, 1.5 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.21 (m, 2H), 3.29 – 2.91 (m, 4H), 1.43 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.36 – 1.16 (m, 4H), 0.81 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.16 (d, *J* = 253.9 Hz), 163.47, 153.91 (d, *J* = 8.1 Hz), 152.96 (d, *J* = 3.6 Hz), 142.24 (d, *J* = 20.5 Hz), 130.15 (d, *J* = 9.0 Hz), 128.72 (d, *J* = 11.8 Hz), 127.12 (d, *J* = 181.0 Hz), 127.03 (q, *J* = 3.7 Hz), 126.57 (q, *J* = 32.7 Hz), 123.99 (q, *J* = 271.6 Hz), 123.78 (d, *J* = 10.9 Hz), 122.87 (d, *J* = 3.3 Hz), 120.69 (d, *J* = 5.1 Hz), 116.41 (d, *J* = 22.2 Hz), 111.17 (d, *J* = 17.1 Hz), 43.28 (d, *J* = 4.4 Hz), 37.29 (d, *J* = 2.1 Hz), 25.94, 22.48 (d, *J* = 8.4 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.06, -106.25; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.75 ; HRMS (ESI) m/z calcd for $C_{30}H_{34}F_4N_2O_3P$ $(M+H)^+$: 577.2238; found: 577.2237. A crystal suitable for X-ray diffraction formed spontaneously via vapor diffusion: a saturated solution of phosphonamidate **10** in *tert*-butyl methyl ether was placed in a chamber filled ~2 cm high with hexanes, covered, and left to stand at room temperature for ~24 hours. Phosphonamidate **10** was determined to be 95% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 21.4 min, t_R(major) = 28.8 min.

Methyl (4-(trifluoromethyl)phenyl) (*R*)-(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphonate (11)

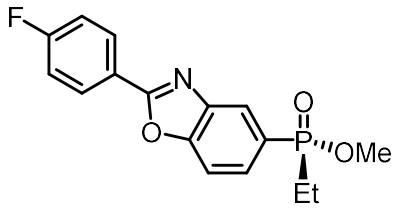


11

Following the **General Procedure E**, phosphonate **11** (55 mg, 65% yield, 94% ee) was produced as a colorless oil from phosphonamidate **10** (108 mg, 0.188 mmol, 95% ee), methanol (1 mL),

and *para*-tolylsulfonic acid monohydrate (107 mg, 0.564 mmol, 3 equiv.). The product was purified using flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.17 (m, 4H), 7.90 (ddd, *J* = 13.3, 8.3, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.4, 3.6, 0.7 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 3.93 (d, *J* = 11.4 Hz, 3H) ; δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.52, 163.99, 163.73, 153.76 (d, *J* = 3.6 Hz), 153.07 (d, *J* = 6.8 Hz), 142.48 (d, *J* = 21.9 Hz), 130.26 (d, *J* = 9.0 Hz), 129.13 (d, *J* = 12.2 Hz), 127.18 (q, *J* = 3.9 Hz), 124.56 (d, *J* = 11.6 Hz), 123.82 (q, *J* = 272.1 Hz), 122.75 (d, *J* = 194.0 Hz), 122.69 (d, *J* = 3.3 Hz), 120.79 (d, *J* = 4.7 Hz), 116.45 (d, *J* = 22.2 Hz), 111.37 (d, *J* = 18.1 Hz), 53.45 (d, *J* = 5.8 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.20, -105.98; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.98; HRMS (ESI) m/z calcd for $C_{21}H_{15}F_4NO_4P$ $(M+H)^+$: 452.0669; found: 452.0668. Phosphonate **11** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 33.1 min, t_R(major) = 27.0 min.

Methyl (*R*)-ethyl(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphinate (12)



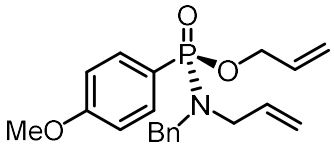
(+)-SMT022332

An oven-dried 2-dram vial with a magnetic stir bar was charged with phosphonate **11** (42 mg, 0.094 mmol, 1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1 mL) and allowed to stir at room temperature for 1 minute. The vial was then cooled to –50 °C for 20 minutes. EtMgCl (280 µL, 0.282 mmol, 3 equiv., 1.0 M solution in THF) was then added through the septum in one portion, and the reaction was subjected to stirring for 24 hours at –50 °C. After 24 hours had elapsed,

isopropanol (50 µL) was added via a syringe at –50 °C and subjected to stirring for 1 minute at –50 °C to quench any remaining EtMgCl. Immediate purification of the mixture via flash column chromatography on a 10-gram silica gel column (0 to 10% MeOH in DCM) afforded phosphinate **12** (30 mg, 98% yield, 94% ee) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.23 (m, 2H), 8.15 (ddd, *J* = 11.7, 1.4, 0.7 Hz, 1H), 7.83 (ddd, *J* = 10.9, 8.3, 1.4 Hz, 1H), 7.71 (ddd, *J* = 8.3, 2.5, 0.7 Hz, 1H), 7.32 – 7.16 (m, 1H), 7.22 (dd, *J* = 212.9, 8.5 Hz, 1H), 3.68 (d, *J* = 11.0 Hz, 3H), 2.11 – 1.80 (m, 2H), 1.14 (dt, *J* = 19.1, 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.31 (d, *J* = 2.9 Hz), 130.18 (d, *J* = 8.9 Hz), 129.03 (d, *J* = 11.0 Hz), 127.01 (d, *J* = 2.7 Hz), 125.78, 123.96, 123.85, 122.88 (d, *J* = 3.4 Hz), 116.42 (d, *J* = 22.2 Hz), 115.53, 111.24 (d, *J* = 14.0 Hz), 51.26 (d, *J* = 6.9 Hz), 22.78 (d, *J* = 103.1 Hz), 5.93 (d, *J* = 4.8 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.31; ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.84 ; HRMS (ESI) m/z calcd for $C_{16}H_{16}FNO_3P$ $(M+H)^+$: 320.0846; found: 320.0847. $[\alpha]^{22}$ = +32.2 (c = 1.0, THF). Absolute stereochemistry was assigned by comparison to literature value.[14a] Phosphinate **12** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 52.0 min, t_R(major) = 45.0 min.

2.5.5 Formal Synthesis of Matrix Metalloproteinase Inhibitor

Allyl (*R*)-*N*-allyl-*N*-benzyl-*P*-(4-methoxyphenyl)phosphonamidate (13)



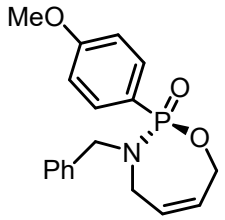
13

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (20 mg, 0.04 mmol), 4 Å mol sieves (200 mg), and *N*-allyl benzylamine (103 µL, 0.66 mmol, 3.3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –40 °C and

subjected to stirring for 20 minutes at that temperature. Then, 4-methoxyphenylphosphonic dichloride (32 µL, 0.2 mmol, 1 equiv.) was then added in one portion as a stock solution in toluene (0.5 mL), and the reaction was subjected to stirring at –40 °C for 60 hours.

A separate oven-dried 20 mL vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and allowed to stir at room temperature for 1 minute. Allyl alcohol (136 µL, 2 mmol, 10 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature for 30 minutes. The resultant allyl alkoxide mixture was then added directly to the catalytic reaction at –40 °C after it had been stirred for 60 hours. The reaction mixture was then subjected to stirring for 24 hours at –40 °C, and then concentrated under reduced pressure. Purification via flash column chromatography on silica gel (0 to 40% Et_2O in DCM) afforded phosphonamidate **13** (63 mg, 88% yield, 89% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.36 – 7.21 (m, 5H), 7.04 – 6.79 (m, 2H), 5.97 (ddt, *J* = 17.1, 10.6, 5.3 Hz, 1H), 5.70 – 5.48 (m, 1H), 5.35 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.6 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.62 – 4.43 (m, 2H), 4.31 – 4.16 (m, 2H), 3.85 (s, 3H), 3.57 – 3.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.35 (d, *J* = 3.1 Hz), 137.92 (d, *J* = 3.4 Hz), 134.21 (d, *J* = 1.7 Hz), 133.58 (d, *J* = 11.0 Hz), 133.38 (d, *J* = 7.6 Hz), 128.54 (d, *J* = 34.0 Hz), 127.25, 122.01 (d, *J* = 182.4 Hz), 118.37, 117.31, 114.07, 113.92, 64.96 (d, *J* = 5.4 Hz), 55.31, 47.90 (d, *J* = 4.9 Hz), 47.10 (d, *J* = 5.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.48 ; HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_3P$ $(M+H)^+$: 358.1567; found: 358.1566. Phosphonamidate **13** was determined to be 89% ee by chiral HPLC analysis (CHIRALPAK AS-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 61.6 min, t_R(major) = 49.8 min.

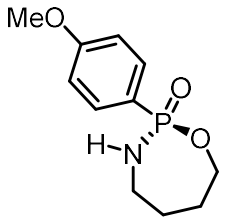
(*R*)-3-benzyl-2-(4-methoxyphenyl)-3,4,7-trihydro-1,3,2-oxazaphosphepine 2-oxide (14)



14

An oven-dried 100 mL flask with a magnetic stir bar was charged with Hoveyda-Grubbs 2nd Generation M720 (18 mg, 0.028 mmol 0.04 equiv.). The flask was then sealed with a septum cap, sealed with parafilm, and put under N_2 atmosphere. The flask was then charged with DCM (30 mL). Phosphonamidate **13** (250 mg, 0.7 mmol, 1 equiv.) dissolved in DCM (5 mL) was then added to the flask via syringe through the septum. The resulting solution was then degassed with N_2 for 30 minutes. The reaction was then subjected to stirring at 40 °C for 24 hours, at which point Hoveyda-Grubbs 2nd Generation M720 (15 mg, 0.025 mmol, 0.035 equiv.) dissolved in DCM (1 mL) was added via a syringe through the septum. The reaction was then subjected to stirring at 40 °C for an additional 24 hours. Upon completion, the crude mixture was dry loaded onto silica gel (~5 grams) and purified via flash column chromatography on silica gel (0 to 40% Et_2O in DCM) to afford the product. Phosphonamidate **14** was obtained as a colorless oil (217 mg, 0.66 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.56 (m, 2H), 7.49 – 7.10 (m, 5H), 6.97 (dd, *J* = 8.8, 3.2 Hz, 2H), 5.65 (ddt, *J* = 13.4, 5.3, 2.4 Hz, 2H), 5.23 (dddd, *J* = 13.1, 8.5, 4.3, 2.1 Hz, 1H), 4.65 (dd, *J* = 15.0, 7.9 Hz, 1H), 4.54 – 4.32 (m, 1H), 4.23 (dd, *J* = 15.1, 5.8 Hz, 1H), 3.85 (s, 3H), 3.68 (dd, *J* = 16.8, 5.0 Hz, 1H), 3.24 – 2.96 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.42 (d, *J* = 3.3 Hz), 138.72 (d, *J* = 4.6 Hz), 133.18 (d, *J* = 10.7 Hz), 128.80, 128.46, 128.23, 127.01 (d, *J* = 50.6 Hz), 120.98 (d, *J* = 187.7 Hz), 114.07, 113.92, 62.35 (d, *J* = 6.5 Hz), 55.33, 50.69 (d, *J* = 4.4 Hz), 43.41 (d, *J* = 4.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.34; HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_3P$ $(M+H)^+$: 330.1254; found: 330.1254.

(*R*)-2-(4-methoxyphenyl)-1,3,2-oxazaphosphepane 2-oxide (15)



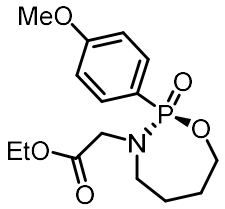
15

**Note: successful hydrogenolysis is dependent on efficient sparging with H_2 at 30 °C and subjection to vigorous stirring.*

To a 1-dram vial equipped with a magnetic stir bar, phosphonamidate **14** (18.0 mg, 0.0547 mmol, 1 equiv.), $Pd(OH)_2/C$ (6 mg, 0.0082 mmol, 0.15 equiv., 20%), and Pd/C (9 mg, 0.0082 mmol, 0.15 equiv., 10%) were added. The vial was then capped with a septum and sealed with parafilm. The vial was evacuated and backfilled three times with N_2, then evacuated and backfilled once with H_2. Isopropanol (0.55 mL) and trifluoroacetic acid (12 µL, 0.164 mmol, 3 equiv.) were introduced sequentially via a syringe through the septum. The mixture was then sparged with H_2 for 10 minutes while subjected to vigorous stirring at 30 °C. The reaction was then subjected to stirring under an H_2 balloon for 20 hours at 30 °C, after which point an additional portion of trifluoroacetic acid (12 µL, 0.164 mmol, 3 equiv.) was added and the reaction was sparged with H_2 again for 5 minutes. The reaction was subjected to stirring under an H_2 balloon for an additional 8 hours at 30 °C, after which point it was sparged with H_2 for an additional 5 minutes. Reaction completion was confirmed after 41 hours by TLC analysis by visualization with $KMnO_4$. The crude mixture was then loaded directly onto a silica gel column and purified using flash column chromatography (0 to 10% MeOH in DCM) to afford the product. Phosphonamidate **15** (9.1 mg, 0.0377 mmol, 69% yield) was afforded as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.63 (m, 2H), 6.94 (dq, *J* = 9.3, 2.7 Hz, 2H), 4.54 (qd, *J* = 11.6, 1.2 Hz, 1H), 4.16 (ddtd, *J* = 19.9, 11.8, 3.7, 3.3, 1.4 Hz, 1H), 3.84 (s, 3H), 3.36 – 2.95 (m, 1H), 2.81 (q, *J* = 9.3, 7.9 Hz, 1H), 2.02 – 1.71 (m, 4H), 1.70 – 1.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.25 (d, *J* = 3.3 Hz), 132.82 (d, *J* = 10.9 Hz), 122.69 (d, *J* = 190.0 Hz), 113.87 (d, *J* = 15.6 Hz), 65.28 (d, *J* = 6.7 Hz), 55.31, 41.23, 32.01, 29.97; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.00; HRMS (ESI) m/z calcd for $C_{11}H_{17}NO_3P$ $(M+H)^+$: 242.0941; found: 242.0940.

Ethyl (*R*)-2-(2-(4-methoxyphenyl)-2-oxido-1,3,2-oxazaphosphepan-3-yl)acetate (16)

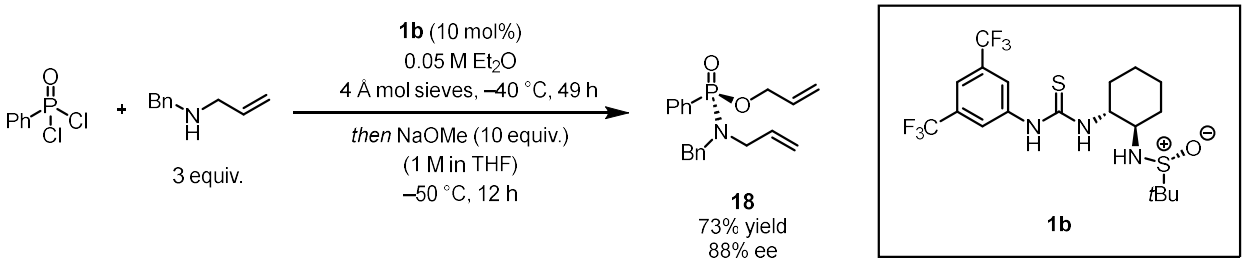


16

An oven-dried 2-dram vial with a magnetic stir bar was charged with phosphonamidate **15** (40 mg, 0.165 mmol, 1 equiv.). The vial was then capped with a septum and sealed with parafilm. The vial was then put under N_2 atmosphere, charged with THF (1.2 mL), and subjected to stirring at 0 °C for 10 minutes. NaHMDS (180 µL, 0.18 mmol, 1.1 equiv, 1.0 M in THF) was then added dropwise via a syringe through the septum to the stirring solution over a 5-minute period. The resulting yellow solution was subjected to stirring for 1 hour at 0 °C. Ethyl bromoacetate (44 µL, 0.36 mmol, 2.2 equiv.,) dissolved in THF (0.2 mL) was then slowly added dropwise via a syringe through the septum to the stirring solution over a 1-minute period. The mixture was then subjected to stirring at 0 °C for 4 hours. The crude mixture was then purified by flash column chromatograph using silica gel (0 to 10% MeOH in DCM) to afford the product. Phosphonamidate **16** (47 mg, 87% yield, 90% ee) was afforded as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 12.7, 8.7 Hz, 2H), 7.14 – 6.78 (m, 2H), 4.62 – 4.44 (m, 1H), 4.35 (ddd, *J* = 18.1, 9.6, 1.3 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 3.94 – 3.67 (m, 1H), 3.16 (dq, *J* = 16.1, 6.1 Hz, 1H), 2.99 – 2.83 (m, 1H), 1.88 – 1.71 (m, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.02 – 6.78 (m, 2H), 4.62 – 4.43 (m, 1H), 4.35 (ddd, *J* = 18.1, 9.6, 1.3 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 3.80 (d, *J* = 9.1 Hz, 1H), 3.16 (ddd, *J* = 16.3, 11.0, 6.0 Hz, 1H), 3.03 – 2.77 (m, 1H), 1.95 – 1.71 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.45 (d, *J* = 2.9 Hz), 162.23 (d, *J* = 3.4 Hz), 133.21 (d, *J* = 11.3 Hz), 122.07 (d, *J* = 191.0 Hz), 113.77 (d, *J* = 15.9 Hz), 65.16 (d, *J* = 6.7 Hz), 60.96, 55.27, 48.51 (d, *J* = 6.0 Hz), 47.33 (d, *J* = 5.2 Hz), 29.51, 26.51, 14.19 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.57; HRMS (ESI) m/z calcd for $C_{15}H_{23}NO_5P$ $(M+H)^+$: 328.1308; found: 328.1309. Phosphonamidate **16** was determined to be 90% ee by chiral HPLC analysis (CHIRALPAK AD-H, 15% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 23.3 min, t_R(major) = 16.1 min.

2.5.6 Synthesis of (*R*)-Methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate



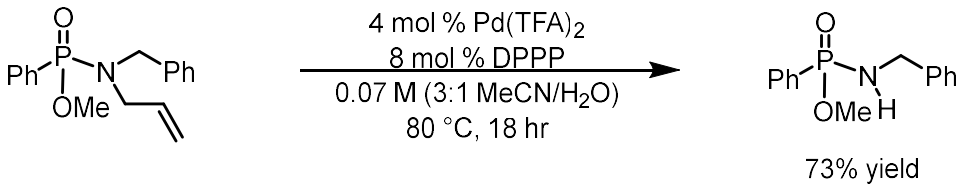
An oven-dried 2-dram mL vial equipped with a magnetic stir bar was charged with catalyst **1b** (3 mg, 0.006 mmol, 0.1 equiv.), 4 Å mol sieves (60 mg), and *N*-allyl benzylamine (28 µL, 0.18 mmol, 3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (1.2 mL), and the reaction mixture was cooled to –40 °C and subjected to stirring for 20 minutes at that temperature. Then, phenylphosphonic dichloride (9 µL, 0.06 mmol, 1 equiv.) was then added in one portion as a stock solution in toluene (0.2 mL), and the reaction was subjected to stirring at –40 °C for 49 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum over a 2-minute period to the stirring mixture, and stirring was continued at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. A 0.7-mL portion of the resultant sodium methoxide mixture was then added directly to the catalytic reaction at –40 °C after it had been stirred for 49 hours. The reaction mixture was then subjected to stirring for 24 hours at –40 °C, and then concentrated under reduced pressure. Purification via flash column chromatography on silica gel (0 to 50% Et_2O in DCM) afforded phosphonamidate **18** (13.2 mg, 73% yield, 88% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 12.8, 8.3, 1.5 Hz, 2H), 7.61 – 7.47 (m, 1H), 7.44 (ddd, *J* = 8.6, 6.5, 3.9 Hz, 2H), 7.34 – 7.13 (m, 5H), 5.60 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.24 (d, *J* = 9.0 Hz, 2H), 3.75 (d, *J* = 11.1 Hz, 3H), 3.49 (dtdd, *J* = 9.1, 7.7, 3.4, 2.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.75 (d, *J* = 3.3 Hz), 134.02 (d, *J* = 1.7 Hz), 131.74 (d, *J* = 3.0 Hz), 131.56 (d, *J* = 9.5 Hz), 130.70 (d, *J* = 175.7 Hz), 128.56 (d, *J* = 32.0 Hz), 128.50 (d, *J* = 36.0 Hz), 128.49 (d, *J* = 14.2 Hz), 127.31, 118.49, 51.37 (d, *J* = 5.9 Hz), 47.89 (d, *J* = 4.8 Hz), 47.02 (d, *J* = 4.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.59. HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_2P$ $(M+H)^+$: 302.1304 ; found: 302.1306.

Phosphonamidate **18** was determined to be 88% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 26.1 min, t_R(major) = 29.1 min.

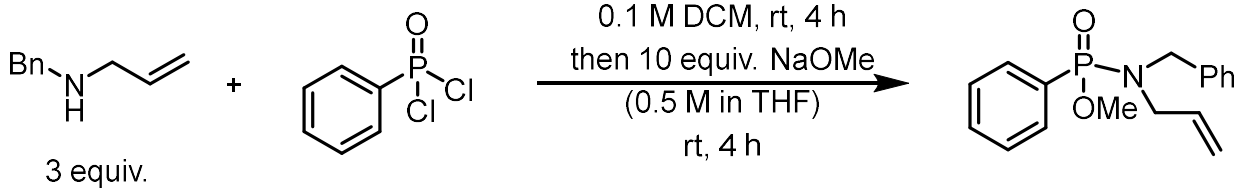
2.5.7 Procedure for Deallylation of Phosphonamidate Nitrogen



Procedure:

Conditions were adapted from a reported procedure for deallylation of amides.[18] $Pd(TFA)_2$ (2 mg, 0.006 mmol, 0.04 equiv.), 1,3-Bis(diphenylphosphino)propane (DPPP) (5 mg, 0.012 mmol, 0.08 equiv.), and methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate (45.2 mg, 0.15 mmol, 1 equiv.) were added to a 2-dram vial equipped with a magnetic stir bar. The vial was then capped with a septum and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. MeCN (1.6 mL) and H_2O (0.5 mL) of water were then added to the vial via syringe. The resulting solution was subjected to stirring at room temperature for ~1 minute, and then subjected to stirring at 80 °C for 18 hours. After 18 hours, the crude mixture was cooled to room temperature, concentrated under reduced pressure until ~1 mL of solvent remained, and then purified via flash column chromatography on silica gel (0 to 10% MeOH in DCM). Methyl *N*-benzyl-*P*-phenylphosphonamidate was afforded as a colorless oil (28.7 mg, 73% yield).

Racemic Synthesis of Methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate



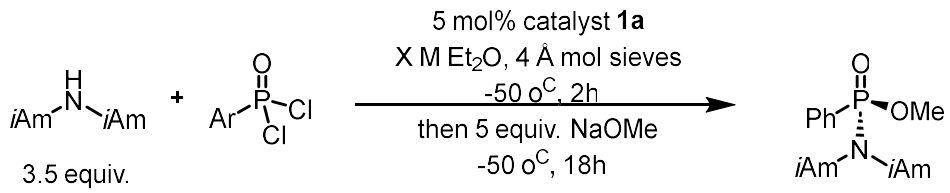
[18] Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. Hydrolytic Deallylation of N-Allyl Amides Catalyzed by PdII Complexes. *European Journal of Organic Chemistry* **2008**, *2008* (30), 5042–5045.

An oven-dried 20 mL vial equipped with a magnetic stir bar was charged with *N*-allyl benzylamine (94 µL, 0.6 mmol, 3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with DCM (2 mL), followed by phenyl phosphonic dichloride (28 µL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL), and the reaction was subjected to stirring at room temperature for 4 hours. The reaction was quenched with sodium methoxide prepared according to the following procedure:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the reaction stirring in DCM at room temperature. Upon addition of sodium methoxide, the reaction was subjected to stirring for 4 hours at room temperature, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 12.8, 8.3, 1.5 Hz, 2H), 7.61 – 7.47 (m, 1H), 7.44 (ddd, *J* = 8.6, 6.5, 3.9 Hz, 2H), 7.34 – 7.13 (m, 5H), 5.60 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.24 (d, *J* = 9.0 Hz, 2H), 3.75 (d, *J* = 11.1 Hz, 3H), 3.49 (dtdd, *J* = 9.1, 7.7, 3.4, 2.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.75 (d, *J* = 3.3 Hz), 134.02 (d, *J* = 1.7 Hz), 131.74 (d, *J* = 3.0 Hz), 131.56 (d, *J* = 9.5 Hz), 130.70 (d, *J* = 175.7 Hz), 128.56 (d, *J* = 32.0 Hz), 128.50 (d, *J* = 36.0 Hz), 128.49 (d, *J* = 14.2 Hz), 127.31, 118.49, 51.37 (d, *J* = 5.9 Hz), 47.89 (d, *J* = 4.8 Hz), 47.02 (d, *J* = 4.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.59. HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_2P$ $(M+H)^+$: 302.1304 ; found: 302.1306.

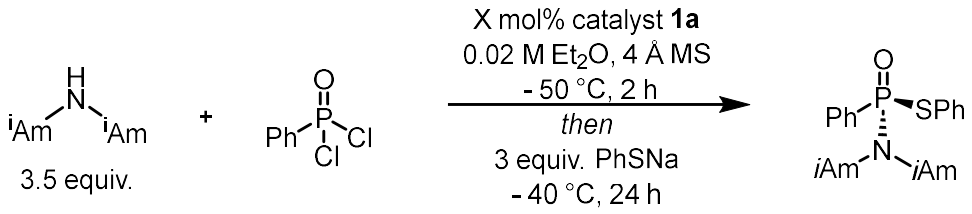
2.5.8 Optimization Studies

Table S2.1 Effect of reaction concentration on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



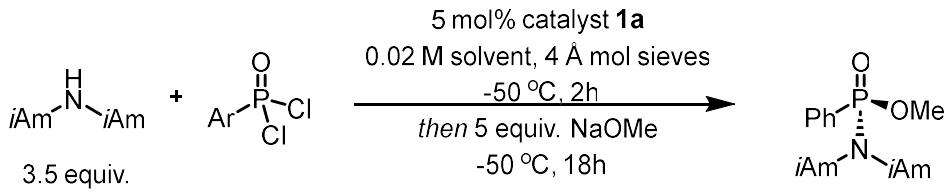
Concentration	% ee	% yield
0.02 M	95	93
0.05 M	94	100
0.1 M	91	98
0.2 M	90	94

Table S2.2 Effect of catalyst loading on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



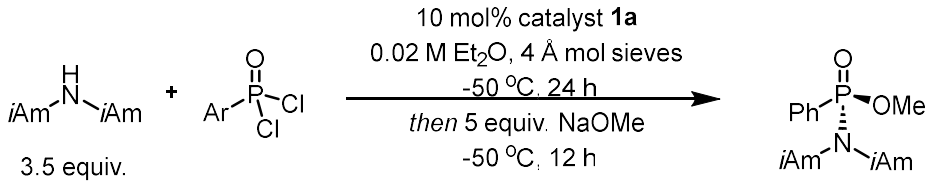
X	% ee	% conversion	% yield
2	94	89	84
5	94	100	100
10	94	100	100

Table S2.3 Effect of solvent on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



Solvent	% ee	% yield
Et_2O	95	93
TBME	93	96
THF	68	89
DCM	5	98
Toluene	91	100

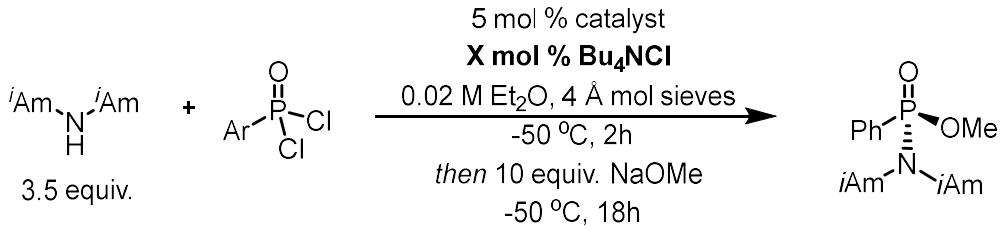
Table S2.4 Effect of molecular sieves on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



Deviation from Conditions	% ee	% yield
--	95	100
No mol sieves	89	94

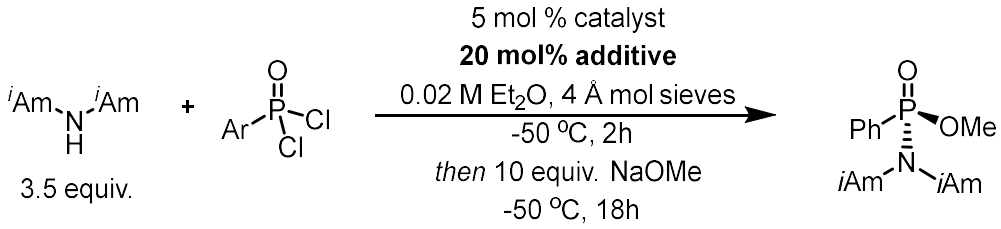
2.5.9 Effect of Tetrabutylammonium Chloride Additive on Catalytic Reaction and Racemic Reaction

Table S2.5 Enantioselectivity of catalytic reaction decreases with increasing amounts of BuN_4Cl. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



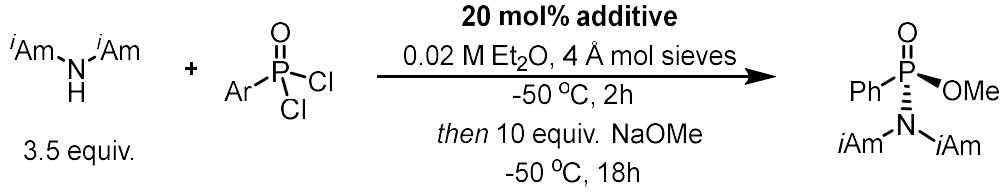
mol % Bu_4NCl	% ee	% yield	% conversion
0	95	93	100
5	92	92	92
10	83	78	84
20	20	73	79
40	9	82	89
80	5	87	90

Table S2.6 Effect of dialkylammonium chloride additives on enantioselectivity of catalytic reaction. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

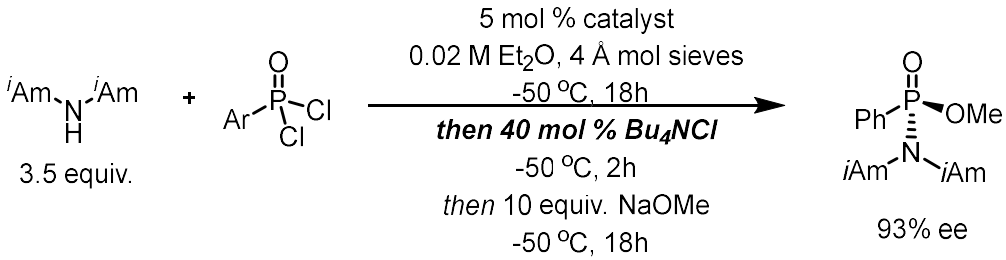


Additive (20 mol%)	% ee	% yield	% conversion
--	95	93	100
$^{i}Am_2NH_2Cl$	93	93	100
Bn_2NH_2Cl	92	97	100

Table S2.7 Effect of ammonium chloride additives on racemic background reaction in the absence of catalyst. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



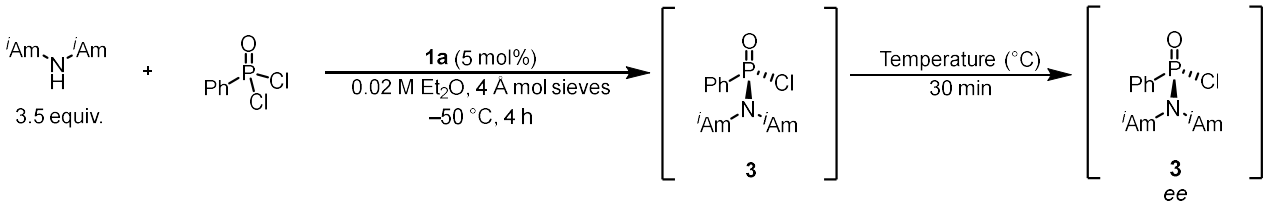
Additive	% yield	% conversion
None	21	38
$^{i}Am_2NH_2Cl$	23	44
Bn_2NH_2Cl	32	65
Bu_4NCl	83	83
Bu_4NBzO	96	100
Bu_4NPF_6	18	48
Bu_4NBF_4	22	54



Scheme S2.1 Enantioenriched chlorophosphonamidate **3** formed under reaction conditions does not undergo racemization in the presence of BuN_4Cl.

2.5.10 Racemization Studies of Chlorophosphonamidate

Table S2.8 Measure of % ee of chlorophosphonamidate **3** after isolation at room temperature at various time points.



Temperature (°C)	% ee
0	94
25	93
35	92
25 (16 h)	82

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with catalyst **1a** (1.4 mg, 0.003 mmol, 0.05 equiv.), 4 Å mol sieves (60 mg), and diisoamylamine (44 µL, 0.21 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (3 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. A solution of phenyl phoshonic dichloride (8.4 µL, 0.06 mmol, 1 equiv.) in toluene (0.2 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 hours. The mixture was filtered at room temperature through ~3 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution of **3** was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. After this procedure, chlorophosphonamidate **3** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0

mL/min, 220 nm, t_R(minor) = 14.7 min, t_R(major) = 18.8 min). Subsequently, the same solution of **3** was heated to 25 °C for 30 min, after which point chlorophosphonamidate **3** was determined to be 93% ee by chiral HPLC analysis. Subsequently, the same solution of **3** was heated to 35 °C for 30 min, after which point chlorophosphonamidate **3** was determined to be 92% ee by chiral HPLC analysis. Then, upon letting the same solution of **3** stand at 25 °C for 16 hours, chlorophosphonamidate **3** was determined to be 82% ee by chiral HPLC analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddt, *J* = 14.9, 6.4, 1.8 Hz, 1H), 7.17 – 6.94 (m, 3H), 3.29 – 2.97 (m, 4H), 1.58 – 1.31 (m, 6H), 0.82 (dd, *J* = 9.7, 6.3 Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.00.

2.5.11 X-ray Crystallography

4-(trifluoromethyl)phenyl (*R*)-*P*-(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)-*N*,*N*-diisopentylphosphonamidate (**10**) was prepared in 95% ee, as described. A crystal suitable for X-ray diffraction formed spontaneously via vapor diffusion: a saturated solution of phosphonamidate **10** in *tert*-butyl methyl ether was placed in a chamber filled ~2 cm high with hexanes, covered, and left to stand at room temperature for ~24 hours.

X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.77 Å resolution was carried out using SAINT V8.37A[19] with reflection spot size optimization.

[19] Bruker AXS APEX3 (2015).

Absorption corrections were made with the program SADABS[19,20]. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014[21] and SHELXL-2014[22] with OLEX 2 interface.[23] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S2.9, and geometric parameters are shown in Table S2.10. The Ortep plots were produced with SHELXL-2014 program, and the three-dimensional supramolecular architecture drawing was produced with Accelrys DS Visualizer 2.06.[24]

[20] Krause, L.; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. Comparison of Silver and Molybdenum Microfocus X-Ray Sources for Single-Crystal Structure Determination. *J Appl Crystallogr* **2015**, *48* (Pt 1), 3–10.

[21] Sheldrick, G. M. SHELXT - Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr A Found Adv* **2015**, *71* (Pt 1), 3–8.

[22] Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Cryst C* **2015**, *71* (1), 3–8.

[23] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. a. K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J Appl Cryst* **2009**, *42* (2), 339–341.

[24] Accelrys Software Inc., Accelrys DS Visualizer v2.0.1 (2007).

Table S2.9 Experimental details

Crystal data	
Chemical formula	$C_{30}H_{33}F_4N_2O_3P$
M_r	576.55
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, *b*, *c* (Å)	14.0169 (7), 5.9557 (3), 18.0856 (10)
β (°)	103.9371 (17)
V (Å^3)	1465.35 (13)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.15
Crystal size (mm)	0.14 × 0.08 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.728, 0.801

No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	15725, 6211, 5220
R_{int}	0.039
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.650
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.059, 0.117, 1.13
No. of reflections	6211
No. of parameters	376
No. of restraints	40
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.43, -0.39
Absolute structure	Flack x determined using 1819 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.05 (8)

Computer programs: *SAINT* 8.37A (Bruker-AXS, 2015), *SHELXT2014* (Sheldrick, 2015), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL* (Sheldrick, 2015).

Table S2.10 Geometric parameters (Å, º)

P1—O2	1.471 (3)	C17—C20	1.494 (6)
P1—O3	1.614 (3)	C18—C19	1.390 (6)
P1—N2	1.628 (4)	C18—H18	0.9500
P1—C4	1.790 (4)	C19—H19	0.9500
F1—C11	1.358 (4)	C21—C22	1.528 (5)
O1—C1	1.370 (4)	C21—H21A	0.9900
O1—C7	1.379 (5)	C21—H21B	0.9900
O3—C14	1.399 (5)	C22—C23	1.527 (6)
N1—C7	1.286 (5)	C22—H22A	0.9900
N1—C6	1.400 (5)	C22—H22B	0.9900
N2—C26	1.472 (5)	C23—C24	1.522 (6)
N2—C21	1.475 (5)	C23—C25	1.523 (6)
C1—C2	1.373 (6)	C23—H23	1.0000
C1—C6	1.391 (6)	C24—H24A	0.9800
C2—C3	1.397 (5)	C24—H24B	0.9800
C2—H2	0.9500	C24—H24C	0.9800
C3—C4	1.403 (6)	C25—H25A	0.9800
C3—H3	0.9500	C25—H25B	0.9800
C4—C5	1.386 (6)	C25—H25C	0.9800
C5—C6	1.386 (5)	C26—C27	1.529 (5)

C5—H5	0.9500	C26—H26A	0.9900
C7—C8	1.468 (5)	C26—H26B	0.9900
C8—C9	1.393 (6)	C27—C28	1.521 (6)
C8—C13	1.393 (6)	C27—H27A	0.9900
C9—C10	1.393 (6)	C27—H27B	0.9900
C9—H9	0.9500	C28—C29	1.521 (6)
C10—C11	1.375 (6)	C28—C30	1.533 (7)
C10—H10	0.9500	C28—H28	1.0000
C11—C12	1.372 (6)	C29—H29A	0.9800
C12—C13	1.383 (5)	C29—H29B	0.9800
C12—H12	0.9500	C29—H29C	0.9800
C13—H13	0.9500	C30—H30A	0.9800
C14—C19	1.377 (6)	C30—H30B	0.9800
C14—C15	1.383 (6)	C30—H30C	0.9800
C15—C16	1.386 (5)	C20—F4	1.303 (5)
C15—H15	0.9500	C20—F2	1.310 (6)
C16—C17	1.389 (6)	C20—F3	1.337 (6)
C16—H16	0.9500	C20A—F4A	1.258 (15)
C17—C18	1.378 (6)	C20A—F2A	1.298 (16)
C17—C20A	1.494 (6)	C20A—F3A	1.36 (2)

O2—P1—O3	114.21 (17)	N2—C21—H21A	109.0
O2—P1—N2	112.07 (18)	C22—C21—H21A	109.0
O3—P1—N2	108.00 (17)	N2—C21—H21B	109.0
O2—P1—C4	114.10 (18)	C22—C21—H21B	109.0
O3—P1—C4	99.22 (17)	H21A—C21—H21B	107.8
N2—P1—C4	108.35 (18)	C23—C22—C21	113.1 (3)
C1—O1—C7	103.3 (3)	C23—C22—H22A	109.0
C14—O3—P1	120.0 (2)	C21—C22—H22A	109.0
C7—N1—C6	104.0 (3)	C23—C22—H22B	109.0
C26—N2—C21	116.6 (3)	C21—C22—H22B	109.0
C26—N2—P1	122.5 (3)	H22A—C22—H22B	107.8
C21—N2—P1	120.7 (3)	C24—C23—C25	110.5 (4)
O1—C1—C2	128.0 (4)	C24—C23—C22	111.5 (4)
O1—C1—C6	108.0 (3)	C25—C23—C22	110.9 (4)
C2—C1—C6	124.0 (3)	C24—C23—H23	107.9
C1—C2—C3	116.1 (4)	C25—C23—H23	107.9
C1—C2—H2	122.0	C22—C23—H23	107.9
C3—C2—H2	122.0	C23—C24—H24A	109.5
C2—C3—C4	120.8 (4)	C23—C24—H24B	109.5

C2—C3—H3	119.6	H24A—C24—H24B	109.5
C4—C3—H3	119.6	C23—C24—H24C	109.5
C5—C4—C3	121.8 (3)	H24A—C24—H24C	109.5
C5—C4—P1	116.1 (3)	H24B—C24—H24C	109.5
C3—C4—P1	121.9 (3)	C23—C25—H25A	109.5
C4—C5—C6	117.5 (4)	C23—C25—H25B	109.5
C4—C5—H5	121.3	H25A—C25—H25B	109.5
C6—C5—H5	121.3	C23—C25—H25C	109.5
C5—C6—C1	119.9 (4)	H25A—C25—H25C	109.5
C5—C6—N1	131.5 (4)	H25B—C25—H25C	109.5
C1—C6—N1	108.6 (3)	N2—C26—C27	112.9 (3)
N1—C7—O1	116.1 (3)	N2—C26—H26A	109.0
N1—C7—C8	128.2 (4)	C27—C26—H26A	109.0
O1—C7—C8	115.6 (3)	N2—C26—H26B	109.0
C9—C8—C13	120.5 (4)	C27—C26—H26B	109.0
C9—C8—C7	119.1 (4)	H26A—C26—H26B	107.8
C13—C8—C7	120.3 (4)	C28—C27—C26	114.9 (4)
C8—C9—C10	119.7 (4)	C28—C27—H27A	108.5
C8—C9—H9	120.2	C26—C27—H27A	108.5
C10—C9—H9	120.2	C28—C27—H27B	108.5

C11—C10—C9	117.8 (4)	C26—C27—H27B	108.5
C11—C10—H10	121.1	H27A—C27—H27B	107.5
C9—C10—H10	121.1	C29—C28—C27	110.4 (4)
F1—C11—C12	118.0 (4)	C29—C28—C30	110.4 (4)
F1—C11—C10	118.0 (4)	C27—C28—C30	112.1 (4)
C12—C11—C10	124.0 (4)	C29—C28—H28	107.9
C11—C12—C13	118.0 (4)	C27—C28—H28	107.9
C11—C12—H12	121.0	C30—C28—H28	107.9
C13—C12—H12	121.0	C28—C29—H29A	109.5
C12—C13—C8	120.0 (4)	C28—C29—H29B	109.5
C12—C13—H13	120.0	H29A—C29—H29B	109.5
C8—C13—H13	120.0	C28—C29—H29C	109.5
C19—C14—C15	122.0 (4)	H29A—C29—H29C	109.5
C19—C14—O3	117.9 (4)	H29B—C29—H29C	109.5
C15—C14—O3	120.0 (4)	C28—C30—H30A	109.5
C14—C15—C16	118.5 (4)	C28—C30—H30B	109.5
C14—C15—H15	120.7	H30A—C30—H30B	109.5
C16—C15—H15	120.7	C28—C30—H30C	109.5
C15—C16—C17	120.2 (4)	H30A—C30—H30C	109.5
C15—C16—H16	119.9	H30B—C30—H30C	109.5

C17—C16—H16	119.9	F4—C20—F2	107.5 (4)
C18—C17—C16	120.3 (4)	F4—C20—F3	104.6 (4)
C18—C17—C20A	120.8 (4)	F2—C20—F3	104.9 (4)
C16—C17—C20A	118.9 (4)	F4—C20—C17	113.5 (4)
C18—C17—C20	120.8 (4)	F2—C20—C17	112.7 (4)
C16—C17—C20	118.9 (4)	F3—C20—C17	112.9 (4)
C17—C18—C19	120.1 (4)	F4A—C20A—F2A	108.0 (14)
C17—C18—H18	119.9	F4A—C20A—F3A	104.9 (13)
C19—C18—H18	119.9	F2A—C20A—F3A	103.9 (13)
C14—C19—C18	118.8 (4)	F4A—C20A—C17	115.7 (10)
C14—C19—H19	120.6	F2A—C20A—C17	111.3 (10)
C18—C19—H19	120.6	F3A—C20A—C17	112.3 (10)
N2—C21—C22	113.1 (3)		
O2—P1—O3—C14	-67.5 (3)	C9—C10—C11—F1	-179.9 (3)
N2—P1—O3—C14	57.9 (3)	C9—C10—C11—C12	-1.3 (6)
C4—P1—O3—C14	170.8 (3)	F1—C11—C12—C13	178.9 (3)

O2—P1—N2—C26	13.7 (4)	C10—C11—C12—C13	0.3 (6)
O3—P1—N2—C26	-112.9 (3)	C11—C12—C13—C8	0.6 (6)
C4—P1—N2—C26	140.5 (3)	C9—C8—C13—C12	-0.5 (6)
O2—P1—N2—C21	-171.4 (3)	C7—C8—C13—C12	177.7 (4)
O3—P1—N2—C21	61.9 (3)	P1—O3—C14—C19	-109.6 (4)
C4—P1—N2—C21	-44.7 (3)	P1—O3—C14—C15	72.3 (4)
C7—O1—C1—C2	-179.9 (4)	C19—C14—C15—C16	0.9 (6)
C7—O1—C1—C6	0.5 (4)	O3—C14—C15—C16	178.9 (4)
O1—C1—C2—C3	-178.8 (4)	C14—C15—C16—C17	-0.4 (6)
C6—C1—C2—C3	0.7 (6)	C15—C16—C17—C18	-0.2 (6)
C1—C2—C3—C4	-0.9 (6)	C15—C16—C17—C20A	179.9 (4)
C2—C3—C4—C5	0.6 (6)	C15—C16—C17—C20	179.9 (4)

C2—C3—C4—P1	-174.6 (3)	C16—C17—C18—C19	0.3 (7)
O2—P1—C4—C5	31.7 (4)	C20A—C17—C18—C19	-179.9 (4)
O3—P1—C4—C5	153.5 (3)	C20—C17—C18—C19	-179.9 (4)
N2—P1—C4—C5	-93.9 (3)	C15—C14—C19—C18	-0.8 (6)
O2—P1—C4—C3	-152.9 (3)	O3—C14—C19—C18	-178.9 (4)
O3—P1—C4—C3	-31.1 (4)	C17—C18—C19—C14	0.2 (6)
N2—P1—C4—C3	81.5 (4)	C26—N2—C21—C22	-90.9 (4)
C3—C4—C5—C6	0.0 (6)	P1—N2—C21—C22	94.0 (4)
P1—C4—C5—C6	175.4 (3)	N2—C21—C22—C23	-177.3 (3)
C4—C5—C6—C1	-0.2 (6)	C21—C22—C23—C24	-82.4 (4)
C4—C5—C6—N1	179.4 (4)	C21—C22—C23—C25	154.0 (4)
O1—C1—C6—C5	179.4 (4)	C21—N2—C26—C27	-82.0 (4)
C2—C1—C6—C5	-0.2 (6)	P1—N2—C26—C27	93.1 (4)
O1—C1—C6—N1	-0.2 (4)	N2—C26—C27—C28	166.9 (4)

C2—C1—C6—N1	-179.8 (4)	C26—C27—C28—C29	-177.3 (4)
C7—N1—C6—C5	-179.8 (4)	C26—C27—C28—C30	59.2 (6)
C7—N1—C6—C1	-0.2 (4)	C18—C17—C20—F4	-122.4 (6)
C6—N1—C7—O1	0.6 (4)	C16—C17—C20—F4	57.4 (6)
C6—N1—C7—C8	178.3 (4)	C18—C17—C20—F2	115.1 (6)
C1—O1—C7—N1	-0.8 (4)	C16—C17—C20—F2	-65.1 (6)
C1—O1—C7—C8	-178.7 (3)	C18—C17—C20—F3	-3.6 (7)
N1—C7—C8—C9	5.6 (6)	C16—C17—C20—F3	176.2 (5)
O1—C7—C8—C9	-176.8 (3)	C18—C17—C20A—F4A	71.3 (17)
N1—C7—C8—C13	-172.6 (4)	C16—C17—C20A—F4A	-108.9 (17)
O1—C7—C8—C13	5.1 (5)	C18—C17—C20A—F2A	-52 (2)
C13—C8—C9—C10	-0.6 (6)	C16—C17—C20A—F2A	127 (2)
C7—C8—C9—C10	-178.8 (4)	C18—C17—C20A—F3A	-168.4 (18)
C8—C9—C10—C11	1.5 (6)	C16—C17—C20A—F3A	11.4 (19)

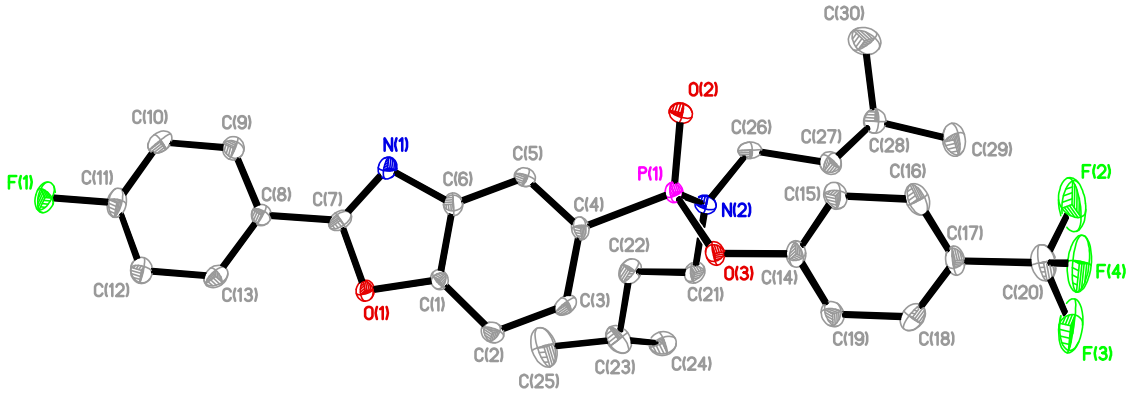


Figure S2.1 Perspective views showing 50% probability displacement.

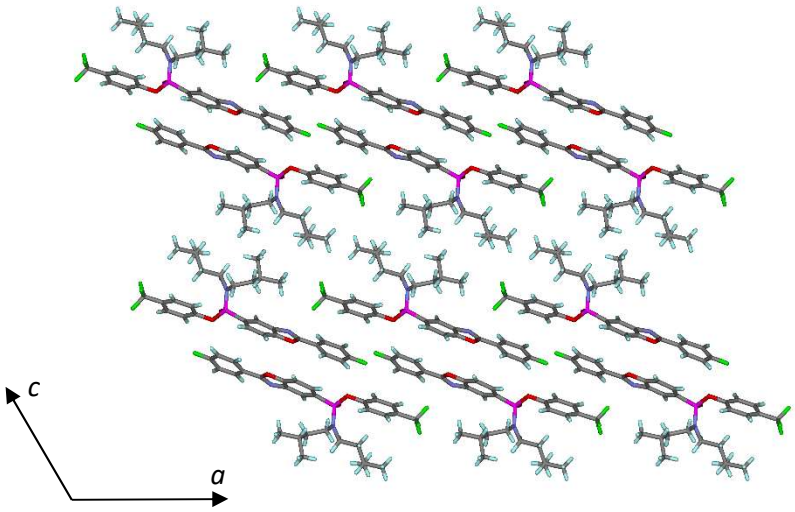


Figure S2.2 Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

Chapter 3

Desymmetrization of Phosphinic Acids via Hydrogen-Bond-Donor Catalyzed Alkylation

3.1 Introduction

Chiral phopshinates represent an important class of molecules in organic chemistry. Phosphinate esters have recently emerged as a functional group with pharmaceutical potential as bioisosteres of sulfones with beneficial medicinal properties[1]. Phosphinate esters are also important chiral building blocks in organic chemistry, serving as synthetic precursors to chiral phosphines[2]. The first synthesis of the chiral phosphine ligand DIPAMP involved the preparation

[1] Chatzopoulou, M.; Emer, E.; Lecci, C.; Rowley, J. A.; Casagrande, A.-S.; Moir, L.; Squire, S. E.; Davies, S. G.; Harriman, S.; Wynne, G. M.; Wilson, F. X.; Davies, K. E.; Russell, A. J. Decreasing HepG2 Cytotoxicity by Lowering the Lipophilicity of Benzo[d]Oxazolephosphinate Ester Utrophin Modulators. *ACS Med. Chem. Lett.* **2020**, *11* (12), 2421–2427.

[2] (a) William S. Knowles. Asymmetric Hydrogenations. Nobel Lecture, Monsanto Co., St. Louis, MO 63167, USA, December 8, 2001. (b) Juge, S.; Genet, J. P. Asymmetric Synthesis of Phosphinates, Phosphine Oxides and Phosphines by Michaelis Arbuzov Rearrangement of Chiral Oxazaphospholidine. *Tetrahedron Letters* **1989**, *30* (21), 2783–2786. (c) Berger, O.; Montchamp, J.-L. A General Strategy for the Synthesis of P-Stereogenic Compounds. *Angewandte Chemie International Edition* **2013**, *52* (43), 11377–11380. (d) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. Efficient Asymmetric Synthesis of P-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-Oxide Agents. *J. Am. Chem. Soc.* **2013**, *135* (7), 2474–2477. (e) Xu, D.; Rivas-Bascón, N.; Padial, N. M.; Knouse, K. W.; Zheng, B.; Vantourout, J. C.; Schmidt, M. A.; Eastgate, M. D.; Baran, P. S. Enantiodivergent Formation of C–P Bonds: Synthesis of P-Chiral Phosphines and Methylphosphonate Oligonucleotides. *J. Am. Chem. Soc.* **2020**, *142* (12), 5785–5792.

of an L-Menthol-derived phosphinate ester precursor which underwent stereospecific nucleophilic substitution to form a chiral phosphine oxide, which served as a common intermediate in the synthesis of multiple chiral phosphine ligands[2a]. Owing to their propensity to undergo highly stereospecific nucleophilic substitution reactions with Grignard reagents and organolithiates to afford the corresponding phosphine oxide products, chiral phosphinate esters remain one of the most reliable chiral building blocks for stereospecific elaboration towards these targets.[2e]

Synthetic strategies for accessing phosphinate esters have often involved appending a chiral alcohol.[2a,2b,2c,2d] While these strategies are useful for accessing phosphinate esters as precursors to chiral phosphine oxides, they do not serve as general approaches for accessing chiral phosphinate esters as targets of interest. Recently, however, Phil Baran's lab has utilized *trans*-limonene oxide-derived auxiliaries for the stereospecific synthesis of enantioenriched phosphinate esters.[2e]

A catalytic asymmetric methodology for the synthesis of phosphinate esters could provide a more versatile, direct route to phosphinate ester products. The Trost lab has reported the enantioselective synthesis of phosphinate esters via a Pd-catalyzed asymmetric allylic alkylation of phosphinic acids (Fig 3.1).[3] Although high levels of enantioselectivity are observed in this reaction with a broad variety of phosphinic acids, the scope of allyl bromides compatible with this method is limited to 3-bromocyclohexene and 3-bromocycloheptene. Consequently, the diversity of phosphinate esters accessible via this approach is restricted with respect to alkoxy-substitution.

---

[3] Trost, B. M.; Spohr, S. M.; Rolka, A. B.; Kalnmals, C. A. Desymmetrization of Phosphinic Acids via Pd-Catalyzed Asymmetric Allylic Alkylation: Rapid Access to P-Chiral Phosphinates. *J. Am. Chem. Soc.* **2019**, *141* (36), 14098–14103.

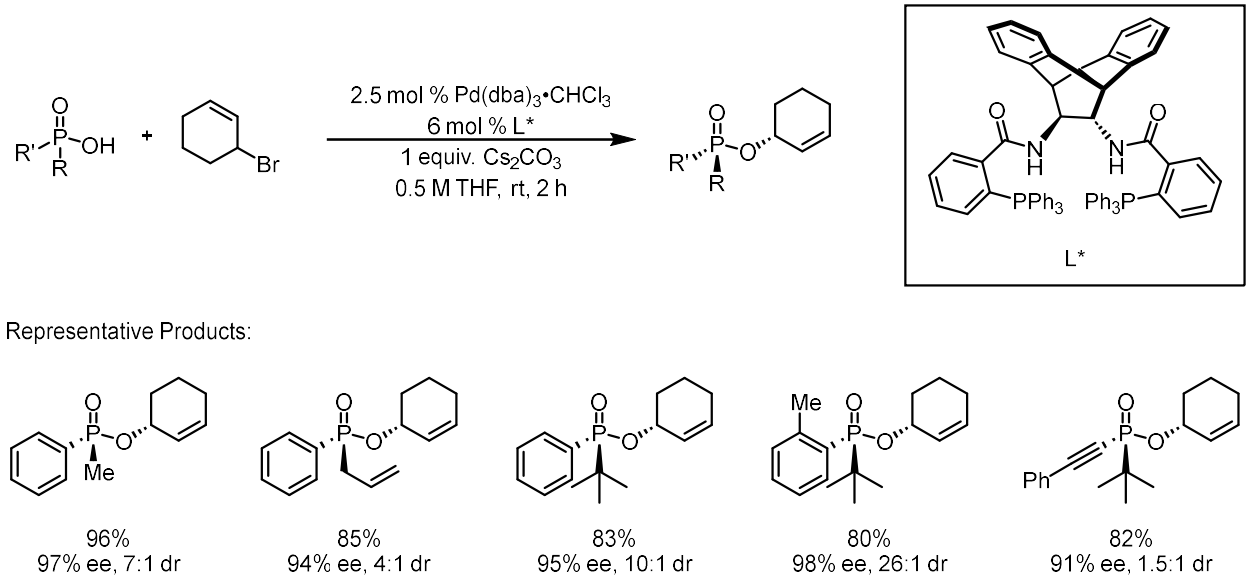


Figure 3.1 Asymmetric synthesis of phosphinate esters via Pd-catalyzed allylic alkylation of phosphinic acids.

We envisioned that a more versatile asymmetric functionalization of phosphinic acids could be facilitated via a hydrogen-bond-donor catalyzed desymmetrization of these substrates with sulfonium electrophiles. Sulfonium reagents are versatile alkylating agents that can undergo reaction with a broad variety of nucleophiles owing to the electrophilic nature of the sulfonium α-carbon.[4] The biological sulfonium compound *S*-adenosylmethionine (SAM) serves as nature's major methylating agent for a broad variety of substrates,[4a] including organophosphorus compounds. The van der Donk lab reported the SAM-dependent methylation of a phosphonate intermediate via an *O*-methyltransferase in the biosynthesis of the antibiotic dehydrophos (Fig.

[4] (a) Fontecave, M.; Atta, M.; Mulliez, E. S-Adenosylmethionine: Nothing Goes to Waste. *Trends in Biochemical Sciences* **2004**, *29* (5), 243–249. (b) Kozhushkov, S. I.; Alcarazo, M. Synthetic Applications of Sulfonium Salts. *Eur J Inorg Chem* **2020**, *2020* (26), 2486–2500.

3.2a),[5] and the Moore lab recently reported the enzymatic SAM-dependent methylation of a phosphate intermediate as the final step in the synthesis of the natural organophosphate guanitoxin (Figure 3.2b).[6] Although sulfonium salts have found a broad variety of applications as alkylating reagents in synthetic organic chemistry,[4b] an asymmetric organocatalytic alkylation of P(V) nucleophiles with sulfonium reagents has yet to be reported.

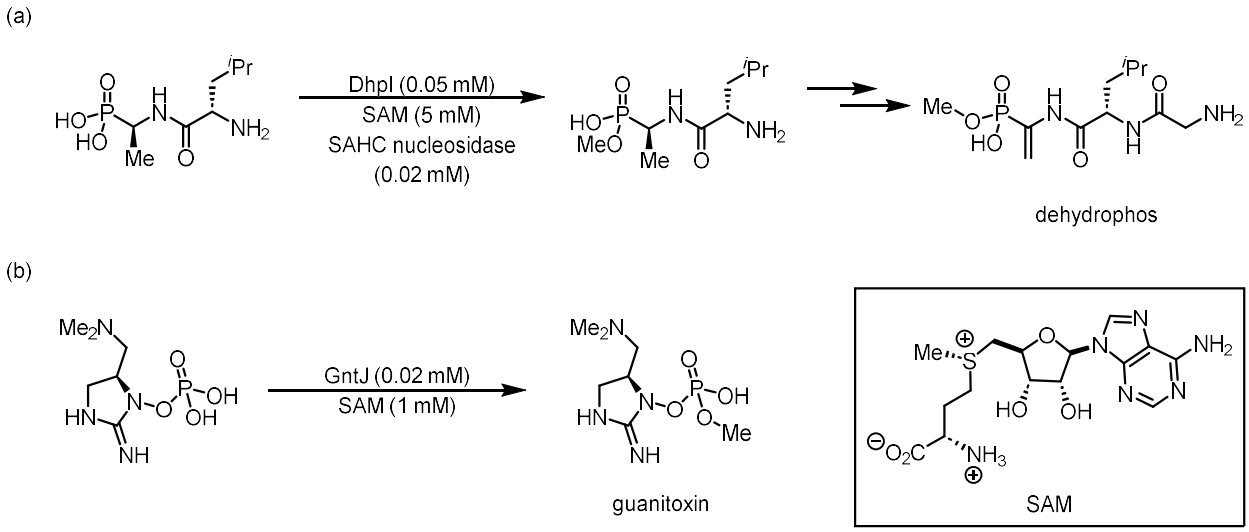


Figure 3.2 Biosynthetic examples of SAM-dependent methylation reactions of organophosphate intermediates catalyzed by *O*-methyltransferases.

The ionic nature of sulfonium salts makes them promising reagents for the development of asymmetric alkylation reactions using hydrogen-bond-donor catalysis. Chiral hydrogen-bond-donor catalysts have been shown to control the enantioselectivity of organic reactions involving

[5] Bougioukou, D. J.; Mukherjee, S.; van der Donk, W. A. Revisiting the Biosynthesis of Dehydrophos Reveals a TRNA-Dependent Pathway. *Proceedings of the National Academy of Sciences* **2013**, *110* (27), 10952–10957.

[6] Lima, S. T.; Fallon, T. R.; Cordoza, J. L.; Chekan, J. R.; Delbaje, E.; Hopiavuori, A. R.; Alvarenga, D. O.; Wood, S. M.; Luhavaya, H.; Baumgartner, J. T.; Dörr, F. A.; Etchegaray, A.; Pinto, E.; McKinnie, S. M. K.; Fiore, M. F.; Moore, B. S. Biosynthesis of Guanitoxin Enables Global Environmental Detection in Freshwater Cyanobacteria. *J. Am. Chem. Soc.* **2022**, *144* (21), 9372–9379.

cationic intermediates by hydrogen-bonding to the associated anion,[7] and we hypothesized that this reactivity principle could be extended to sulfonium salts. Association of a chiral hydrogen-bond-donor with the counterion of the sulfonium could result in the formation of a chiral sulfonium complex, thus engendering enantioselectivity in the reaction of the sulfonium with a prochiral nucleophile. The application of chiral hydrogen-bond-donors for this purpose was previously demonstrated by Cahard and coworkers, who reported the enantioselective trifluoromethylation of β-keto esters with Umemoto's reagent using a stoichiometric chiral guanidinium additive.[8] A catalytic, enantioselective alkylation of β-keto esters with dibenzothiophenium salts was previously developed in the Jacobsen lab using a chiral urea catalyst (Fig. 3.3).[9] In this work, it was found that chiral urea catalysts bind and increase the solubility of these sulfonium salts, consistent with phase-transfer catalysis being a mode of enantioselectivity in this reaction (Table 3.1).[9] It was observed that both primary and secondary sulfonium salts reacted readily with similar enantioselectivity in this reaction, allowing a broad variety of alkyl groups to be installed (Fig 3.3). We hypothesized that this system could be extended to the enantioselective desymmetrization of phosphinate anions, facilitating the selective alkylation of one of the phosphinate's two enantiotopic oxygens to generate enantioenriched phosphinate esters. The generality with respect to alkyl groups compatible with this chemistry could allow a broad variety of phosphinate esters to be accessed using this approach.

[7] (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107* (12), 5713–5743. (b) Gillespie, J. E.; Fanourakis, A.; Phipps, R. J. Strategies That Utilize Ion Pairing Interactions to Exert Selectivity Control in the Functionalization of C–H Bonds. *J. Am. Chem. Soc.* **2022**, *144* (40), 18195–18211.

[8] Noritake, S.; Shibata, N.; Nomura, Y.; Huang, Y.; Matsnev, A.; Nakamura, S.; Toru, T.; Cahard, D. Enantioselective Electrophilic Trifluoromethylation of β-Keto Esters with Umemoto Reagents Induced by Chiral Nonracemic Guanidines. *Org. Biomol. Chem.* **2009**, *7* (17), 3599–3604.

[9] Kedrowski, S.A.; Jacobsen, E. N., unpublished results.

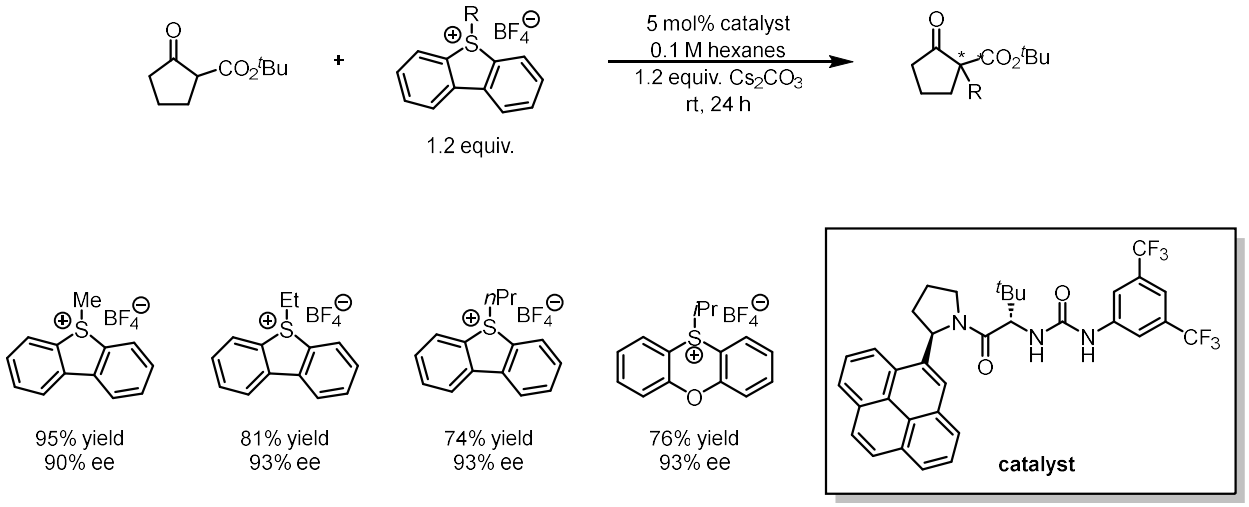
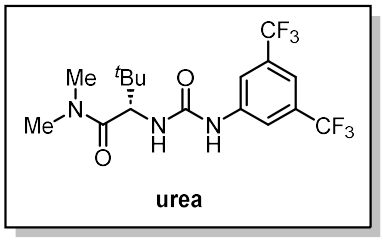


Figure 3.3 Enantioselective alkylation of β-keto esters via chiral urea-catalyzed sulfonium alkylation.

Table 3.1 Effect of chiral urea on solubility of sulfonium salts in toluene



Conditions (in toluene-d_8)	**[$Ph_2MeSOTf$]**	**[Ph_2MeSBF_4]**
no urea	0.38 mM	0.024 mM
10 mM urea	2.2 mM	0.25 mM
Increase	***6x***	***11x***

3.2 Reaction Development

We began using a model system with methyl(phenyl)phosphinic acid (**2a**) and *S*-methyldibenzothiophenium tetrafluoroborate (**3a**) under conditions previously established by Kedrowski and Jacobsen to evaluate the performance of different urea catalysts in the reaction (Fig. 3.4). Catalyst **1a** was found to give low but significant levels of enantioselectivity in this reaction (Fig 3.3). Use of thiourea analog **1b** resulted in nearly racemic product, whereas arylpyrrolidino ureas **1c** and **1d** gave comparable levels of selectivity to **1a**.

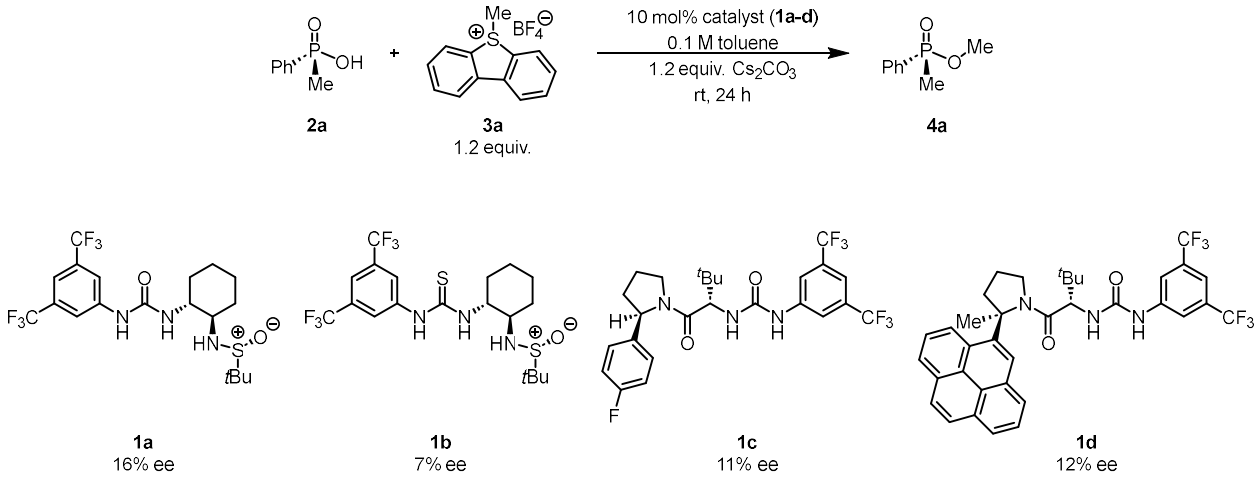
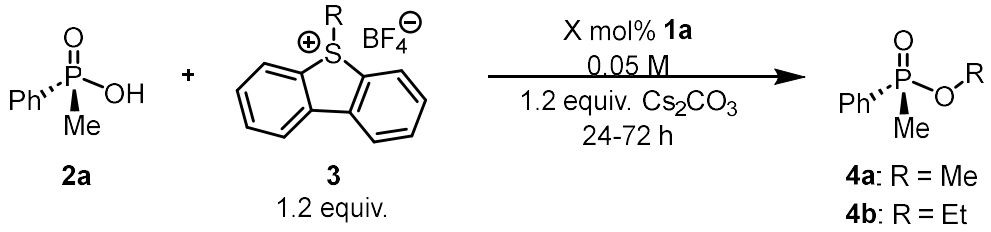


Figure 3.4 Effect of catalyst structure on enantioselectivity in alkylation of **3a**.

Different solvents were evaluated in this reaction, and a small increase in enantioselectivity was observed using TBME (Table 3.2). A more significant increase in selectivity was observed upon decreasing the reaction temperature to –40 °C, which resulted in the production of phosphinate ester **4a** in 36% ee and 72% yield. While the product was not observed using *S*-ethyldibenzothiophenium tetrafluoroborate under these conditions, ethyl phosphinate ester **4b** was observed in 36% ee and 79% yield when the reaction was carried out at 4 °C.

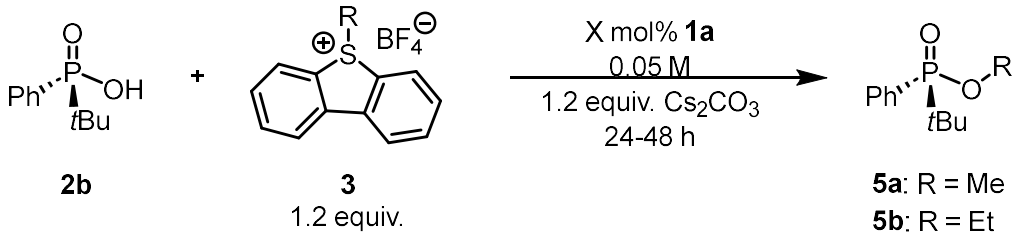
Table 3.2 Reaction optimization studies with substrate **2a**. Experiments were run on 0.05 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard. NR = not recorded. *Reaction was carried out at 0.1 M concentration.



R	solvent	Catalyst loading (mol%)	°C	% NMR yield	% ee
Me (**3a**)*	DCM	10	25	NR	6
Me (**3a**)*	TBME	10	25	NR	20
Me (**3a**)	TBME	20	–40	72	36
Et (**3b**)	TBME	10	25	NR	30
Et (**3b**)	TBME	10	4	79	36
Et (**3b**)	Hexanes	10	4	71	24

To interrogate the effect of phosphinic acid structure on enantioselectivity, *tert*-butyl(phenyl)phosphinic acid (**2b**) was also examined in this reaction (Table 3.3). Substrate **2b** underwent alkylation with similar levels of selectivity to **2a** at room temperature, with formation of product **5a** observed in 22% ee and **5b** observed in 23% ee. A significant increase in selectivity in the reaction of **2b** was observed upon changing the solvent from TBME to hexanes. Lowering the temperature to 4 °C resulted in an additional increase in enantioselectivity, yielding **5b** in 82% yield and 47% ee. However, further lowering the temperature to –40 °C resulted in a decrease in enantioselectivity.

Table 3.3 Reaction optimization studies with substrate **2b**. Experiments were run on 0.05 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



2b **3** 1.2 equiv. **5a**: R = Me **5b**: R = Et

R	Solvent	Catalyst loading (mol %)	°C	% NMR yield	% ee
Me (**3a**)	TBME	10	25	84	22
Et (**3b**)	TBME	10	25	97	23
Et (**3b**)	Hexanes	10	25	86	42
Et (**3b**)	Hexanes	20	25	89	33
Et (**3b**)	Hexanes	10	4	84	47
Et (**3b**)	Hexanes	20	4	82	47
Et (**3b**)	Hexanes	20	–40	71	23

The effect of catalyst structure on enantioselectivity was re-examined with substrate **2b** (Fig 3.5). Catalyst **1e**, an analog of catalyst **1a** with a less electron-deficient aniline, resulted in formation of the product with lower enantioselectivity, indicating that the strength of the hydrogen-bond-donor is important for selectivity. Catalyst **1f**, an analog of **1a** with a mesityl-substituted sulfinamide moiety, yielded the product with the opposite sense of enantioinduction and very low selectivity. Use of arylpyrollidino catalyst **1i** resulted in formation of product **5b** in –27% ee, whereas analogs of this catalyst possessing a pyrrole in place of the carbazole (**1g**, **1h**) yielded the product with lower levels of selectivity.

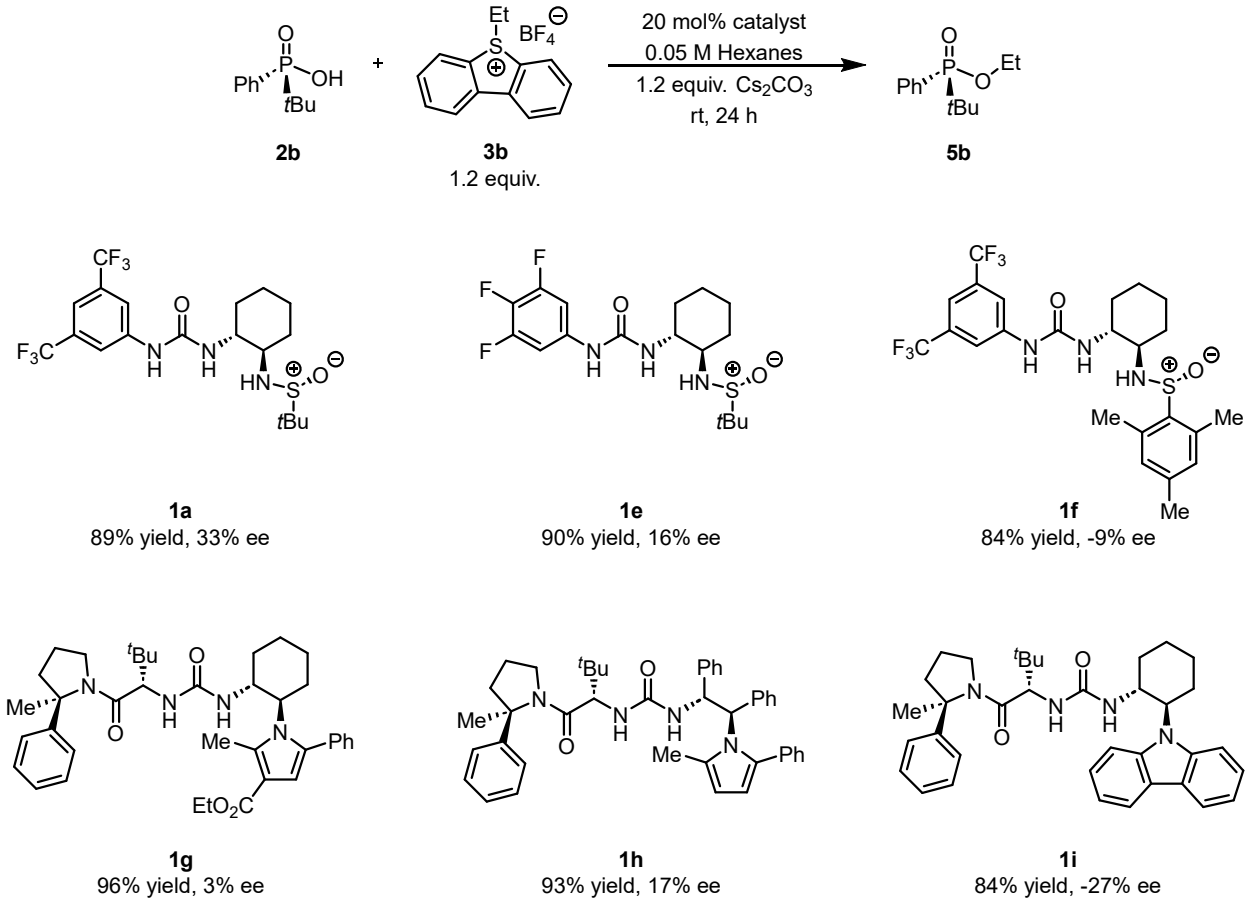
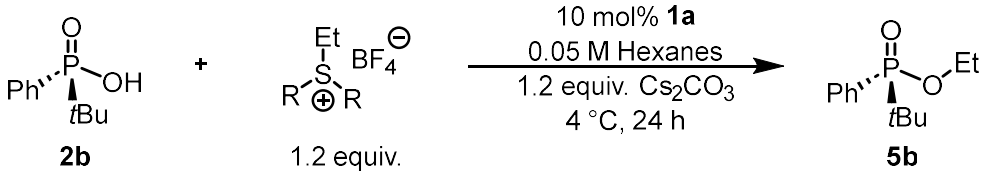
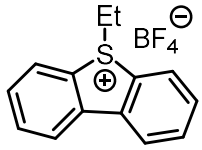
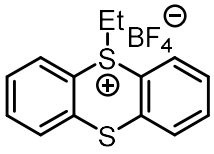
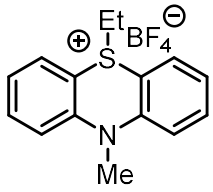


Figure 3.5 Studies investigating the effect of catalyst structure on enantioselectivity with substrate **2b**. Experiments were run on 0.05 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

The effect of the sulfonium structure on enantioselectivity was also examined (Table 3.4). Using a sulfonium reagent derived from thianthrene (**6**) instead of dibenzothiophene resulted in an increase in enantioselectivity, affording product **5b** in 63% ee and 87% yield. Alternatively, use of thiazine-derived sulfonium **7** afforded **5b** in 10% ee and 71% yield. These results reveal that both the steric and electronic nature of the sulfonium reagent play an important role in the enantioselectivity of this reaction.

Table 3.4 Optimization of sulfonium reagent with substrate **2b**. Experiments were run on 0.05 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard. *reaction was carried out at 25 °C.



Sulfonium reagent	% NMR yield	% ee
 (**3b**)	84	47
 (**6**)	87	63
 (**7**)	71*	10*

3.3 Conclusion and Future Directions

In conclusion, we have discovered an enantioselective desymmetrization of phosphinic acids via a hydrogen-bond-donor catalyzed sulfonium alkylation reaction. Evaluation of different sulfonium reagents revealed a significant effect of the structure of the reagent on

enantioselectivity of the reaction, and future studies will aim to further probe the effects of both the electronic and steric nature of the sulfonium on selectivity. The lack of solubility of these sulfonium salts in nonpolar solvents and the existing data demonstrating that urea catalysts increase the solubility of these reagents are consistent with a phase-transfer mechanism between the sulfonium and the hydrogen-bond donor. However, the hydrogen-bond-donor catalyst may also competitively form a complex with the anionic phosphinate intermediate resulting from deprotonation of the phosphinic acid by cesium carbonate. Thus, future studies may also focus on investigating the resting state of the catalyst in this reaction, as well as the effect of the solubility of each reagent in the reaction medium on enantioselectivity. Moving forward, efforts may also focus on the expansion of the scope of this reaction beyond phosphinic acids to other prochiral P(V) acids, such as phosphates and phosphonates.

3.4 Experimental

3.5.1 General Considerations

All reactions were performed in standard, oven-dried glassware fitted capped with rubber septa. Concentration of solutions was carried out under reduced pressure using house vacuum (40 torr) at 35 °C unless otherwise described. Concentrations refer to solution volumes at room temperature (~22 °C). High-vacuum was achieved using a vacuum pump at 400 mTorr. Flash column chromatography was performed using a Biotage Isolera One system.

3.5.2 Materials and Instrumentation

Materials and Reagents

Catalyst **1a** ((R)-N-[(1R,2R)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl]-tert-butyl-sulfinamide ; CAS = 934762-68-2) was purchased from Sigma-Aldrich and used as received. All other reagents and solvents were purchased from commercial suppliers including Sigma-Aldrich, TCI, Alfa Aesar, Acros Organics, Matrix Scientific, Cambridge Isotope Laboratories, or Strem and used as received. Anhydrous solvents (diethyl ether, toluene, tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), and dichloromethane (DCM) were dried using activated alumina columns. Deuterated solvents were purchased from Cambridge Isotope Laboratories.

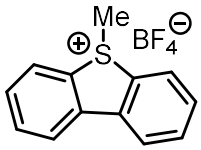
Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE NEO 400 or Bruker AVANCE NEO 400B spectrometer. Proton NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced using the NMR solvent ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Proton-decoupled ^{13}C NMR spectra are reported in ppm downfield from tetramethylsilane, and are referenced using the NMR solvent ($CDCl_3$: 77.16 ppm, C_6D_6: 128.06

ppm). Proton-decoupled ^{31}P NMR spectra are reported in ppm downfield from 85% H_3PO_4. ^{19}F NMR spectra are reported in ppm downfield from chlorotrifluoromethane. Splitting patterns for peaks on NMR spectra are represented as: (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, m = multiplet). Coupling constants are measured in Hertz (Hz). Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1200 series quaternary HPLC system with commercially available CHIRALCEL and CHIRALPAK analytical columns (4.6 x 250 mm).

3.5.3 Synthesis of Sulfonium Salts

S-methyldibenzothiophenium tetrafluoroborate (3a)



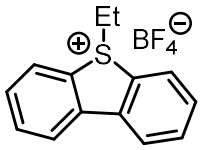
The synthesis of **3a** was performed using a procedure from a previous literature report.[10] A 20-mL vial equipped with a magnetic stir bar was charged with dibenzothiophene (760 mg, 3.9 mmol, 1 equiv.) and $AgBF_4$ (780 mg, 3.9 mmol, 1 equiv.). The vial was then equipped with a septum cap and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. Dichloroethane (12 mL) was then added via a syringe through the septum cap, and the mixture was allowed to stir for 1 minute. Iodomethane (1.45 mL, 23.4 mmol, 6 equiv.) was then added dropwise to the stirring mixture via syringe through the septum cap. The resulting yellow mixture was allowed to stir for 18 hours at room temperature. The mixture was then filtered via vacuum filtration through a fritted funnel into a 250 mL round bottom flask to remove the precipitated AgI,

[10] Simkó, D. Cs.; Elekes, P.; Pázmándi, V.; Novák, Z. Sulfonium Salts as Alkylating Agents for Palladium-Catalyzed Direct Ortho Alkylation of Anilides and Aromatic Ureas. *Org. Lett.* **2018**, *20* (3), 676–679.

and the filter cake was rinsed with DCM. The filtrate was then concentrated under reduced pressure until it became cloudy with only ~2 mL of solvent remaining. Then, 80 mL of Et_2O was added to the flask, causing the product to precipitate out of solution as a white solid. The flask was then sealed with a septum cap and cooled in a refrigerator at 4 °C for 1 hour. The precipitate was then filtered using a Buchner funnel lined with filter paper to collect the product as a white solid. The filter cake was washed with cold Et_2O. The product was then dried under vacuum to remove any remaining solvent. *S*-methyldibenzothiophenium tetrafluoroborate (812 mg, 73% yield) was afforded as a fluffy white solid. The spectral data matched the literature report.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.43 (m, 2H), 3.56 (s, 3H), 8.10 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.86 (td, *J* = 7.7, 1.1 Hz, 2H), 7.75 (td, *J* = 7.8, 1.2 Hz, 2H) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -149.61 ;

_S_-ethyldibenzothiophenium tetrafluoroborate (3b)

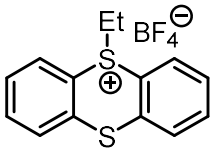


The synthesis of **3b** was performed using a procedure from a previous literature report.[10] A 20-mL vial equipped with a magnetic stir bar was charged with dibenzothiophene (585 mg, 3 mmol, 1 equiv.) and $AgBF_4$ (584 mg, 3 mmol, 1 equiv.). The vial was then equipped with a septum cap and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. Dichloroethane (12 mL) was then added via a syringe through the septum cap, and the mixture was allowed to stir for 1 minute. Iodoethane (1.45 mL, 18 mmol, 6 equiv.) was then added dropwise to the stirring mixture via syringe through the septum cap. The resulting yellow mixture was allowed to stir for 48 hours at room temperature. The mixture was then filtered via vacuum filtration through a fritted funnel into a 250 mL round bottom flask to remove the precipitated AgI, and the filter cake was rinsed with DCM. The filtrate was then concentrated under reduced

pressure until it became cloudy with only ~2 mL of solvent remaining. Then, 80 mL of Et_2O was added to the flask, causing the product to precipitate out of solution as a white solid. The flask was then sealed with a septum cap and cooled in a refrigerator at 4 °C for 1 hour. The precipitate was then filtered using a Buchner funnel lined with filter paper to collect the product as a white solid. The filter cake was washed with cold Et_2O. The product was then dried under vacuum to remove any remaining solvent. *S*-ethyldibenzothiophenium tetrafluoroborate (591 mg, 66% yield) was afforded as a fluffy white solid. The spectral data matched the literature report.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.0, 1.0 Hz, 2H), 8.24 – 8.01 (m, 2H), 7.81 (dtd, *J* = 46.0, 7.7, 1.2 Hz, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 0.93 (t, *J* = 7.1 Hz, 3H) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -150.43 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.11, 133.96, 131.51, 128.96, 127.09, 123.41, 45.46, 6.95.

_S_-ethylthianthrenium tetrafluoroborate (6)

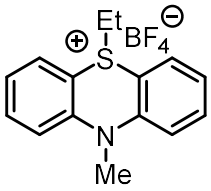


The synthesis of **6** was adapted from a procedure from a previous literature report preparing similar reagents.[10] A 50-mL round-bottom flask equipped with a magnetic stir bar was charged with thianthrene (648 mg, 3 mmol, 1 equiv.) and $AgBF_4$ (584 mg, 3 mmol, 1 equiv.). The vial was then equipped with a septum cap and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. Dichloroethane (12 mL) and tetrahydrofuran (20 mL) were then added via a syringe through the septum cap, and the mixture was allowed to stir for 1 minute. Iodoethane (1.45 mL, 18 mmol, 6 equiv.) was then added dropwise to the stirring mixture via syringe through the septum cap. The resulting yellow mixture was allowed to stir for 72 hours at room temperature. The mixture was then filtered via vacuum filtration through a fritted funnel into a 250 mL round bottom flask to remove the precipitated AgI, and the filter cake was rinsed with

DCM. The filtrate was then concentrated under reduced pressure until it became cloudy with only ~2 mL of solvent remaining. Then, 80 mL of Et_2O was added to the flask, causing the product to precipitate out of solution as a yellow solid. The flask was then sealed with a septum cap and cooled in a refrigerator at 4 °C for 1 hour. The precipitate was then filtered using a Buchner lined with filter paper to collect the product as a white solid. The filter cake was washed with cold Et_2O. The product was then extracted from the impure filter cake using chloroform and filtered to remove any remaining solids. The filtrate was then concentrated under reduced pressure, then dried under vacuum to afford *S*-ethylthianthrenium tetrafluoroborate **6** as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.82 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.75 (td, *J* = 7.6, 1.5 Hz, 2H), 7.68 (td, *J* = 7.6, 1.5 Hz, 2H), 3.82 (q, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7.3 Hz, 3H) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -151.25 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.54, 135.11, 134.42, 130.00, 129.85, 117.26, 36.30, 9.42.

_S_-ethyl-10-methylphenothiazin-5-ium tetrafluoroborate (7)



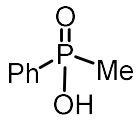
A 20-mL vial equipped with a magnetic stir bar was charged with 10-methylphenothiazine (639 mg, 3 mmol). The vial was then equipped with a septum cap and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. Dichloromethane (3 mL) was then added to the vial via a syringe through the septum. Triethyloxonium tetrafluroborate (2 mL, 1 equiv., 1 M solution in DCM) was then added dropwise to the vial via a syringe through the septum. The resulting solution was then refluxed at 40 °C for 16 hours. After 16 hours, the resulting brown solution was transferred to a 250-mL round-bottom flask and concentrated under

reduced pressure until less than ~3 mL of DCM remained. The solution was then poured into a 250-mL flask filled with TBME (100 mL) and the flask was allowed to cool at 24 °C for 24 hours. The solvent was then removed from the flask, leaving behind a pink solid adhered to the bottom of the flask. The flask was then put under vacuum to remove any remaining solvent. *S*-ethyl-10-methylphenothiazin-5-ium tetrafluoroborate (**7**) was afforded as a pink solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.77 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.33 (m, 2H), 3.77 (s, 3H), 3.37 (q, *J* = 7.3 Hz, 2H), 1.26 – 1.11 (m, 3H) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -151.83 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.15, 135.41, 132.42, 124.37, 116.82, 104.22, 41.07, 35.88, 8.66.

3.5.4 Synthesis of Phosphinic Acids

Methyl(phenyl)phosphinic acid (2a)



2a

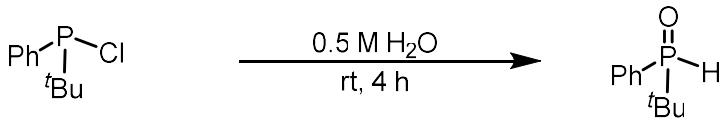
Methyl(phenyl)phosphinic acid (2a)

Compound **2a** was prepared on 5.88 mmol scale following the procedure reported by Trost and coworkers.[3] Phosphinic acid 2a was afforded as a white solid (197 mg, 21% yield). The spectral data matched the literature report.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.64 (m, 2H), 7.54 – 7.47 (m, 1H), 7.41 (ddd, *J* = 8.5, 6.6, 3.3 Hz, 2H), 1.62 (d, *J* = 14.7 Hz, 3H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.52 ; ^{13}C NMR (101 MHz,

$CDCl_3$) δ 133.21 (d, *J* = 133.7 Hz), 131.97 (d, *J* = 2.7 Hz), 130.51 (d, *J* = 10.6 Hz), 128.44 (d, *J* = 13.1 Hz), 16.86 (d, *J* = 101.5 Hz).

***Tert*-butyl(phenyl)phosphine oxide (7)**

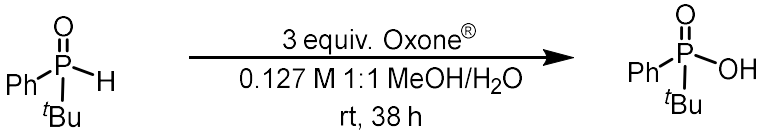


7

Commercially available chloro(phenyl)-tert-butylphosphine (1 g, 4.99 mmol, 1 equiv.) was added to a 20-mL vial equipped with a magnetic stir bar. 10 mL of H_2O was then added to the vial, which was then capped with a septum. The resulting mixture was subjected to stirring at room temperature for 4 hours. The aqueous phase was extracted three times with DCM (5 mL). The combined organic fractions were dried over $MgSO_4$, filtered through cotton, and concentrated under reduced pressure to afford the phosphine oxide **7** (702 mg, 77% yield) as a colorless oil. The spectral data matched the literature report.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 2H), 7.62 – 7.44 (m, 3H), 1.15 (d, *J* = 16.6 Hz, 9H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.54 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.49 (d, *J* = 2.8 Hz), 130.96 (d, *J* = 9.9 Hz), 128.53 (d, *J* = 11.7 Hz), 32.03 (d, *J* = 69.1 Hz), 23.48 (d, *J* = 2.2 Hz).

***Tert*-butyl(phenyl)phosphinic acid (2b)**



2b

This procedure was adapted from the synthesis of **2b** reported by Trost and coworkers.[3] *Tert*-butyl(phenyl)phosphine oxide (**7**) was added to a 100 mL round-bottom flask equipped with a

magnetic stir bar. MeOH (15 mL, 0.26 M) was then added to the flask. Oxone® (3.5 g, 3 equiv.) dissolved in 15 mL of H_2O was then added to the flask. The flask was then capped with a septum and the cloudy suspension was subjected to stirring at room-temperature for 38 h. The resulting mixture was then diluted with 50 mL of H_2O, and aqueous phase was extracted three times with DCM (30 mL). The combined organic fractions were then extracted with 30 mL of 1 M aqueous NaOH. The combined basic aqueous fractions were then acidified by slowly adding 37% HCl via pipette until a pH strip confirmed that the solution had a pH of 2, and subsequently extracted three times with DCM (50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered through cotton, and concentrated under reduced pressure to afford the phosphinic acid **2b** (443 mg, 58% yield) as a white solid. The spectral data matched the literature report.[3]

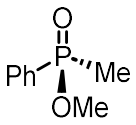
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.58 (m, 2H), 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.38 (td, *J* = 7.5, 3.2 Hz, 2H), 1.03 (d, *J* = 15.7 Hz, 9H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.01 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.64 (d, *J* = 9.0 Hz), 131.68 (d, *J* = 2.7 Hz), 127.86 (d, *J* = 12.0 Hz), 32.32 (d, *J* = 100.0 Hz), 23.80.

3.5.5 General Procedure for Enantioselective Alkylation Reaction

A 1-dram vial equipped with a magnetic stir bar was charged with catalyst **1a**, phosphinic acid (0.05 mmol, 1 equiv.), Cs_2CO_3 (20 mg, 0.06 mmol, 1.2 equiv.) and the sulfonium tetrafluoroborate (0.06 mmol, 1.2 equiv.). The vial was then capped with a septum and sealed with electrical tape. Solvent (1 mL) was then added via a syringe through the septum, and the reaction was subjected to stirring for 24 to 72 hours. The reaction was then diluted with ~1 mL of toluene-d8 and passed through a fritted filter to remove any remaining solids. Triphenylphosphine (13.1 mg, 1 equiv.) was then added to the crude filtrate as an internal standard. The resulting solution was then analyzed

by ^{31}P NMR (64 scans with a 10-second relaxation delay) to obtain an NMR yield. The products were purified via flash column chromatography.

Methyl (*S*)-methyl(phenyl)phosphinate (4a)

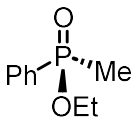


4a

Methyl methyl(phenyl)phosphinate (**4a**) was prepared from methyl(phenyl)phosphinic acid (7.5 mg, 0.05 mmol, 1 equiv.) and *S*-methyldibenzothiophenium tetrafluoroborate (**3a**, 17 mg, 0.06 mmol, 1.2 equiv.), catalyst **1a** (5 mg, 0.01 mmol, 0.2 equiv.), and TBME (1 mL) at –40 °C for 72 hours. The product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 2H), 7.62 – 7.52 (m, 1H), 7.55 – 7.42 (m, 2H), 3.61 (d, *J* = 11.3 Hz, 3H), 1.67 (d, *J* = 14.6 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.37 (d, *J* = 2.8 Hz), 131.33 (d, *J* = 10.2 Hz), 131.04 (d, *J* = 126.8 Hz), 128.72 (d, *J* = 12.6 Hz), 51.04 (d, *J* = 6.2 Hz), 15.53 (d, *J* = 103.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.07.

Phosphinate **4a** was determined to be 36% ee by chiral HPLC analysis (CHIRALPAK AS-H, 30% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 12.1 min, t_R(major) = 9.7 min).

Ethyl (*S*)-methyl(phenyl)phosphinate (4b)



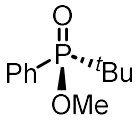
4b

Ethyl methyl(phenyl)phosphinate (**4b**) was prepared from methyl(phenyl)phosphinic acid (**2a**, 7.5 mg, 0.05 mmol, 1 equiv.), *S*-ethyldibenzothiophenium tetrafluoroborate (**3b**, 18 mg, 0.06 mmol, 1.2 equiv.), catalyst **1a** (2.4 mg, 0.005 mmol, 0.1 equiv.), and TBME (1 mL) at 4 °C for 24 hours

using the general procedure. The product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H), 7.59 – 7.43 (m, 3H), 4.16 – 3.77 (m, 2H), 1.66 (d, *J* = 14.6 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.14 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.22 (d, *J* = 2.8 Hz), 131.85 (d, *J* = 126.8 Hz) 131.25 (d, *J* = 10.1 Hz), 60.52 (d, *J* = 6.0 Hz), 16.48, 15.93 (d, *J* = 96.0 Hz).

Phosphinate **4b** was determined to be 36% ee by chiral HPLC analysis (CHIRALPAK AS-H, 20% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 13.5 min, t_R(major) = 11.3 min).

Methyl (*S*)-*tert*-butyl(phenyl)phosphinate (5a)

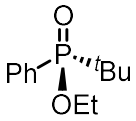


5a

Methyl tert-butyl(phenyl)phosphinate (**5a**) was prepared from *tert*-butyl(phenyl)phosphinic acid (**2b**, 10 mg, 0.05 mmol, 1 equiv.) and *S*-methyldibenzothiophenium tetrafluoroborate (**3a**, 17 mg, 0.06 mmol, 1.2 equiv.) catalyst **1a** (2.4 mg, 0.005 mmol, 0.1 equiv.), and TBME (1 mL) at room temperature for 24 hours using the general procedure. The product was purified using flash column chromatography (0 to 5% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (ddd, *J* = 10.1, 8.2, 1.4 Hz, 2H), 7.60 – 7.43 (m, 3H), 3.68 (d, *J* = 10.5 Hz, 3H), 1.13 (d, *J* = 15.6 Hz, 9H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 52.89 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.26 (d, *J* = 8.8 Hz), 132.07 (d, *J* = 2.8 Hz), 128.33 (d, *J* = 11.6 Hz), 127.89 (d, *J* = 114.4 Hz), 51.54 (d, *J* = 7.3 Hz), 32.59 (d, *J* = 100.9 Hz), 24.24.

Phosphinate **5a** was determined to be 22% ee by chiral HPLC analysis (CHIRALPAK AS-H, 3% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 24.7 min, t_R(major) = 29.2 min).

Ethyl (*S*)-tert-butyl(phenyl)phosphinate (5b)



5b

Ethyl tert-butyl(phenyl)phosphinate (**5b**) was prepared from *tert*-butyl(phenyl)phosphinic acid (**2b**, 10 mg, 0.05 mmol, 1 equiv.), *S*-ethylthianthrenium tetrafluoroborate (**6**, 20 mg, 0.06 mmol, 1.2 equiv.), catalyst **1a** (5 mg, 0.01 mmol, 0.2 equiv.), and hexanes (1 mL) at 4 °C for 24 hours using the general procedure. The product was purified using flash column chromatography (0 to 5% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (ddt, *J* = 10.1, 6.7, 1.4 Hz, 2H), 7.59 – 7.42 (m, 3H), 4.01 (ddt, *J* = 91.0, 10.1, 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 15.6 Hz, 9H) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 51.00 ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.18 (d, *J* = 8.7 Hz), 131.92 (d, *J* = 2.6 Hz), 128.81 (d, *J* = 114.8 Hz), 128.21 (d, *J* = 11.6 Hz), 60.72 (d, *J* = 7.2 Hz), 32.51 (d, *J* = 100.9 Hz), 24.22, 16.53 (d, *J* = 6.3 Hz).

Phosphinate **5b** was determined to be 56% ee by chiral HPLC analysis (CHIRALPAK IC, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 18.1 min, t_R(major) = 16.2 min).