A Preparative Route Investigation of *N*-Heterocyclic Phosphine Catalysts and their Application Towards the Synthesis of Colchinoid Analogues

by

Adam Beckett

Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
December 2020

To my loved ones

Table of Contents

List of Tables

List of Figures

List of Schemes

Abstract

A growing field in chemistry is the reduction of small molecules employing main group element catalysts. A recent advance has been the use of N-heterocyclic phosphines (NHPs) in the reduction of imines to produce secondary amines. NHPs can also perform conjugate reductions of electron poor alkenes.[1] (-)-Colchicine is a natural product of biological interest due to its antimitotic properties. Current synthetic methods require expensive and toxic transition metal catalysts to generate colchinoids.[2] The second chapter explores an alternative route towards the total synthesis of (-)-colchicine analogues by utilizing NHPs instead of traditional metal catalysis. A chemoselective conjugate reduction mediated by NHPs allows the expedient assembly of a precursor to a cyclization reaction. The next chapter provides a unique synthetic route towards the synthesis of previously inaccessible NHP moieties and preliminary exploration of their reactivity that aims to simplify current synthetic techniques by proposing an efficient one-pot synthesis.

List of Abbreviations and Symbols Used

α	alpha (carbon position)
β	beta (carbon position)
δ	chemical shift
Δ	heat (addition of heat in a reaction)
λ	wavelength
Å	angstrom
APCI	atmospheric pressure chemical ionization
BArF	tetrakis(pentafluorphenyl)borate
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
br	broad
CAL-B	Candida antartica lipase B
d	doublet
DAP	diazaphospholene
d.r.	diastereomeric ratio
dd	doublet of doublets
ddd	doublet of doublet of doublets
DMA	dimethylacetamide
DMS	dimethyl sulfide
e.e.	enantiomeric excess
equiv.	equivalent
e.r.	enantiomeric ratio

ESI	electrospray ionization
FLP	Frustrated Lewis pairs
HB(cat)	catecholborane
HB(pin)	pinacolborane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
J	coupling constant(s)
ligand	2-(dicyclohexylphosphinobiphenyl)
m	multiplet(s)
m/z	mass-to-charge-ratio
Mes	mesityl
N/A	not applicable
NBS	*N*-bromosuccinimide
NCME	*N*-acetylcholchinol-O-methyl-ether
NHC	*N*-heterocyclic carbene
NHP	*N*-heterocyclic phosphine
NMR	nuclear magnetic resonance
p	para
p	pentet(s)
P_2	DAP dimer
Pin	pinacol
PMP	*para*-methoxyphenyl
ppm	parts per million

q	quartet
R	generic group
R	rectus
s	singlet
SPO	secondary phosphine oxide
S_NAr	addition-elimination substitution mechanism (aromatic systems)
superhydride	sodium triethylborohydride
t	triplet(s)
t_{major}	Elution time of major isomer
t_{minor}	elution time of minor isomer
Tf	trifluoromethanesulfonyl
TMS	trimethylsilyl

Acknowledgements

First and foremost, I would like to extend thanks to my supervisor, Dr. Alex Speed, for his patience and guidance over the past few years. A combination of his extensive chemical knowledge, friendly demeanor and overall accommodation are what made this work possible. Truly, thank you.

I would like to thank my committee members, Dr. Mark Stradiotto and Dr. Saurabh Chitnis for taking time out of their busy schedules to participate as members on my committee.

I would like to thank my lab colleagues, Blake Huchenski (PhD candidate), Erin Welsh (PhD Candidate) and Dr. Travis Lundrigan for providing both a fun lab environment and their unconditional help with my projects.

Additionally, I would like to thank Dr. Mike Lumsden for the use of the NMR-3 facility. Dr. Xiao Feng for the collection of the mass spectrometric data for all of my compounds. Dr. Katherine Robertson at Saint Mary's University for the collection and excellent solving/refinement of my X-ray crystallography samples. I would also like to thank Dalhousie University and the Chemistry Department for supporting and helping me.

Finally, I am grateful to my family for the endless encouragement, academically and otherwise. Their continued support with my life's hurdles have helped shape me into the person I am today.

Chapter 1. Introduction

1.1 Introduction

The production of fine chemicals in the 21st century is of paramount importance, since fine chemicals have a range of everyday applications. Nature has found discrete ways of synthesizing complex molecules with tremendous efficiency, typically relying on complicated enzymatic avenues that have subtly developed over millions of years. Enzymes, proteins acting as biological catalysts, operate in an unrivalled fashion, selectively turning out highly specialized molecules at unprecedented rates. The scientific community prioritized efforts to mirror the efficiency of enzyme performance through the continued development of catalysis with a more recent focus on incorporating sustainable aspects of green chemistry.[3]

Catalysis is an essential tool in modern day synthetic chemistry that enables or enhances chemical synthesis for numerous chemical needs. Catalysts aim to produce chemical targets by decreasing activation energy requirements for chemical reactions and reducing the need for stoichiometric reagents.[4,5] Asymmetric catalysis is an important subclass of catalysis encompassing the synthesis of enantioenriched molecules. This is especially valuable in the pharmaceutical industry as the intrinsic chemical structure of molecules, including the absolute configuration, has a huge impact on how different molecules interact in a biological environment.[6,7] Traditional asymmetric catalysis tends to take advantage of the chemistry of transition-metals and chiral transition metal complexes as they have been able to facilitate reactions resulting in a wide range of enantiopure products.[8] This can mainly be attributed to their capability of accessing various oxidation states and presence of multiple coordination sites which allow reacting partners to be

brought together. There are growing concerns with both the cost and negative environmental repercussions of the use of such complexes, and transition metal residues in pharmaceutical products must be stringently controlled.[4,9] A growing field of chemical research aspires to combat these concerns by using main group elements instead of conventional transition-metal complexes to construct alternative synthetic routes with competitively high efficiencies.

Throughout drug design and fine chemical synthesis there are many distinct chemical reactions employed, however transformations of immense importance for creating stereocentres are hydrogenation, hydroboration and hydrosilylation. These reductive methods are commonly used in the synthesis of bioactive compounds. Traditional catalysts for such reactions typically involve transition-metal complexes of groups 8, 9, 10 and 11.[10] These catalysts, however, can have the aforementioned disadvantages associated with the use of transition metals, allowing for an opening for the emergence of new and exciting main group catalysts. These have garnered attention as they typically have lower toxicity and the elements may have higher abundance than their transition-metal counterparts (or at least the rare platinum group metals).[9] The following introductory section summarizes the development of organocatalysis and its shift towards incorporating main group elements to illustrate the foundation of phosphorus-based reductive catalysis. The appeal of this chemistry will outline the need for more sustainable pharmaceutical synthesis. A specific example pertinent to this thesis will be given through the analysis of preparative routes for the potent alkaloid, (-)-colchicine, and its analogues. Improvements to the synthesis, efficiency, selectivity and design of main group catalysis are essential in creating more sustainable chemical practices in the future.

1.2 Carbenes and N-Heterocyclic Carbenes

The inception of organocatalysis had an early start with the emerging popularity of *N*-heterocyclic carbenes (NHCs). Carbenes are defined as compounds with a neutral divalent carbon atom possessing six electrons in its valence shell.[11] The pioneering isolation of metal-free imidazole-2-ylidene in 1991 by Arduengo et *al*. paved the way for further exploration of NHCs as their relatively straightforward synthesis was also coupled with remarkable stability and the carbene could be stored as a crystalline material.[12] The reactive carbene species were previously investigated only indirectly, as reactive intermediates, but Arduengo's contribution allowed for their isolation as pure substances. Arduengo's isolation of carbenes motivated research towards other N-heterocyclic carbenes with differing elements in their ring system. Carbenes have become abundant chemical species in catalysis spanning fields as diverse as organocatalysts to ligands on transition-metal complexes.[13]

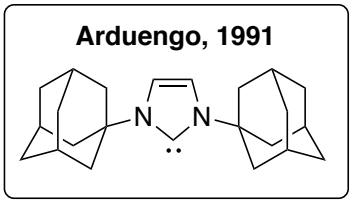
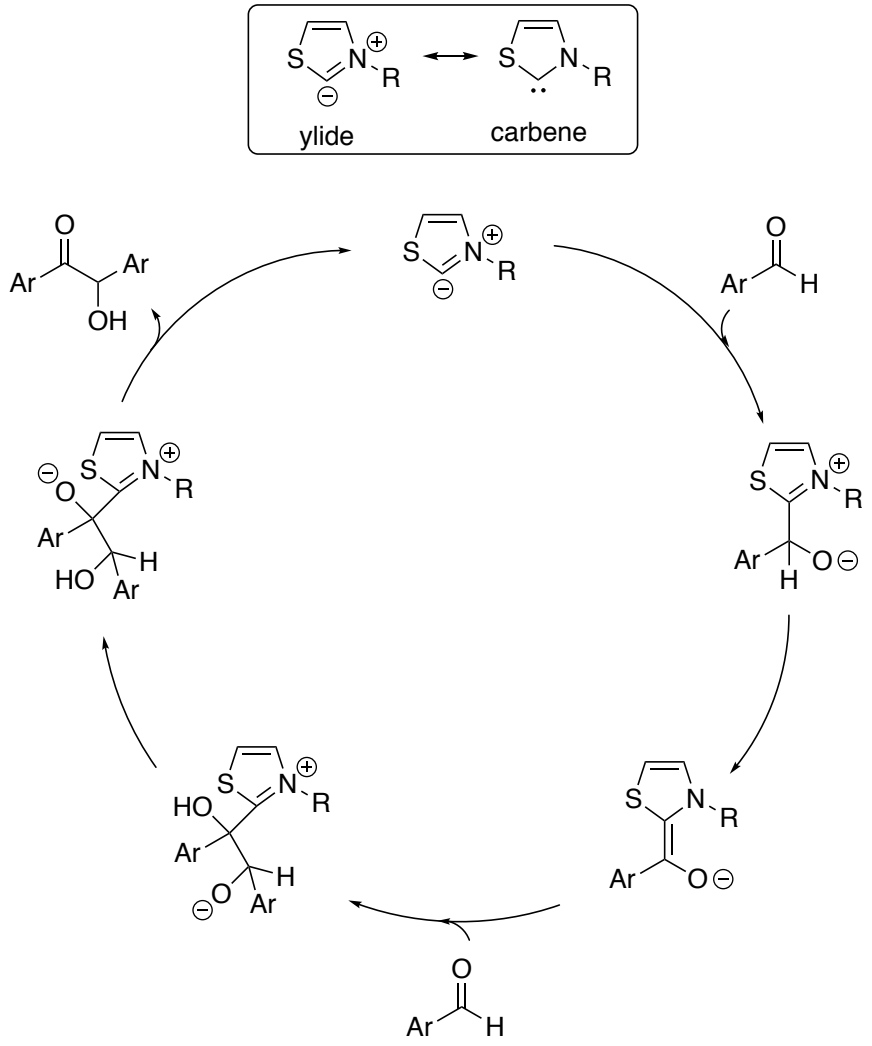


Figure 1. Free and stable 1,3-di-1-adamantyl-imidazol-2-ylidene carbene.

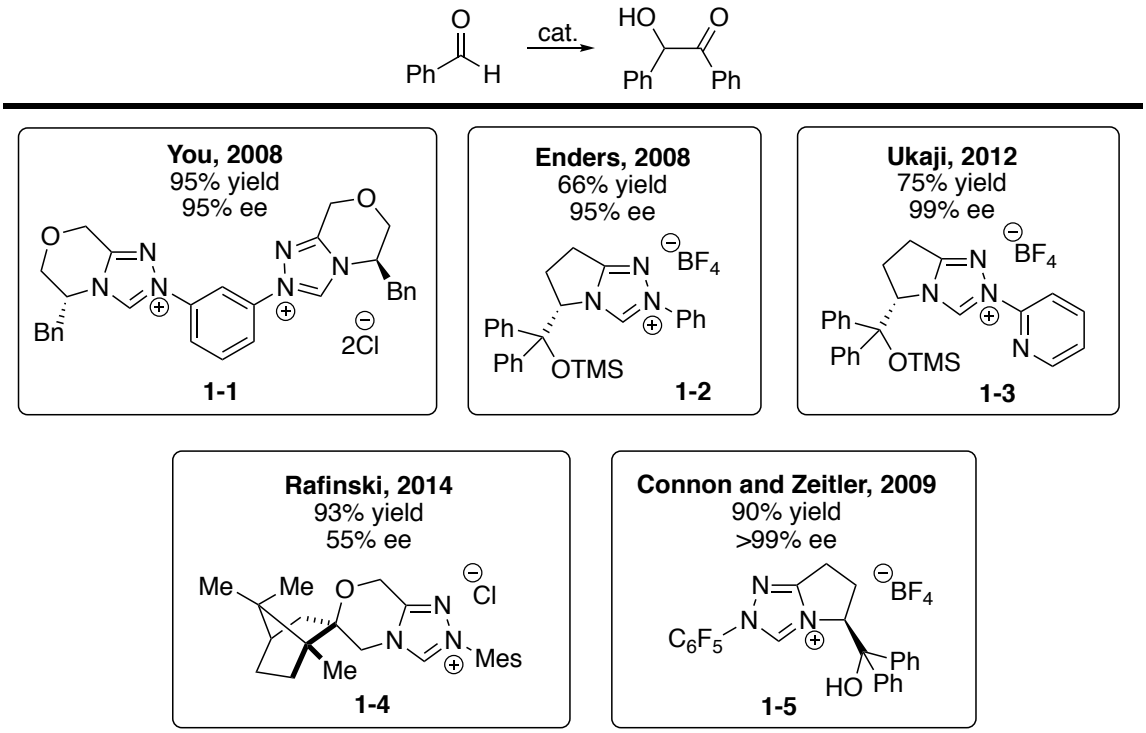
Carbenes are renowned for having high tunability because of their modular construction, allowing for customizable chemical properties which can then be tuned to efficiently carry out a number of catalytic reactions.[14] NHC organocatalysis has been investigated thoroughly in the form of the benzoin reaction, a carbon-carbon bond forming reaction between two aromatic aldehydes that was historically facilitated by cyanide anions, but now is known to also be catalyzed by NHCs as seen in Scheme 1.[15] Ukai

reported that thiazolium salts could catalyse this reaction and it was later proposed that the catalytically active species was a thiazolium zwitterion or ylide.[16]



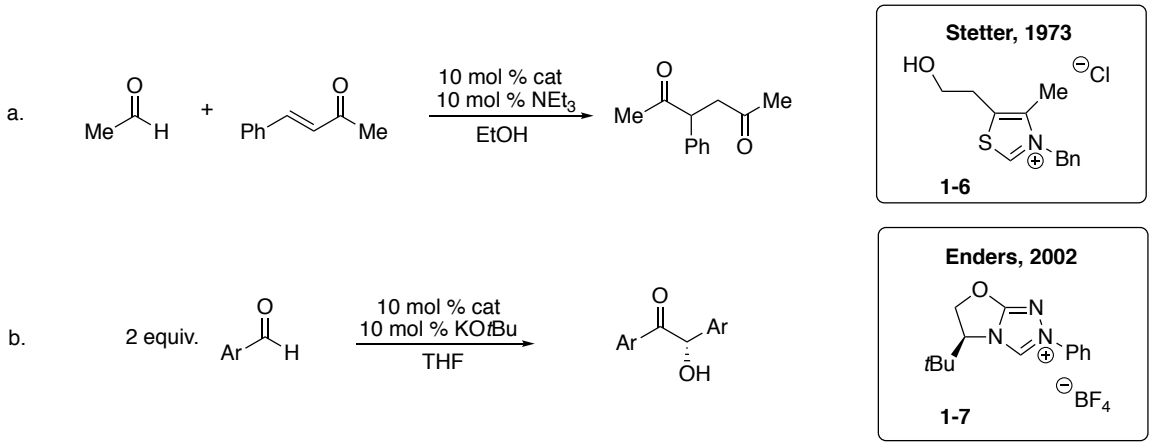
Scheme 1. Breslow benzoin condensation mechanism.

The Enders group used chiral NHC catalysts to mediate asymmetric benzoin condensations with up to 95% *e.e.*.[13,17] The benzoin transformation has been a topic of interest during the emergence of NHCs as organocatalysts, and many reports have successfully demonstrated enantioselective benzoin reactions using NHC catalysis with high efficiency and selectivity, setting the benchmark for future NHC catalyzed benzoin condensations.[18]



Scheme 2. Examples of carbenes that mediate benzoin reactions.

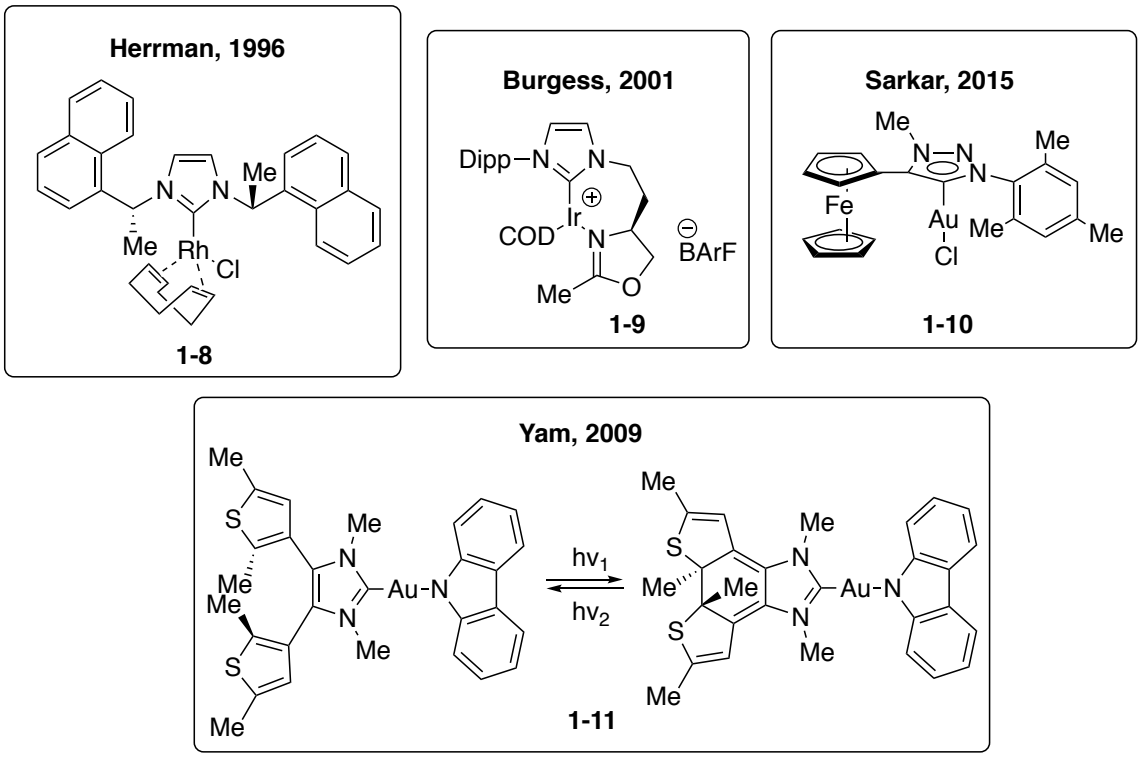
NHCs have become a hallmark of organocatalysis ranging across a wide variety of other popular transformations. Another reaction of note is the Stetter reaction, a common tool in synthetic organic chemistry to form carbon-carbon bonds through a 1-4 addition mechanism. First reported by Stetter in 1973, he demonstrated a then new method for the addition of aldehydes to activate double bonds using NHC catalysis that predated the isolation of NHCs. Shortly thereafter, new variants were discovered by the Enders group in which they reported a Stetter reaction using NHC catalysis as seen in Scheme 3.[19] Since this work, the Stetter reaction has been of particular interest in expansion to synthesis of biologically active compounds as well as expanding the scope beyond the popular chromanone scaffold.[13] Modern examples of the Stetter reaction have modified the NHC scaffold to tolerate more complex substrates.[20]



Scheme 3. Examples of carbenes that mediate Stetter and benzoin reactions.

In addition to the high catalytic activity of NHCs in these important organic reactions, a huge component of carbene research is attributed to integrating these compounds as ligands in transition-metal catalysis. NHCs have garnered enormous popularity as ligands for transition-metals, since they are electron rich and capable of forming strong NHC-transition metal bonds. The Hermann group reported NHC-Rh complexes could perform the selective hydrosilylation of ketones.[21] Later, in 2001, the Burgess group reported a highly enantioselective hydrogenation facilitated by an NHC-Ir complex.[22] These early successes incorporating NHC ligands into catalysis have allowed for major growth in the area into new realms such as multicyclic NHCs, chiral bis(NHC)s and bidentate NHCs, amongst others.[8] As a result of this expansion, transition-metal catalysts with NHC ligands have become a burgeoning area of research with the first photo-switchable NHC-based ligand being reported by the Yam group in 2009 with potential for switchable catalytic, regio- and enantioselectivities enabled by reversible photochromic reactions.[23] Transition metal catalysis has seen considerable attention as the need for fine chemicals grows. This need has resulted in a unique findings, such as mesoionic carbene

ligands on a bimetallic complex which was reported by the Sarkar group in 2015, the first of its kind.[24]



Scheme 4. Examples of carbene-supported transition metal complexes.

The progress of development of NHCs has been crucial in developing new strategies in synthetic chemistry. NHCs have become powerful tools to aid in the construction of complex molecules for various applications. The area of NHCs continues to flourish and aid in the development of sustainable chemical synthesis. Crucial to this thesis, NHCs are important in understanding the background of main group catalysis and its resulting impact, leading to recent attention in the area.

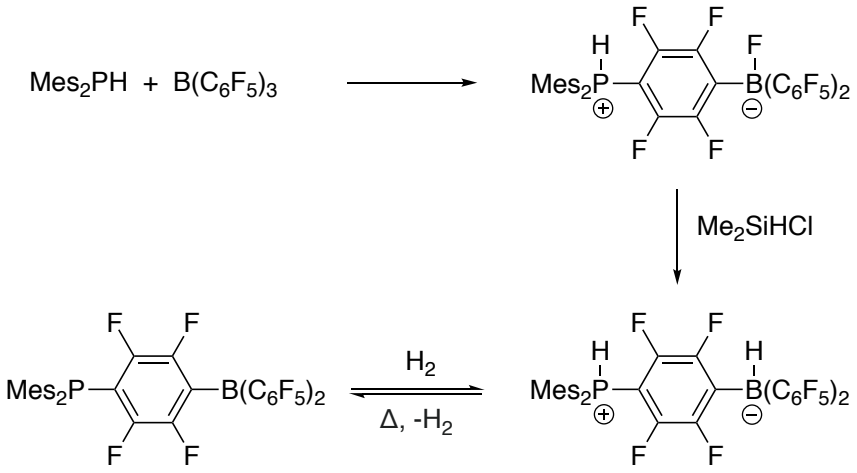
1.3 Main Group Catalysis

In this thesis, the term "reduction" will solely refer to hydrogenation, hydroboration and hydrosilylation of functional groups. This process of adding an organic fragment to a multiple bond has far-reaching applications with uses spanning from materials science to

pharmaceutical synthetises. Main group catalysis with *s* and *p*- block elements, unlike transition metal catalysis and traditional organocatalysis, is in its infancy, however since the early 1990's there has been considerable progress in the field.[9] New generations of main group catalysts are able to facilitate crucial reductions of olefins, alkynes, carbonyls and imines.

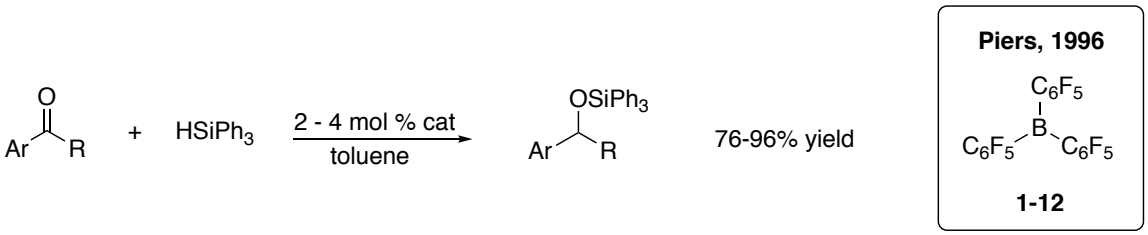
1.3.1 Frustrated Lewis-Pairs

The discovery of metal-free activation H_2 and other small molecules by bulky Lewis acid/base adducts has come to be known as Frustrated Lewis Pair (FLP) chemistry.[25] This concept conceived by Dr. Doug Stephan has huge implications in main group catalysis. Stephan and coworkers discovered that a system comprising of a sterically bulky Lewis basic phosphine in conjunction with a sterically bulky Lewis acidic borane can activate H_2 with sufficient heat, a process previously thought to be dominated by transition metal catalysis and unheard of in main group literature at the relatively low temperatures used by Stephan. In a typical Lewis acid/base interaction the two species easily form an adduct without the loss of a leaving group. In FLP chemistry, the steric bulk of the two species prevents the conventional adduct formation. Instead, in the first example showed by Stephan, the base nucleophilically attacks the acid para to the boron centre in a S_NAr reaction. This "frustrated" species has been shown to split H_2 and more importantly, release it upon heating as seen in Scheme 5. The newly liberated hydrogen atoms are capable of hydrogenating various functional groups. FLPs have since provided a platform for hydrogenation reactions with far-reaching chemical ramifications prompting continued emphasis on growing substrate scopes, improved catalytic activities and new catalyst designs.[26]



Scheme 5. Reversible activation of H_2 using FLP system.

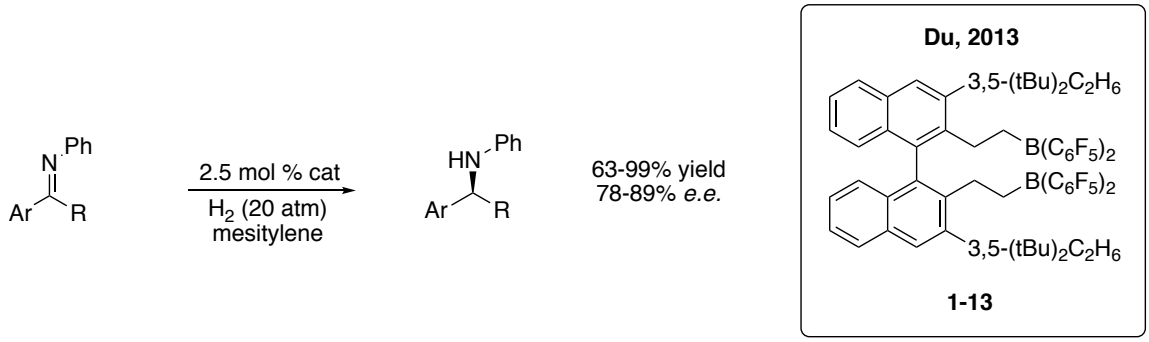
Bulky boron complexes have surfaced as versatile main group catalysts for reductive chemistry.[27] Early work in the field carried out by Piers demonstrated reductions by activating triphenylsilane using tris(pentafluorophenyl)borane to reduce aromatic aldehydes, ketones and ester functional groups under mild reaction conditions as seen in Scheme 6. Piers' early efforts studying the unique reactivity of boron complexes made it a primary research focus in main group catalysis moving forward.[27]



Scheme 6. Boron catalyzed reduction of aldehydes.

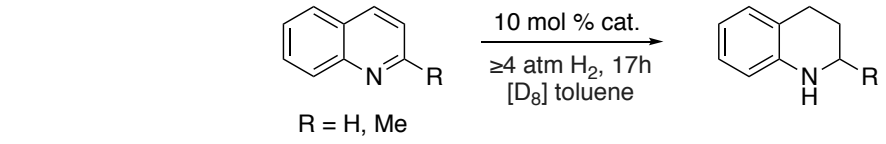
Chemoselectivity and functional group tolerance are two pivotal considerations when going about chemical transformations. Imine reductions continue to be an emphasis of synthetic chemistry due to the abundance of nitrogen moieties in pharmaceuticals and the ever-growing need for metal-free synthesis. Years after Piers' discovery, Du showed selective reduction of aromatic imines using a boron catalyst with a chiral diene "ligand"

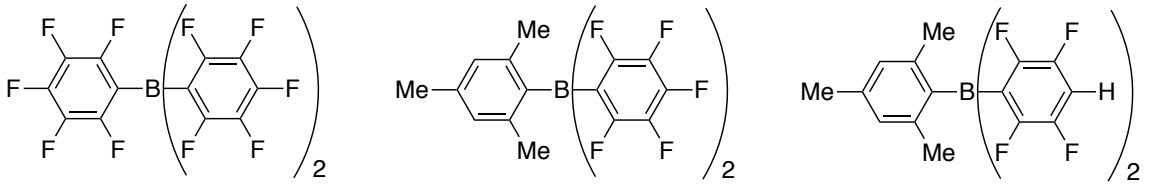
as seen in Scheme 7. The work reported imine reduction with high yield and selectivity, however the complex boron catalyst requires a more complex synthesis then previously investigated main group catalysts.[28]



Scheme 7. Boron catalyzed reduction of imines.

A milestone in imine reduction was the incorporation of increasingly sterically shielded boron Lewis acid complexes. Unique boron complexes were generated by modifying the substituents on the boron atom and effectively increasing the steric profile on the Lewis acid component as seen in Scheme 8. This alteration was shown to enhance the scope of imine hydrogenations to include imines with less sterically demanding substituents by limiting unwanted FLP reactivity. The catalyst demonstrated high chemoselectivity through the reduction of imines, ketones and quinolines with conversions up to 99%.[29] These bulky boron complexes, however, hindered catalytic turnover via a potentially slow hydride delivery and required the use of high pressure equipment.

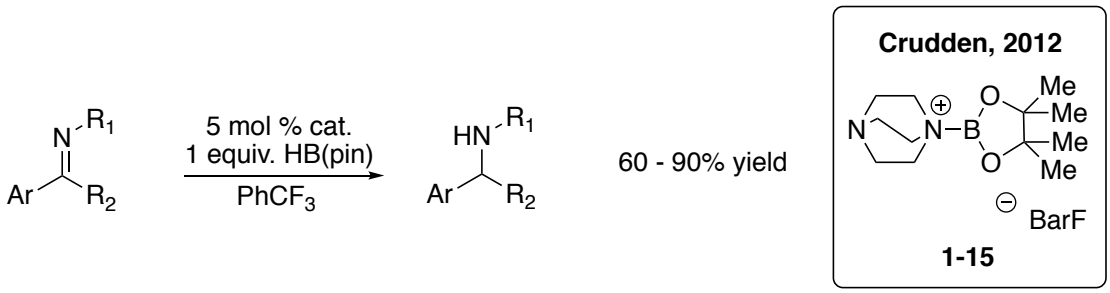




1-14a **1-14b** **1-14c**

Scheme 8. Lewis acid catalysts for metal-free hydrogenation of quinolines.

In 2012 the Crudden group developed a Lewis base- stabilized borenium cation catalyst that used HBpin as a terminal reductant, an available Lewis acid as seen in Scheme 9. This work popularised the use of borenium ions for reductions of unsaturated species.[30]



Scheme 9. Borenium catalyzed hydroboration of imines

Although early research primarily investigated boron chemistry, it should be noted that main group reductive catalysis is not limited to that of boron and early alkaline earth metals have also seen considerable attention. Harder and coworkers have shown that calcium, potassium and strontium, elements previously underutilized in catalytic literature, can hydrogenate conjugated alkenes through a sigma-bond metathesis at low temperatures and pressures. These catalysts have generally required long reaction times as well having a potentially limited substrate scope.[31]

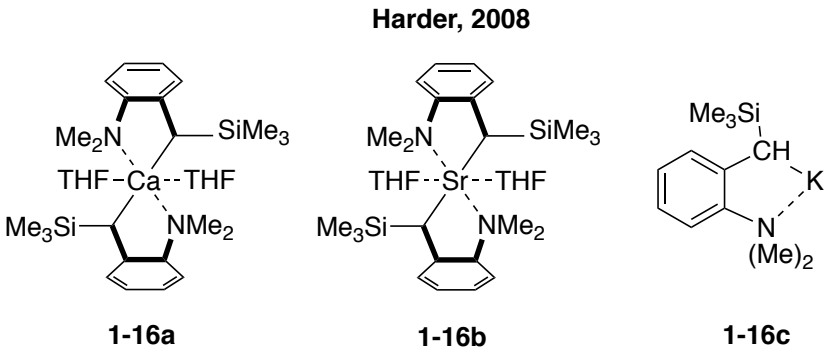
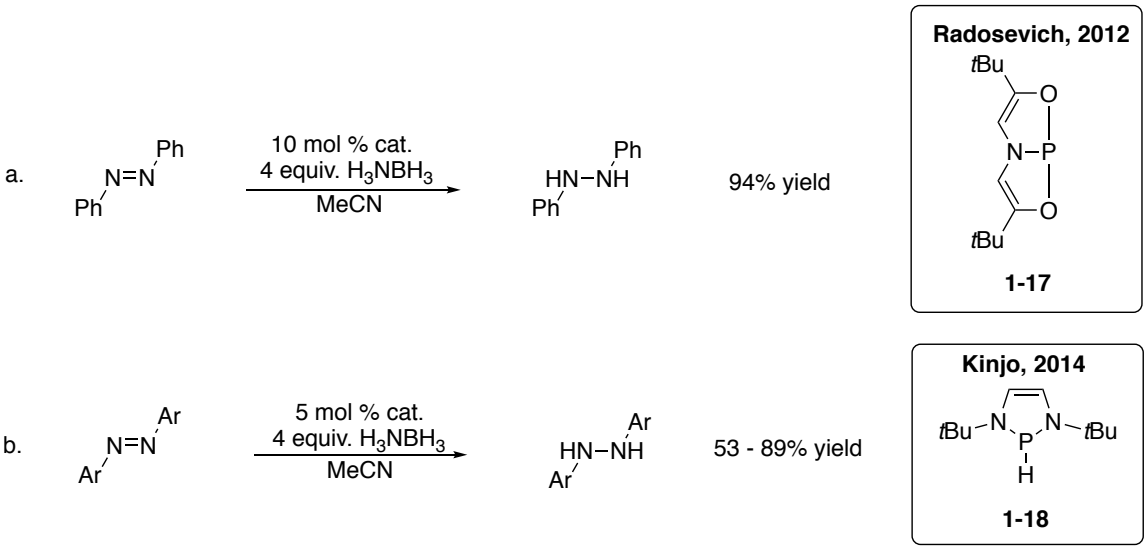


Figure 2. Examples of alkaline earth metal catalysts.

1.3.2 Phosphorus-Based Catalysts

Phosphorus compounds have regularly been used as ligands on transition metal complexes as well as simple nucleophilic species in organocatalysis, yet compounds with chemically active phosphorus centres where bonds were broken and fashioned more akin to transition metals were previously rare in the catalytic literature. One of the premier works in the field was carried out by Radosevich and coworkers in which they use phosphines to hydrogenate azobenzene as seen in Scheme 10(a). The unique trivalent phosphorus centre provides a main group platform for two-electron redox cycling similar to those seen in transition-metal complexes.[32] Although other main group elements have been shown have both the n and n+2 oxidation states in certain diatomic molecules[33], the reversible oxidation in Radosevich's system has accounted for great advances in phosphorus-based catalysis with the first example of a P^{III} species able to readily transform into a P^{V} species then be recycled to P^{III} with a terminal reductant.[32] Another major contributor, Kinjo, demonstrated phosphorus-based transfer hydrogenation of N=N bonds using ammonia borane and 1,3,2-diazaphospholenes as seen in Scheme 10(b). Unlike Radosevich's report, Kinjo's work did not have a redox cycling mechanism. Instead, he demonstrated addition of a P-H bond to the N=N bond which was followed by

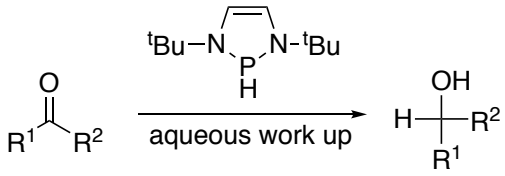
hydrogenolysis of the newly formed P-N bond by hydrogen transfer from the hydrogen source.[34] Kinjo's work uses an isoelectronic analogue of NHCs, N-heterocyclic phosphines (NHPs). These chemical species are of paramount importance to this thesis. NHCs have been much more extensively researched, however recent attention in phosphorus-centred catalysis has made NHPs an intriguing and fruitful area of catalysis.



Scheme 10. Transfer hydrogenation of diazenes by phosphorus-based catalysts.

The Gudat group was the first group to comprehensively research NHP reactivity using an array of different computational, experimental and structural techniques that examined NHP's molecular structures, bonding situations and Lewis acid properties. Their efforts revealed the interesting finding that the P-Cl bond in NHPs had a high extent of ionic character associated with the high degree of polarization of the phosphorus-substituent bond.[35,36] In addition to this discovery, they showed that that NHPs bearing a P-H bond behaved unlike typical secondary phosphines. These P-H bearing NHPs have hydridic character as opposed to the protic character of typical secondary phosphines. This reactivity was extensively studied as they demonstrated that aldehydes and ketones alike were stoichiometrically reduced to their corresponding alcohols using this unique hydridic

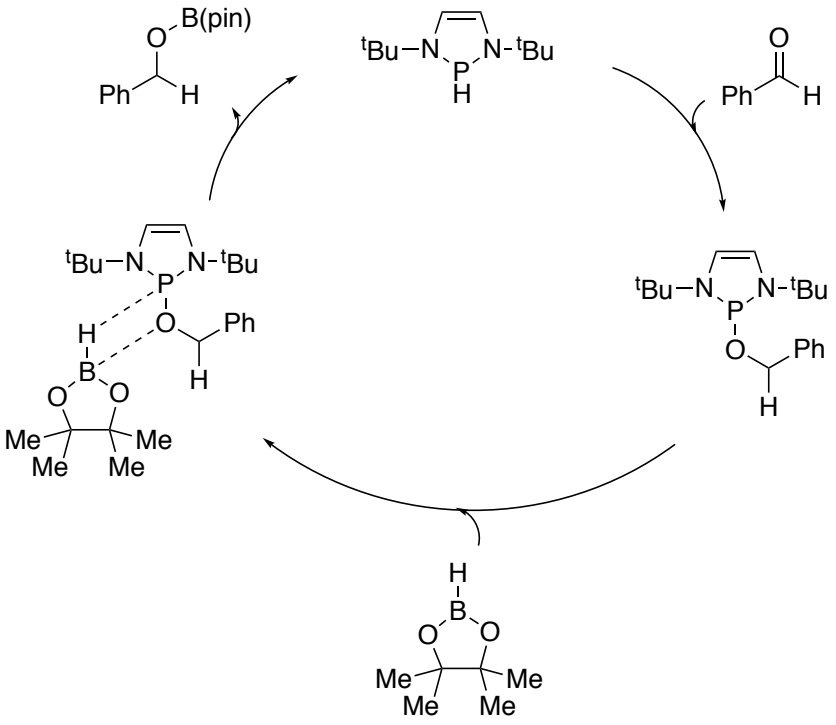
reactivity of NHPs as seen in Scheme 11.[37] These findings were the first examples of the use of NHPs for such transformations. These revelations, although important in the infancy of NHP reductive chemistry, did not immediately garner huge interest as other established reagents such as sodium borohydride could conduct the same reductive transformations efficiently. Only when NHPs could be used in a catalytic setting did they begin to reveal themselves as significant tools in synthesis.



Scheme 11. Generic stoichiometric reduction of carbonyl compounds via NHP-H.

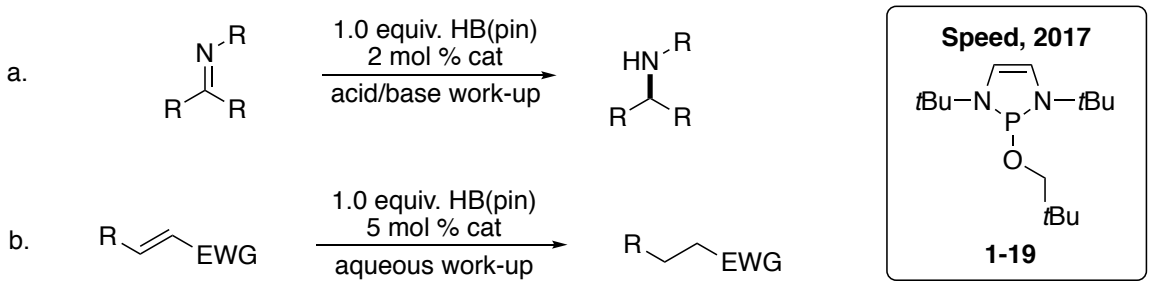
The first example of NHPs being used in catalysis was demonstrated by Kinjo's work that showed a catalytic metal free transfer hydrogenation of N=N using the air-stable ammonia-borane as the terminal reductant under mild reaction conditions.[34] Using stoichiometric reactions as well as kinetic and computational studies they concluded that the catalytic cycle differs from that of the redox mechanism reported earlier by Radosevich where a phosphorus centre cycled between the (III) and (V) oxidation states.[32] A follow-up study was conducted by the Kinjo group in which they employed NHP-H complexes as catalysts for the hydroboration of carbonyl derivatives and carbon dioxide. These transformations were previously dominated by transition-metal catalysts and Kinjo's work showed the potential for main group catalysts to go about the same transformations with efficient catalytic ability. In the carbonyl reduction paper, the Kinjo group revealed insight into the catalytic cycle which was gathered through evidence from multiple avenues, theoretical studies and experimental data.[38] They surmised that the cycle proceeds through a σ-bond metathesis mechanism, four-membered transition state as seen in Scheme 12 for

main group catalytic cycles. The product, a borylated alcohol, is subjected to an aqueous workup to generate the desired product.



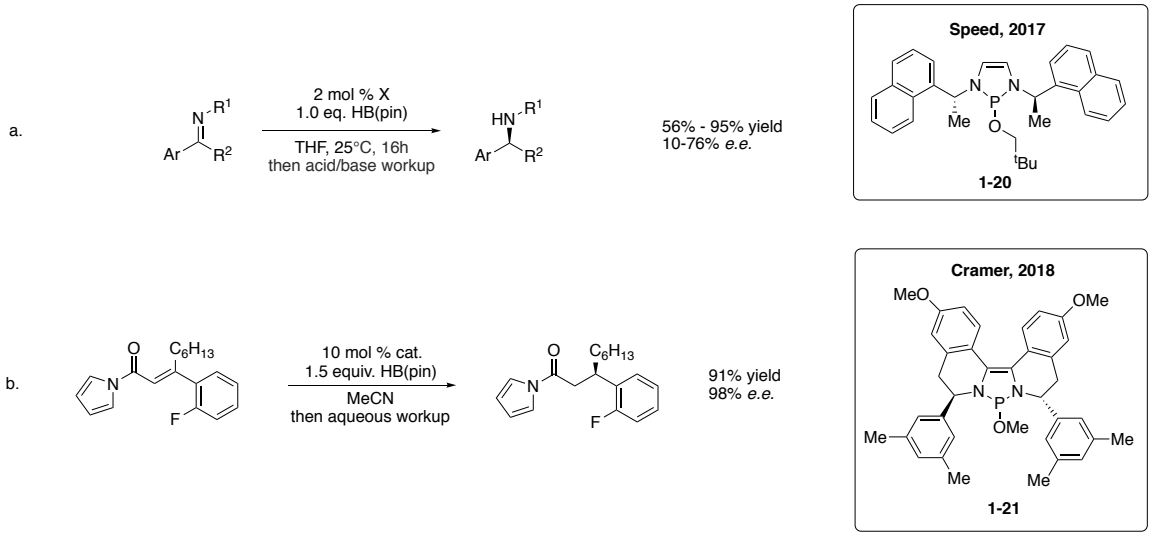
Scheme 12. Catalytic cycle for hydroboration of carbonyl compounds.

The next major contributions to the field involved research from the Speed group. Demonstrated was the first examples of 1,3,2-diazaphospholene catalyzed imine and conjugate reductions. Importantly, the catalyst was readily synthesized and able to be briefly handled in relatively dry open atmosphere, a major discovery for this field as seen in Scheme 13.[1]



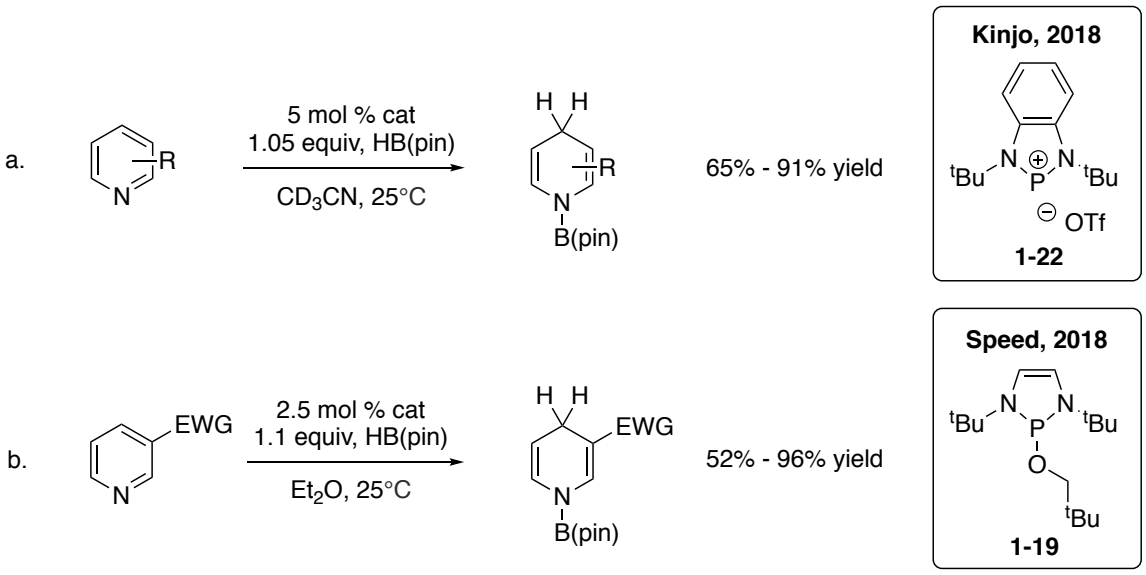
Scheme 13. Achiral (a.) imine and (b.) conjugate reductions by NHP-alkoxide precatalyst.

This work was soon improved upon as asymmetric hydroborations of imines by a neutral chiral NHP were reported**.** The aim of this work was to synthesize and investigate a library of NHP precatalysts and test them for their reductive capacities while exploring the effects of steric and electronic profiles on the catalyst activity. The Speed group developed a library of precatalysts able to reduce a broad scope of imines. Initial studies carried out by the Speed group report NHP **1-23** gave a modest enantioinduction of 88:12 with the best substrate.[1] One potential hypothesis is that increasing the rigidity of in the DAP scaffold through steric interactions may result in minimizing the amount of catalyst conformations. This, in turn, may result in an increase in catalyst selectivity. This methodology is strongly supported by Cramer's work in the synthesis of a pentacyclic DAP **1-21** with good to excellent enantioselectivities of conjugate reductions seen in Scheme 14. However these catalysts have more tedious synthetic route than the Speed catalysts.[39]



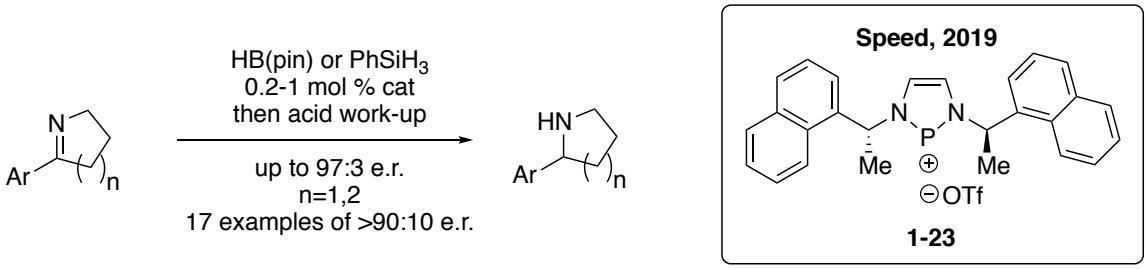
Scheme 14. Asymmetric (a.) hydroboration of imines with chiral neutral NHP-OR precatalysts and (b.) reduction of an α,β-unsaturated ketone with rigid polycylic NHP-OR precatalyst.

The Kinjo group investigated achiral variants of NHPs for a different application in their examination of N-heterocyclic phosphenium triflates as catalysts for regio- and chemoselective hydroboration of various pyridine substrates under ambient conditions.[40] The work differs from previous NHP work in that the phosphorus centre on the NHP is cationic in nature with a resulting enhancement in the Lewis acidity. The activity of these cationic NHPs can be contrasted with work done within the Speed group, which also studied pyridine reductions at the same time as the Kinjo group. This work showed neutral NHP **1-19** could effectively hydroborate pyridines as long as they had an electron withdrawing group in the 3-position. This contrasts with Kinjo's more general substrate scope, showing the neutral diazaphospholenes were less catalytically active than the cationic counterpart **1-22** demonstrated by Kinjo as seen in Scheme 15(a).[41]



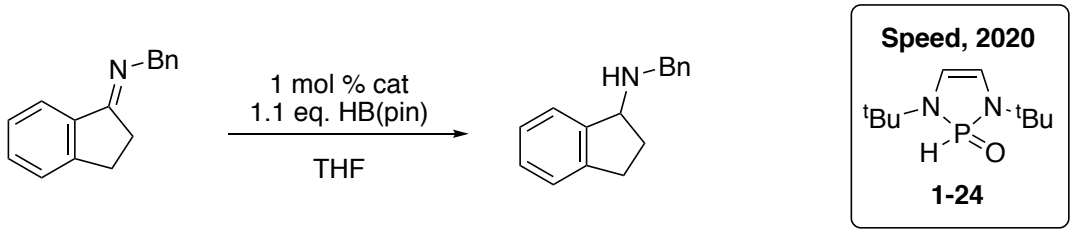
Scheme 15. Pyridine reductions catalyzed by (a.) NHP-OTf and (b.) NHP-OR catalysts

Following this discovery, cationic NHPs became an emerging area of investigation in asymmetric NHP catalysis. The Speed group synthesized enantiopure cationic diazaphospheniums and these complexes were the first phosphenium cations to be used in asymmetric catalysis for the reduction of imines.[42] The movement from neutral catalysts to phosphenium cations was fruitful, as these readily synthesized complexes were able to catalyze reductions of cyclic imines with enantiomeric ratios up to 97:3 with low catalyst loadings. A broad scope of aryl and heteroaryl pyrrolidines were prepared using this method. This class of catalyst was functional in both hydroborations and hydrosilylations using the relatively common silane reducing agents as seen in Scheme 16.



Scheme 16. Asymmetric hydroboration/silylation of cyclic imines via cationic NHP-OTf precatalysts (17 examples >90:10 e.r.).

The Speed group has also recently developed air-stable secondary phosphine oxides (SPOs) as another class of NHP precatalysts. This study stemmed from the fact that DAPs have hydrolyzed to SPOs relatively rapidly when removed from a dry atmosphere. In a controlled synthesis, the SPOs were generated by combining the DAP bromide analogue and triethylamine in dichloromethane and adding water. The new SPO complex was then easily transformed into the NHP hydride in the presence of HB(pin) in dry solvent. The air and water stability of these SPO precatalysts and their ability to purified through column chromatography may allow for isolation of diazaphospholenes that are not readily purified on the basis of solubility, which has been the standard method used in the Speed group to purify moisture-sensitive NHP bromides and triflates.[43] This area, although relatively recent, will be investigated in some capacity later in this work.



Scheme 17. Imine reduction catalyzed by SPO precatalyst.

Unlike transition-metal catalysis and organocatalysis, phosphorus-based reductive chemistry is a relatively new field. In the past 30 years, organocatalysis has become a useful

alternative to address issues with large-scale chemical synthesis utilizing precious-metal compounds. Continued development of the field aims to further develop metal-free catalysts and provide a real-world alternative to modern synthetic practices.

1.4 Overview of Thesis

This thesis is divided into two major section. Chapter 2 describes the design of a unique synthetic route towards the total synthesis of the (-)-colchicine analogue, *N*-acetylcolchinol-O-methyl-ether (NCME). This method aims to improve upon previous synthesis by incorporating an NHP-mediated reduction to assemble the colchinoid backbone with ring systems A and C before the assembly of the challenging ring B through a transition-metal mediated cross-coupling reaction inspired by work by Fagnou and coworkers.[44] The third chapter of this thesis describes the design of new preparative routes of phosphorus-based heterocycles. This new approach intends to eliminate the need for isolation of difficult to purify intermediates by utilizing a one-pot synthesis to generate the desired precatalyst. In turn, the precatalysts can be used without isolation for the reduction of saturated species. In doing so, the selection and synthesis of diimine ligands and phosphorus reagents are inaugural steps necessary to investigating the suggested synthetic avenue towards unexplored NHPs. The reactivity of these new catalysts will be explored through the asymmetric reduction of an imine substrate and the enantioselectivity assessed.

Chapter 2. Application of NHP catalysis Towards the Synthesis of NCME.

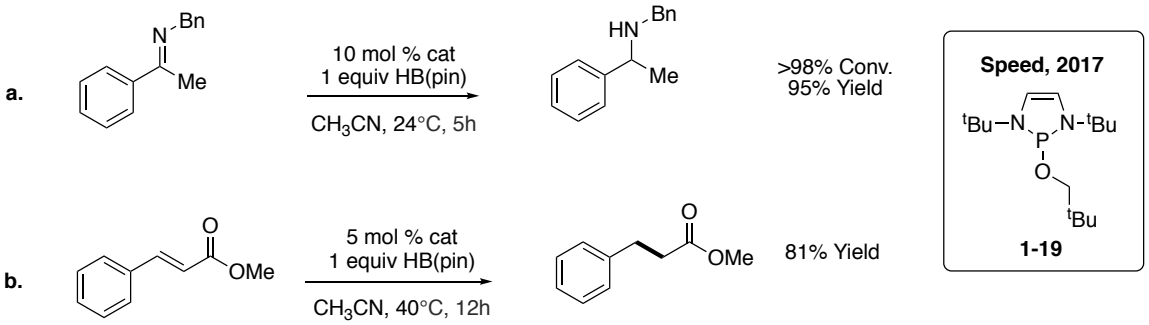
2.1 Contributions

Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University) is thanked for the acquisition of mass spectrometric data.

2.2 Introduction

A growing field in chemistry is the catalytic reduction of small molecules employing main group element catalysts as opposed to conventional methods using precious-metal catalysts. A recent advance in this field has been the use of *N*-heterocyclic phosphines, or NHPs, in the reduction of imines to produce secondary amines, which are common in pharmaceuticals and alkaloids. NHPs demonstrate unique chemical reactivity in part due to their uncommon hydridic P-H bond. Several research groups have since exploited this phenomena to perform conjugate reductions of electron poor alkenes and other saturated species. Previous efforts in the Speed group have demonstrated the first example of 1,3,2 diazaphospholene-catalyzed imine reduction and conjugate reductions by hydroboration using readily synthesized air-stable precatalysts with high synthetic utility.[1] Hydroboration is generally seen an attractive reduction route on small-scales avoiding the use of high-pressure equipment associated with the use of H_2 gas. The ease of use of the common hydroboration reagent, pinacolborane, HB(pin), has made it especially attractive. Metal-free catalyzed hydroborations are rare in the literature as this transformation was previously dominated by metal catalysis. The active catalyst is highly moisture sensitive which prioritized efforts for the concise synthesis of benchtop-stable precatalysts through the treatment of bromodiazaphospholene with benzyl alcohol and triethylamine. The developed alkoxy-diazaphospholene species was effectively converted to the hydridic P-H

species with a single equivalent of the aforementioned [HB(pin)], making this complex an appropriate and accessible system for reductions as seen in Scheme 18.



Scheme 18. Hydroboration of (a.) imines and (b.) conjugate acceptors with NHP-OR precatalysts.

This development brought forth a convenient route to 2-alkoxy-1,3,2 diazaphospholenes and the application of such species as precatalysts for imine and conjugate reductions. We chose to exhibit the utility of the reductive chemistry with diazaphospholenes by integrating it into a total synthesis project, demonstrating the flexibility of the catalytic system to reduce more complex substrates than the modest scope in the initial disclosure. The Speed group's interests lie in synthesis and catalysis carried out by main-group containing complexes. Priorities within the group aspire to both increase the generality and ease of known transformations in addition to researching new and exciting ways of applying main group reductive chemistry. For these reasons, the concise assembly of an moderately complex molecule such as NCME appropriately aligns with the group's overall direction, by showcasing the catalysts that were synthesized.

(-)-Colchicine is a natural product extracted from meadow saffron and is of medicinal interest due to its antimitotic properties.[45,2] Current synthetic methods for (-)-colchicine and its analogues generally require expensive and toxic transition metal catalysts in some form as well as lengthy and inefficient synthesis.[46,47] The previous asymmetric

synthesis of colchinoid analogues in the literature use methods that don't align with the Speed groups' synthetic preferences. These methods incorporate harsh reaction conditions, several transition metal-mediated reactions and the need for expensive reagents and equipment.[48] This chapter's goal is to use fundamental organic chemistry as well as new techniques to provide an alternative route toward the total synthesis of (-)-colchicine analogues by utilizing the reductive chemistry of NHPs instead of traditional metal catalysis.

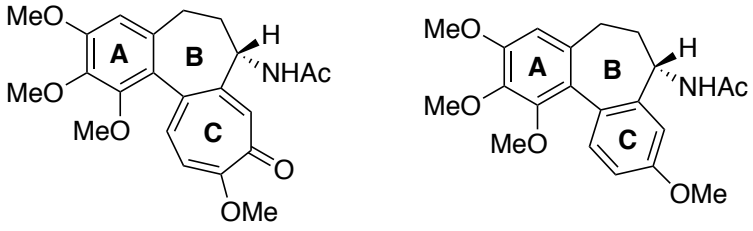


Figure 3. Structures of (-)-colchicine (left) and NCME (right) with indicated ring systems.

The aim of this research is to perform chemoselective conjugate reduction mediated by NHPs that allows for the expedient assembly of NCME.[44] First the existing synthesis of colchinoids will be briefly summarized.

2.3 Previous Synthesis of Colchicine and Colchinoid Analogues

Colchicine is an alkaloid molecule consisting of a unique 6-7-7 ring structure derived from the *Colchicum autumnale* plant. Colchicine and similar alkaloids are best known for their pharmacological properties and their role as therapeutics dating back to Ancient Egypt to treat inflammation and other minor ailments. These sorts of naturally occurring compounds have great importance in the development of modern therapeutics as their natural scaffolds providing a great platform for the development of new synthetic

analogues. The isolation of natural products, however, is not an appealing method to access these molecular scaffolds, making them attractive targets in synthetic chemistry.[45]

It is now known that colchicine's main mechanism of action is its influence on tubulin disruption within the cell.[49] Microtubules are cellular polymers that play important roles in cellular division and transport.[48] Colchicine's ability to modify the microtubule polymerization equilibrium directly impacts the cytoskeleton of eukaryotic cells during cell division. Interference during this process can ultimately lead to apoptotic death of the cell as the arrangement of organelles, subcellular entities with specialized operations within the cell, are disrupted.[50] Initially, colchicine was a drug used in small doses for its ability to affect inflammatory response as well as a treatment for gout and familial Mediterranean fever, amongst other ailments.[48,45] Modern medicine has demonstrated that colchicine may be a much more impressive therapeutic than previously thought. Its intrinsic antimitotic properties have the capacity to aid in serious medical conditions including, but not limited to, cardiovascular issues, neurodegenerative disease, chronic diseases and many types of cancer. The intriguing potential of colchicine, however, is not without drawbacks. Its potent ability to damage cellular structure, like all antimitotic drugs, has also lead to toxic side effects, especially when used in large doses.[49] Most notably, these compounds are known to negatively impact the nervous system, bone marrow and encourage various gastro-intestinal issues.[51] For these reasons, colchicine and its derivatives have been major topics of interest in biological research and synthetic chemistry with newfound emphasis on development of molecules that limit the negative side-effects associated with many of these alkaloid compounds.[52] These potential alterations have been guided by recent studies that specify the distinct segments of the molecule that are more applicable when

undergoing modifications to enhance drug activity.[50,2] Notably, ring A can be subject to very little modification as the three methoxy-groups are thought to be crucial for tubulin binding. Much of the potential variation lies in rings B and C where new functionalities and ring structures can be incorporated without severely affecting the desired drug activity.[53]

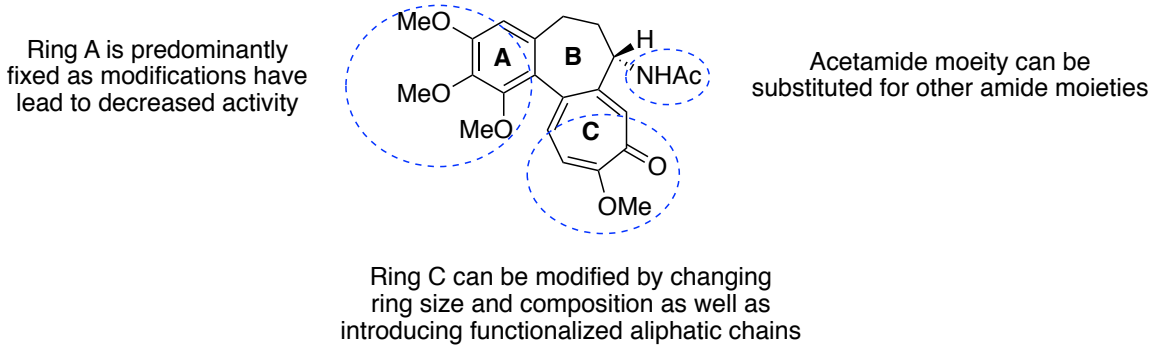
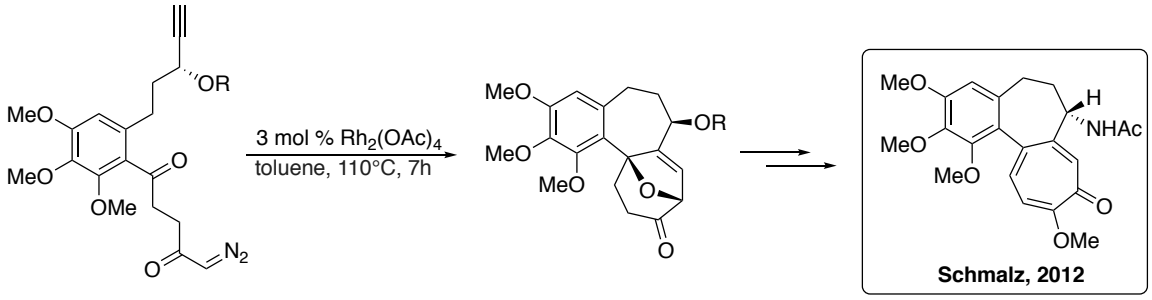


Figure 4. Colchicine with outlined areas of potential variation.

As with many ancient medicines, colchicine was initially isolated from its natural product. Isolation from natural products, however, is often an inconvenient method of generating large quantities of a specific substance and does not readily lend itself to making analogues. Colchicine's combination of intriguing chemical structure and potential pharmaceutical uses has made the molecule a significant topic of interest for synthetic chemists to find alternative methods of generating the target molecule in large enough quantities to effectively study these types of molecules in real world scenarios. Although there have been many reported methods in the literature of the total synthesis of colchicine and its derivatives, modern synthesis generally involve lengthy synthesis, frequent transition-metal mediated reactions and the use of harsh reaction conditions.[54,2]

A method demonstrated by the Schmalz group employed an enantioselective strategy in the total synthesis of (-)-colchicine and (-)-isocolchicine as well as

"pseudocolchicine" analogues. The target compounds were synthesized in 15 steps with an overall calculated yield of 1%.[54] The key step in their synthetic scheme demonstrated a rhodium-catalyzed domino transformation as seen in Scheme 19. This method is frequently used within the group for the synthesis of alkaloid molecules as is indicated in subsequent work demonstrating the synthesis of additional colchicine backbones. This crucial step the group displayed in this method used 3 mol% $Rh_2(OAc)_4$ as a catalyst to obtain their next synthetic intermediate at 64% yield with enantiomeric purity exceeding 99% *e.e.*. The transformation was likely initiated by a Rh-carbene which is ultimately attacked by the benzylic ketone to furnish a reactive carbonyl ylide which can undergo a cycloaddition reaction.



Scheme 19. Enantioselective synthesis of (-)-colchicine via cycloaddition reaction.

The unique 6-7-7 ring structure of colchicine has become an issue for synthetic chemists. The challenging synthesis as well as potent toxicity of colchicine itself has led to the exploration of medicinal properties of colchicine analogues. The desired analogues have more synthetically appealing structures without compromising the drug activity. Many colchicine analogues have garnered pharmaceutical interest, namely N-acetylcolchinol, N-acetylcolchinol-O-methyl ether (NCME) and allocolchicine as seen in Figure 5. This collection of compounds share the 6-7-6 ring structure and incorporate unique functional groups on their respective C ring. The focus of the following introductory

section will be the colchicine analogue, N-acetylcolchinol-O-methyl ether. It is comprised of a 6-7-6 ring system with a distinct methyl ether on its C-ring.

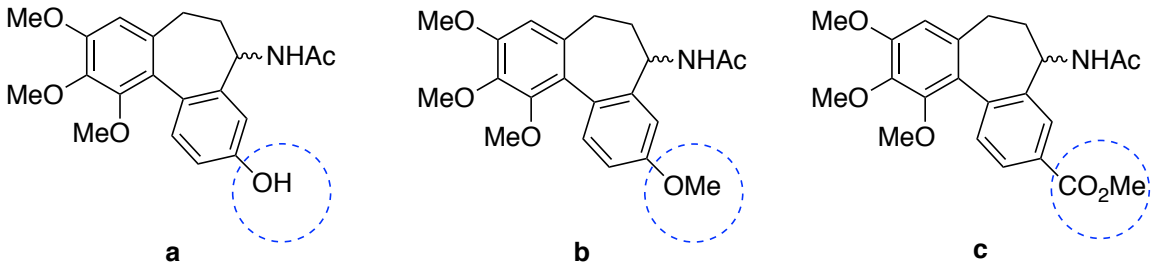
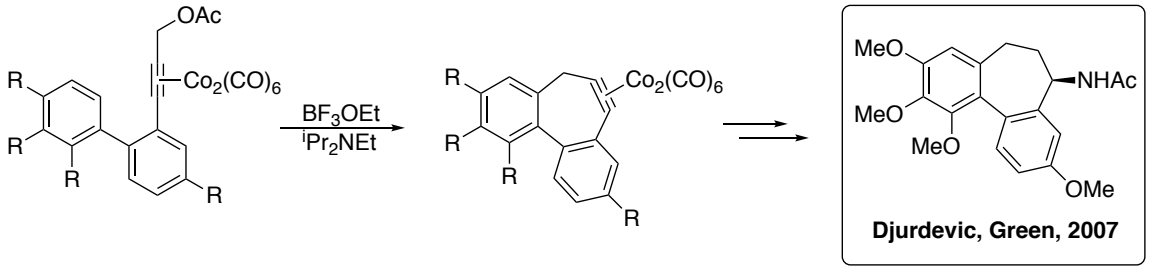


Figure 5. Structures of (a.) N-acetylcolchinol, (b.) NCME and (c.) allocolchicine.

2.3 Previous Synthesis of Colchicine and Colchinoid Analogues

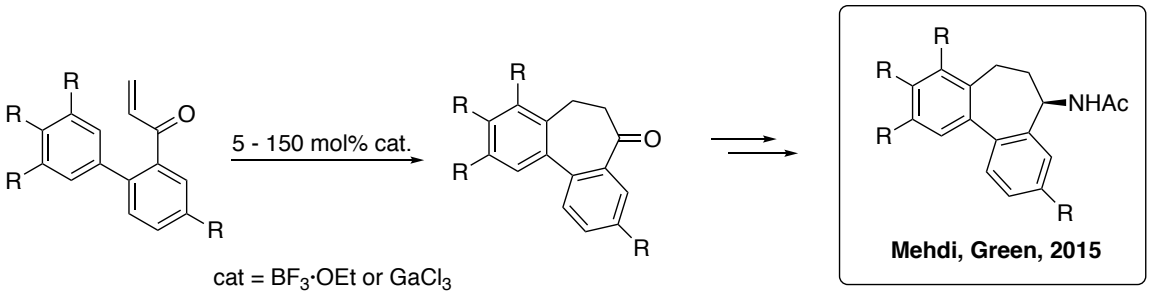
There are several different strategies to date employed to go about the synthesis of NCME. One of the first strategies to go about a concise synthesis of NCME incorporated an intramolecular Nicholas reaction under Lewis acid mediation to generate the challenging ring B.[55] This was the first example of an enantioselective synthesis of NCME with 93% *e.e.*. This method required a dicobalt octacarbonyl complex to generate an enantioinriched intermediate before 9 subsequent steps to furnish the desired product as seen in Scheme 20. Notably, this method could generate other colchicine analogues with superior enantioselectivity, but with a relatively long synthesis and low overall yield.



Scheme 20. Synthesis of (-)-colchicine via cobalt intermediate

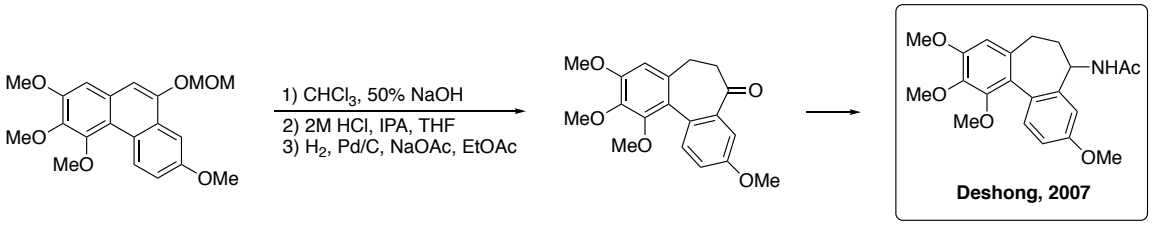
This work was then improved upon in a more concise synthesis via a Lewis-acid catalyzed intramolecular conjugate addition in good yields with improved functional group

tolerance on both rings A and C including benzoyl, methoxy and alkyl groups as seen in Scheme 21.[56] This process furnished highly enantioenriched products of 99% *e.e.*, however with generally large catalyst loadings. Notably, functionalities on ring A are not in the positions known to have high activity, however this work has enabled a strong platform for future colchinoid syntheses.



Scheme 21. Lewis acid catalyzed synthesis of colchicine.

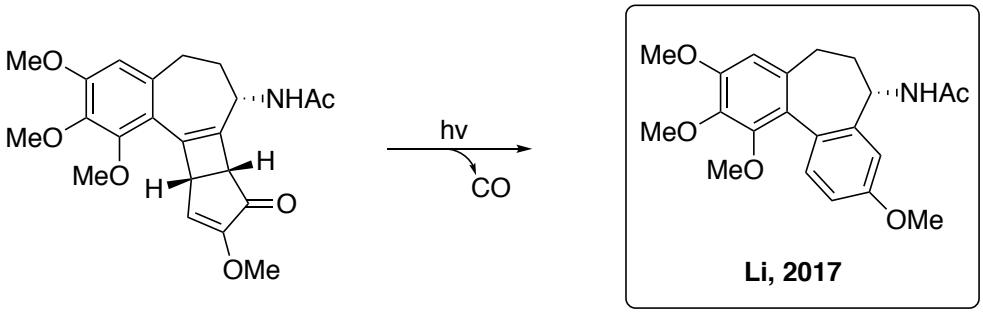
Deshong and coworkers used a different approach towards the synthesis of NCME. Their work used a Friedel-Crafts acylation to form the challenging ring B through a ring expansion reaction as seen in Scheme 22. The colchinoid backbone comprising of rings A and C are built through a siloxane coupling reaction prior to the phenanthrol ring expansion reaction. This protocol provides a relatively concise route for the synthesis of colchinoid scaffold applicable for other analogues. This method allows for selective functionalization of backbone carbons to incorporate unique electronic and steric profiles.[57]



Scheme 22. Synthesis of colchicine via ring expansion reaction.

A new approach was demonstrated in which a conversion of colchicine to *β*-lumocolchicine was exhibited in 2017 by Li and coworkers. NCME was formed through

an unprecedented decarbonylation and electrocyclic ring-opening cascade reaction with >99% *e.e.* and an overall yield of 9% as seen in Scheme 23. This photochemical reaction is unlike previous synthetic procedures for the synthesis of NCME, working retrosynthetically from a colchicine-esque analogue without the need for protecting groups.[58]

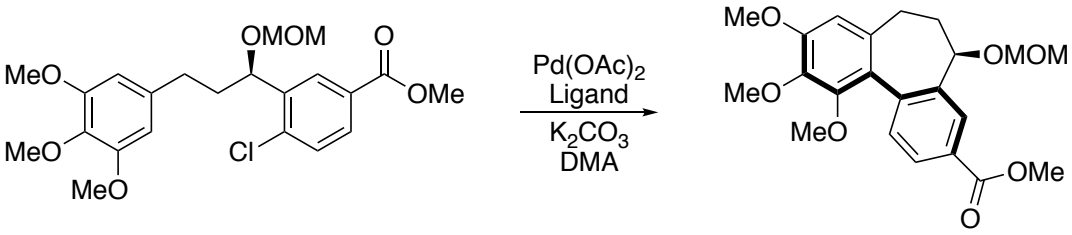


Scheme 23. Synthesis of colchicine via electrocyclic ring-opening cascade.

(-)-Colchicine and its analogues continue to be therapeutics of interest with opportunity beyond their traditional treatments of gout and inflammation. Many of these alkaloid molecules have reached phase II clinical trials only to be sidelined due to acute toxicity. The continued synthesis and development of novel colchicine analogues are crucial in eliminating the limitations associated with these conceivably strong antimitotic pharmaceuticals.[2] (-)-Colchicine itself is hindered by its nonspecific toxicity, but the analogues of this compound have showed promise as treatments against different strains of cancer and other conditions. The design of new synthesis of these alkaloid compounds aims to provide a powerful tool in chemical synthesis. Shortened and sustainable synthesis coupled with improved medicinal technology may make these potential drugs a real-world treatment in years to come.

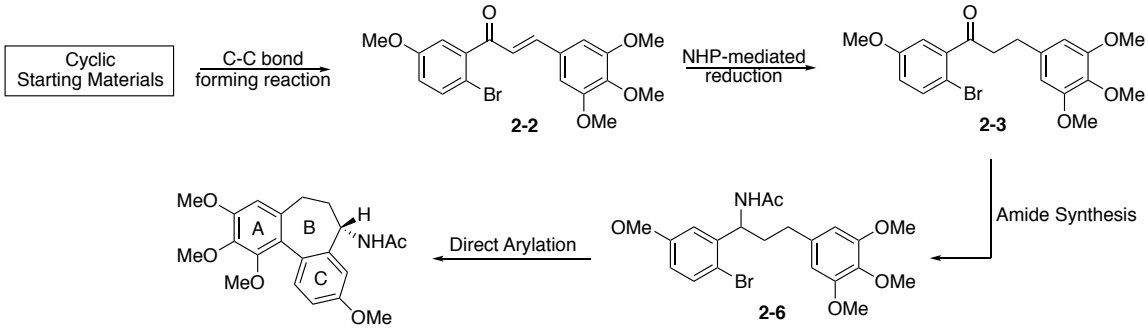
2.4 Attempted Total Synthesis of NCME

Our proposed synthesis of NCME sought to showcase advances in diazaphospholene catalysis and prompt the further investigation of diazaphospholene chemistry. A non-diazaphospholene related key step involves a transition-metal mediated direct arylation reaction in the presence of an amide to synthesize the final and most challenging segment, ring B, culminating in the desired product. The final ring construction is inspired by the direct arylation by Fagnou as seen in Scheme 24.[44] The formation of a 7-membered ring through direct arylation is rare, especially considering aryl chlorides as opposed to aryl iodides and triflates. The Fagnou group successfully synthesized and optimized colchinoid molecules en route to the total synthesis of allocolchicine using this method and reported important considerations to minimize unwanted dehalogenation reactions.



Scheme 24. Direct arylation demonstrated by Fagnou and coworkers.[44]

The chemistry to assemble the direct arylation precursor in our proposed route would be enabled by diazaphospholene catalysis.

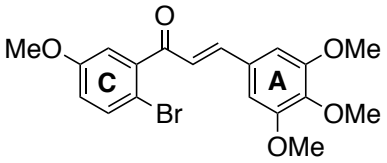


Scheme 25. Proposed generic synthetic route for the total synthesis of NCME.

2.4.1 Synthesis and Optimization of Conjugate Acceptor 2-2

2.4.1.1 Attempted Aldol Reaction

The first key step in our planned total synthesis of NCME is the synthesis and optimization of α,β-unsaturated ketone **2-2** that makes up the framework for ring systems A and C as seen in Figure 6.



2-2

Figure 6. Structure of α,β-unsaturated ketone **2-2**

Double bonds are often easier to construct than single bonds: formation of a carbon-carbon bonds from inexpensive and accessible aldehyde starting materials is often feasible via aldol condensation or Wittig reaction. The synthesized ketone will then undergo a conjugate reduction using NHP reductive catalysis before going about distinct functional group transformations to introduce the nitrogen from the ketone functionality. The functional-group compatibilities of the diazaphospholene catalysis should enable the reduction of the enoate to occur in the presence of the bromide, providing a rapid approach to the direct arylation substrate. The motivation behind choosing this synthetic avenue is to demonstrate the flexibility of our catalytic system, showcasing the selectivity of NHP catalysis for enoate reduction. A conventional transition-metal catalysis that would likely perform unwanted side reactions with the bromide in the starting material. The hydrogenation of the enoate with palladium on carbon would likely lead to the reduction of the aryl bromide as well. We initially sought to use commercially available 3-methoxyacetephenone as a starting point for ring C as well as the commercially available

aldehyde, 3,4,5-trimethoxybenzaldehyde, for ring A and go about a prototypical aldol condensation following modified procedures from Ke and coworkers for this initial step.[59] Crossed aldol condensations can effectively deliver an α,β-unsaturated ketone through a simple mechanism involving nucleophilic addition of an enolizable ketone to a non-enolizable aldehyde before the elimination of water.

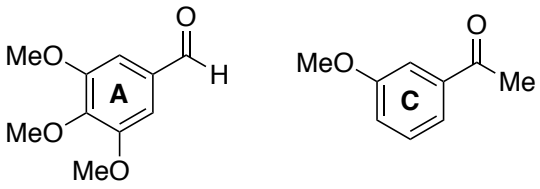
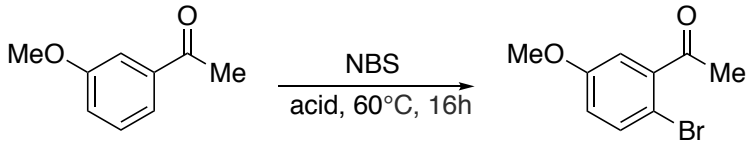


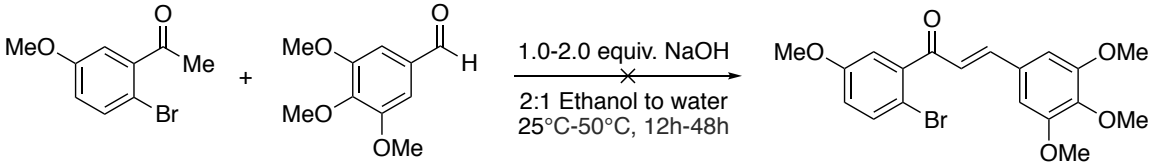
Figure 7. 3,4,5-trimethoxybenzaldehyde (left) and 3-methoxyacetephenone (right) with denoted ring systems.

These two cyclic starting materials have all of the desired functional groups in the appropriate positions on their respective aryl rings, making them appealing starting points, except for an easily installed bromine on the 3-methoxyacetephenone. Installation of a bromine atom to the 3-methoxyacetphenone was performed successfully using N-bromosuccinimide (NBS), a convenient source of bromine radical. NBS is practical in bromination reactions because it is both easier to handle and inherently safer that other bromination reagents which are known to cause multiple forms of irritation. Initial attempts at this reaction used conditions of 10 mol% I_2 in acetonitrile in the absence of light for 10 hours at 25°C, which primarily resulted in unreacted starting material. The more successful literature method incorporated NBS in water with 40 wt% sulfuric acid at 60°C for 16h, giving approximately 50% yield of the desired product.[60] This was accomplished through quenching with saturated $Na_2S_2O_3$, extracting with 3 x 30 mL of EtOAc and purifying the product by column chromatography.



Scheme 26. Synthesis of 1-(2-Bromo-5-methoxyphenyl)ethanone.

With the 1-(2-Bromo-5-methoxyphenyl)ethanone and the unmodified 3,4,5-trimethoxybenzaldehyde in hand, the previously mentioned crossed aldol reaction appeared at first glance to be the easiest and most robust route for the synthesis of the desired chalcone **2-2**. A literature procedure that successfully synthesized structurally similar chalcone molecules was followed. The procedure combined the aldehyde and ketone in ethanol with one equivalent of NaOH, however the desired product was not generated, rather unreacted starting material as seen through ^{1}H NMR spectroscopy.[61] Appropriate attempts were made to potentially encourage chalcone formation such as increasing the concentration of NaOH and increasing reaction temperatures and durations, but these efforts were fruitless. To be complete, the reaction was run additional times modifying the literature procedure to involve a solvent-less system (grinding in a mortar and pestle) and substituting NaOH for another common base, KOH, however none of these changes resulted in the desired product.[62] We hypothesize that the electron withdrawing effect of the bromide coupled with the electron-rich nature of the aldehyde electrophile were responsible for the lack of success with this reaction.

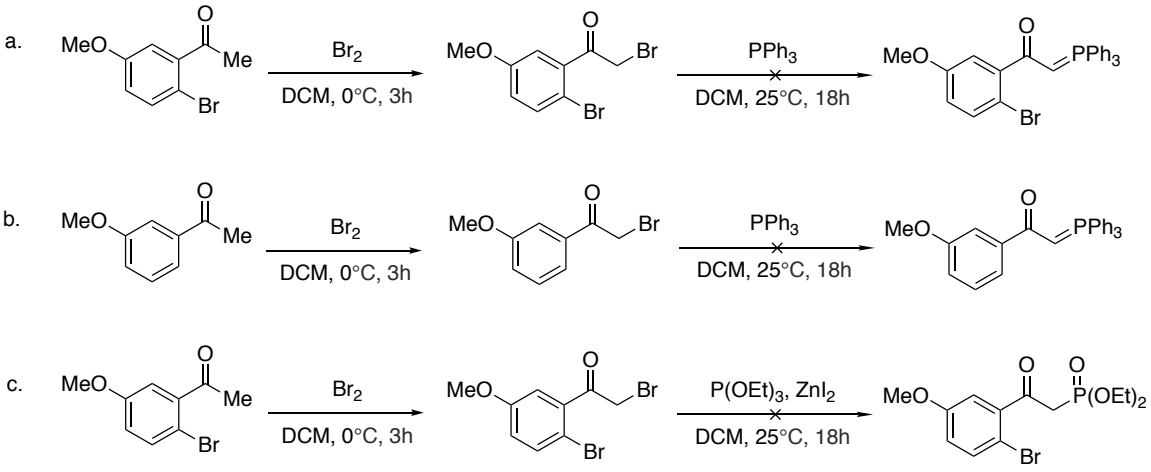


Scheme 27. Attempted aldol reaction.

2.4.1.2 Attempted Wittig Reaction

The lack of positive results with the aldol condensation lead to the investigation of other reliable carbon-carbon bond forming reactions, in this case, the Wittig reaction. A Wittig reaction results in the generation of an alkene and is a prevalent tool in organic synthesis. Wittig reactions occur through a (2+2) cycloaddition of an ylide and a carbonyl compound which proceed through a 4-membered transition state. The reaction is driven by the stability of the resulting phosphine oxide. This modified route involves substantial changes to the ketone starting material. Unlike the aldol condensation, an α-bromination of the ketone was essential to produce 1-(2-bromo-5-methoxyphenyl)ethanone. This molecule was appropriate for subsequent generation of a ylide from a phosphonium salt. The α-bromination was carried out successfully using Br_2 in DCM at 0° C for 18 h, affording the desired product in 65% yield following a modified procedure from Udd et al.[63] The resulting product was then reacted with triphenylphosphine unsuccessfully using a literature procedure that used one equivalent of triphenylphosphine in DCM for 18h at room temperature which primarily resulted in unreacted starting material.[64] Although initial attempts were unsuccessful, a range of temperatures and solvents were employed after the fact with no success at forming the desired ylide. Unsure of the issue as to why the Wittig reagent was unable to be generated, model systems were selected with less sterically and electronically complex starting materials. In this scenario where the bromine moiety may have contributed to the unsuccessful reaction, a system comprising of simpler molecules were used. This new substrate was considered less complex and in turn, had a greater chance of producing the desired product with a known dependable reaction like the Wittig reaction employed here. Unfortunately, the modified substrate also did not result in

product formation. An Arbuzov reaction was briefly investigated with the brominated ketone on a small scale. Arbusov reactions use a trialkyl phosphite reagent to produce an alkyl phosphonate product. These reactions follow a similar protocol and often use Lewis acids to catalyze the transformation. This adaptation was unsuccessful in generating the desired phosphonate, however it led us to consider other carbon-carbon bond forming options, such as the Horner Wadsworth-Emmons reaction.



Scheme 28. Attempted ylide formation from (a.) initial synthetic route, (b.) model system modification and (c.) Arbusov reaction.

2.4.1.3 Attempted Horner Wadsworth-Emmons Reaction

The starting materials for previous reactions have been stubborn, so an initial model system was used for the Horner Wadsworth-Emmons reaction (HWE). The Horner Wadsworth-Emmons reaction is known to be *E*-selective, generating olefin products with high stereocontrol. This protocol reacts a phosphonate molecule with ketones and aldehydes to make alkenes. Two different routes were explored in this section using two different carbonyl starting materials, the first being an aldehyde. In this reaction, 2-bromo-5-methoxybenzaldehyde was reacted with the accompanying phosphonate. This transformation was performed successfully using the lithiation of 4 equivalents of dimethyl

methylphosphonate using 4 equivalents *n*-butyllithium at –78°C in THF followed by the addition of the aldehyde. Despite synthesizing the crude desired alcohol, another oxidation step would be necessary to establish the ketone derivative wanted for further reactions. Not desiring addition of unnecessary steps to a potentially lengthy synthesis, we rationalized that substituting the aldehyde for the methyl ester analogue would avoid the extra oxidation step, if a monoaddition of the phosphonate ester could be accomplished. In doing so, a substitution of 2-bromo-5-methoxybenzaldehyde starting material for 2-bromo-5-methoxybenzoate was implemented.

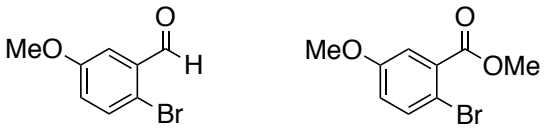
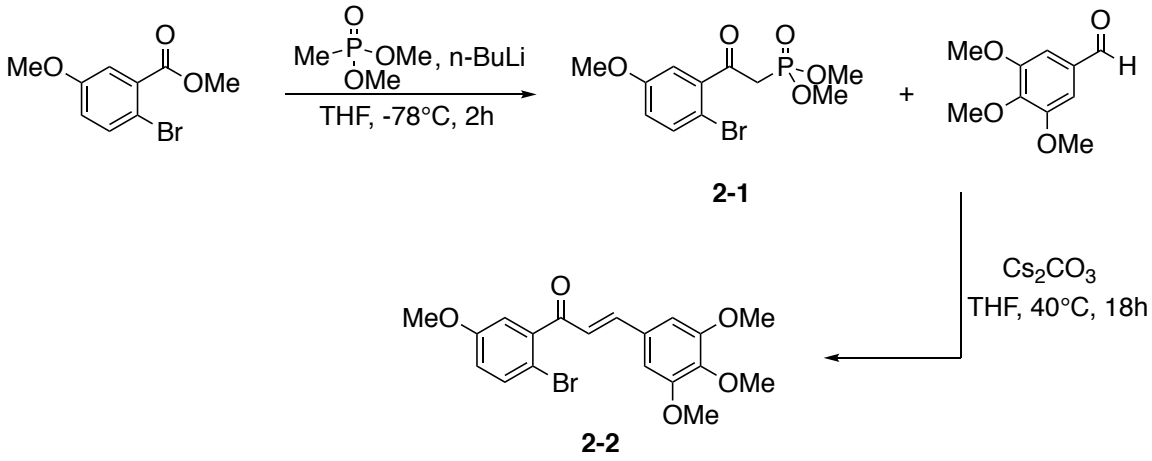


Figure 8. 2-bromo-5-methoxybenzaldehyde (left) and 2-bromo-5-methoxybenzoate (right).

The first step, generation of the ketophosphonate **2-1**, was carried out by the lithiation of 4 equivalents of dimethyl methylphosphonate using 4 equivalents of *n*-butyllithium at –78°C followed by the addition of the brominated methyl ester starting material.[65] Gratifyingly, after work-up, the desired ketophosphonate was obtained. The resulting ketophosphonate was then reacted with 3,4,5 trimethoxybenzaldehyde in the presence of base to form the first key synthetic intermediate, the desired chalcone **2-2**. Product formation was confirmed by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and Mass Spectrometry. Optimization of this step was tedious as reaction times, temperatures and bases were found to greatly impact product formation. Several bases were screened for optimum output including LiCl and NEt_3, LiHMDS, LDA and nBuLi, but Cs_2CO_3 was the most effective for reasons that are not completely clear but may be related to the high

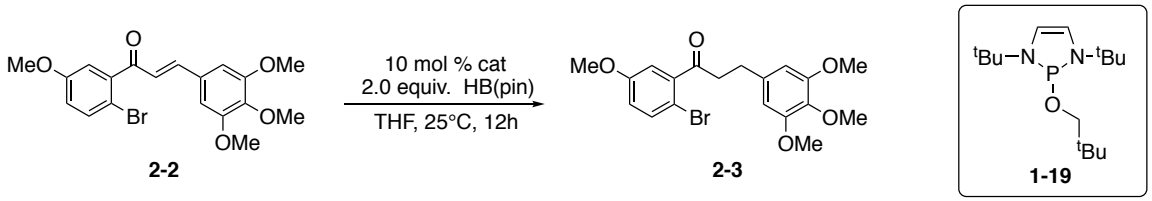
solubility of Cs salts in THF and low basicity. Optimization of this step yielded α,β-unsaturated ketone **2-2** in yields of 65% after purification by column chromatography.



Scheme 29. Compound **2-2** formation via Horner-Wadsworth-Emmons Reaction.

2.4.2 Synthesis of ketone 2-3 via NHP-Mediated Conjugate Reduction

The resulting chalcone was reduced using achiral NHP **1-19** as a precatalyst. Initial reductions followed previously established methods within the group, employing a system of 10 mol% precatalyst and 2 equivalents of HB(pin), however it is likely that this excess of HB(pin) could be reduced upon further optimization.



Scheme 30. NHP-mediated reduction of chalcone **2-2** to ketone **2-3**.

The achiral catalyst was used for this transformation. The reduction afforded a high yield of 85% with near complete conversion. Notably, this is the most elaborate molecule the Speed group has successfully reduced using NHP chemistry.

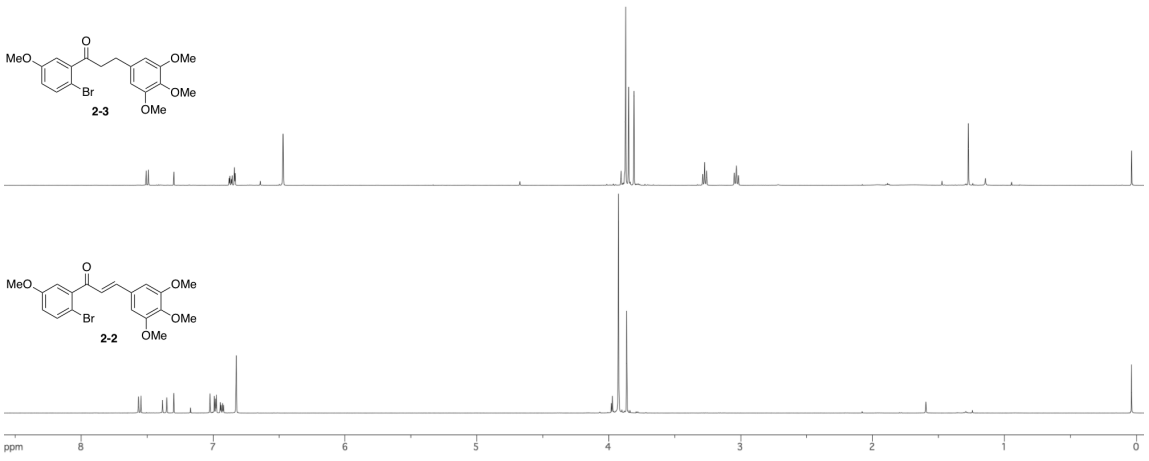
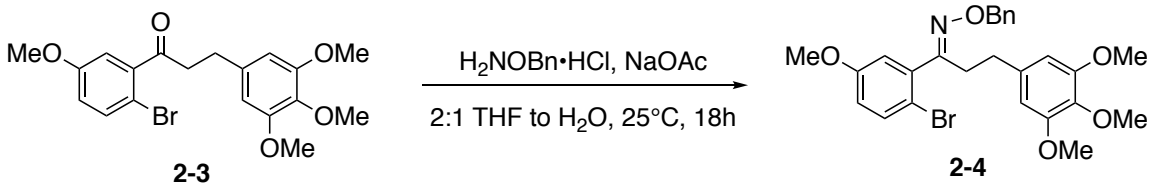


Figure 9. [1]H NMR spectrum of compounds **2-2** and **2-3**.

2.4.3 Synthesis of Oxime Ether 2.4

With the reduced ketone now in hand, the following steps were transformations to install an amide functional group before the crucial palladium cross-coupling reaction to furnish the desired product, NCME. While we ultimately wanted to install the amide using diazaphospholene chemistry, the preparation of primary amines using diazaphospholene chemistry is currently an unknown transformation. We wished to investigate the feasibility of the direct arylation in the presence of the amine, accordingly we used the reliable reduction of an oxime ether to deliver an amine from the ketone. The first reaction employed in this sequence is transformation of the ketone to an oxime ether. Oxime ether functional groups are important in both medicinal chemistry as well as synthetic chemistry. The oxime ether group is a useful block in synthetic strategies due to it being an attractive starting material for nitrogen containing compounds such as amines, nitriles, pyrroles and N-heterocycles.[66] This transformation of a ketone to an oxime ether used reagents O-benzylhydroxylamine hydrochloride and sodium acetate in a solvent system of 2:1 THF to H_2O for 48h at room temperature following a modified literature procedure.[67] The reaction

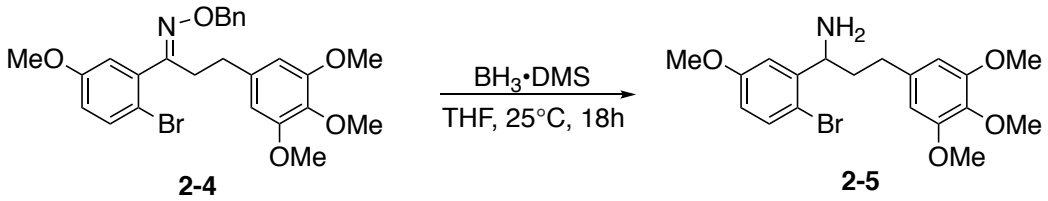
underwent an aqueous workup and was washed with DCM before being concentrated *in vacuo*. The crude product was subjected to ^{1}H NMR spectroscopy which showed evidence of the desired product as well as minimal starting material. Column chromatography was used with a solvent system of 1:1 ethyl acetate to hexanes to further purify the oxime ether. A resulting 65% yield was recovered and used for the following transformations. The product of this reaction was confirmed using ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and Mass Spectrometry.



Scheme 31. Synthesis of oxime ether **2.4**.

2.4.4 Synthesis of Amine 2-5

Following the transformation from ketone to oxime ether, BH_3•DMS in THF was used to generate an amine **2-5** from the oxime ether. Amines are known to be generated through the reduction of oxime ethers as first published by Feuer and Braunstein using borane.[68] This both reduces the double bond of the oxime and cleaves the N-O bond. Now there are more convenient borane reagents that can be used for such reductions such as BH_3•DMS used here. BH_3•DMS was used due to its increased stability and solubility compared to other similar borane-containing reagents. This reaction proceeded for 18h at room temperature before an acidic work-up. The following crude product was dried and concentrated to reveal minimal amounts of starting material evident in the ^{1}H NMR spectrum. The crude product was purified by column chromatography with a solvent system of 9:1 EtOAc to hexanes to yield the final product in a moderate yield of 50%.

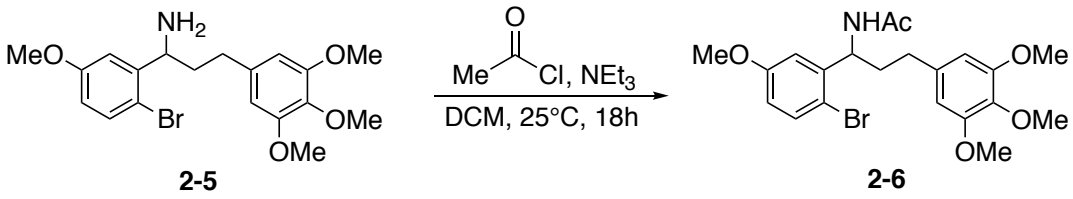


2-4 **2-5**

Scheme 32. Reduction of oxime ether **2-4** to amine **2-5**.

2.4.5 Synthesis of Amide 2-6

The final functional group transformation prior to cross-coupling was the synthesis of an amide, **2-6,** from the amine. Reactions of acid chlorides and amines tend to be both robust and general in their nature that use a suitable base to allow the reaction to proceed. This protocol used acetyl chloride and triethylamine in DCM. This procedure was carried using Schlenk techniques to alleviate unwanted side reactions that could be associated with atmospheric moisture and wet solvents. The crude reaction mixture was quenched with sodium bicarbonate and worked up accordingly. The ^{1}H NMR spectrum showed the desired product, however in poor yields of 31%.

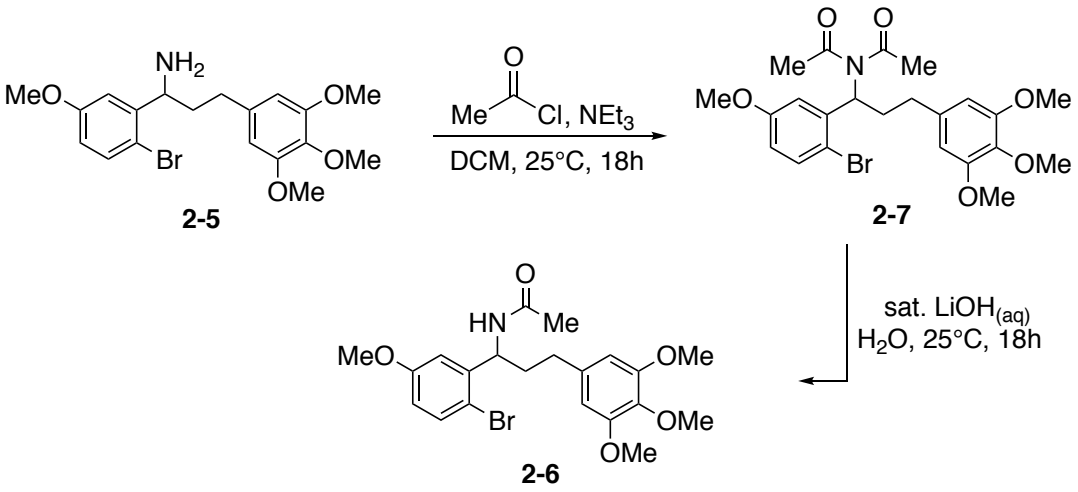


2-5 **2-6**

Scheme 33. Synthesis of amide **2.6**.

Noting the poor yield of the amide synthesis, optimization of this reaction was a priority. This reaction was replicated a number of times throughout the project. When repeating this reaction, we were met with intriguing results. The reaction used a slight excess of acetyl chloride, however in some instances there was evidence of 2 acetate groups attached to the nitrogen as seen through both ^{1}H NMR Spectroscopy as well as Mass Spectrometry. In situations where this was the case, a solution of saturated $LiOH_{(aq)}$ was

used to cleave one of the acetate groups from the nitrogen. This was performed successfully, giving the desired amide product.

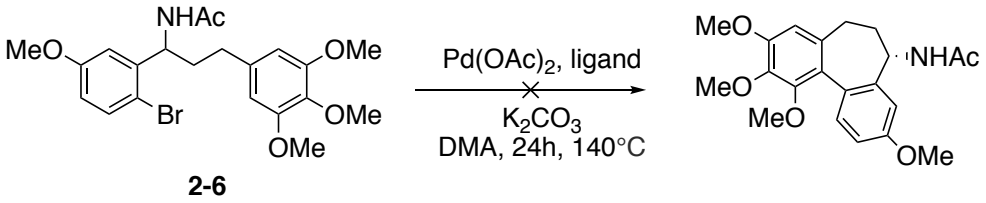


Scheme 34. Isolation of monoamide **2-6** from bisamide **2-7**.

2.4.6 Attempted Synthesis of NCME

The final step in the total synthesis is a palladium cross-coupling reaction using methods reported by the Fagnou group.[44] They used an intramolecular direct arylation technique to form the 7-membered ring B of the tricyclic colchinoid core. Their investigation describes these reactions as challenging because the reactivity and amount of unwanted side reactions are potent issues when considering the ligand-to-palladium ratio.[44] Conditions of a 1:1 ratio of palladium to ligand at 10 mol % catalyst and 2 equivalents of potassium carbonate in dimethylacetamide (DMA) were employed for this transformation. This protocol was carried out using Schlenk techniques due to the high degrees of moisture sensitivity of such precious compounds. The reaction mixture was heated to 145° for 18h with a short path distillation apparatus used for subsequent removal of solvent *in vacuo*. The crude reaction mixture was used for ^{1}H NMR spectroscopy and unfortunately, there was no evidence of product formation. The product collected was unlike the precedent set

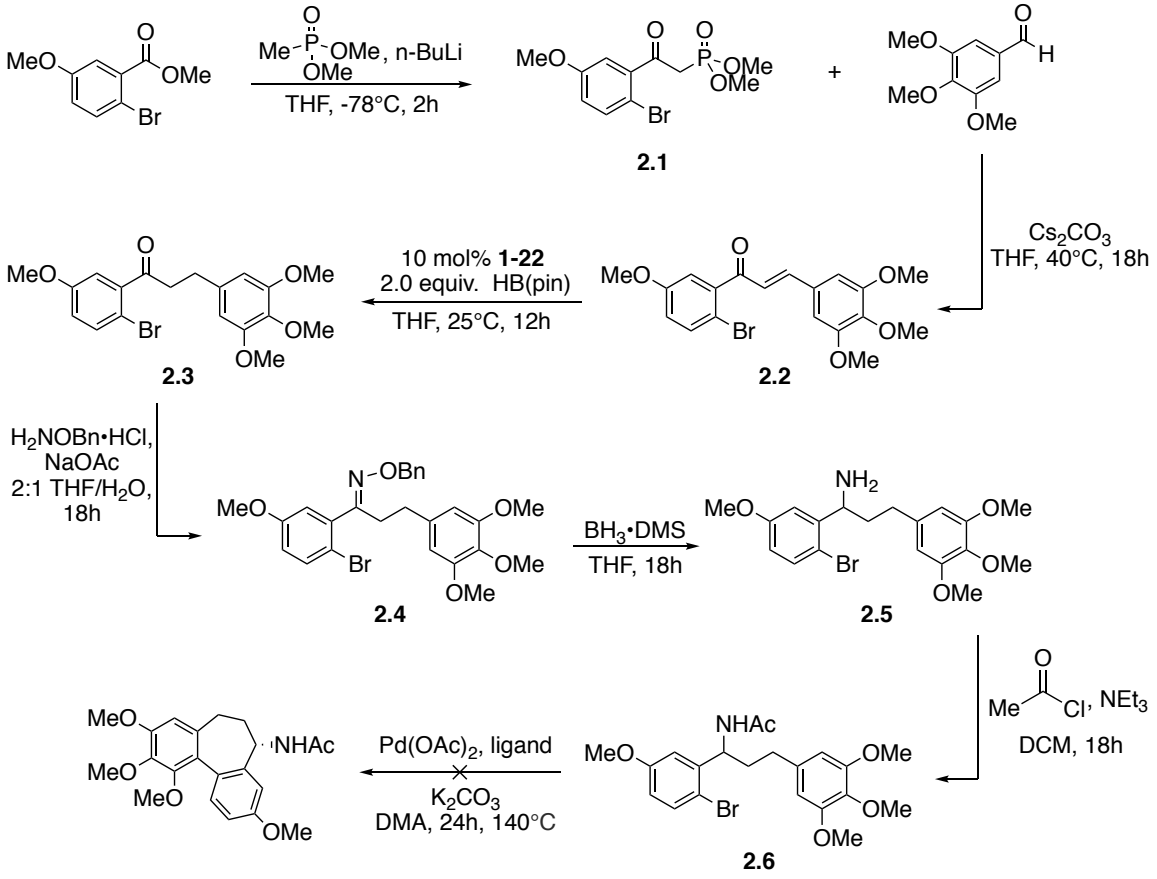
by literature as what called for off-white powder was instead an intractable black sludge. One potential issue with product collection was the small-scale nature of this reaction given the precious materials at hand. Another reaction with the same protocol was set-up with similar results, an intractable black sludge. The total synthesis of NCME was left at this point as major revisions to the synthetic route would likely have to be made to compete with these issues. A difference between this substrate and Fagnou's substrate was that Fagnou's direct arylation substrate contained a masked oxygen rather than amide. Changing the route to intercept Fagnou's would remove any chance of using diazaphospholene chemistry to introduce the nitrogen, removing one of the primary motivators to showcase our chemistry. Replacing the direct arylation with an intramolecular Suzuki-coupling was considered, however the requisite borylated tri-methoxy benzaldehyde is not readily available, and we had some trepidation the Lewis-acidic boron could interfere with the key Horner-Wadsworth-Emmons reaction. A Stille coupling would likely have been successful but would require carrying toxic organotin reagents through multiple steps. In addition, restarting the synthesis from the first step would be necessary to explore this result. A cross-electrophile coupling between an aryl iodide and aryl bromide was also considered for the ring closure, but this would necessitate redesigning the synthesis from the first step. In addition, intramolecular cross-electrophile couplings are in their infancy, especially for systems of this complexity, and we did not wish to rely on such a high-risk step for the key step of our synthesis.



2-6

Scheme 35. Attempted synthesis of NCME from amide **2-6**.

The goal of this work was to establish a concise route towards the total synthesis of the budding pharmaceutical, NCME. This synthesis, although presently unsuccessful in building the desired product, used several synthetic tools and incorporated unique NHP-mediated reductive chemistry which has not yet been reported in the total synthesis of such molecules. It was shown that an aryl bromide retained intact in the NHP conjugate reduction step, which was conducted on the most complicated substrate explored to date. It is likely that modifications to the proposed synthetic avenue could feasibly generate the desired NCME while still incorporating the novelty of NHP catalysis for crucial reduction steps, however our attention instead turned to the exploration of cyclization reactions for a new generation of NHP catalysis.



Scheme 36. Total attempted synthetic route towards the synthesis of NCME.

2.5 Summary

The steps leading up to the cyclization were accomplished, however further optimization could be established. Modest yields were obtained throughout the synthesis which lead to sparse amounts of amide for the final step. This turned exploration of the final step into a tedious process as the small-scale syntheses would need to be scaled-up significantly to have sufficient material for the optimization of the cross-coupling reaction, which gave no traces of products in our initial attempts. As shown by the Fagnou group, the cross-coupling of such molecules required more effort than anticipated. More time on this step may have ultimately lead to the desired product formation, but time and resources were a limiting factor. The priority behind this work was demonstrating phosphorus-based

reductive chemistry on an example with more synthetic complexity than previous examples. Although this was performed in-part successfully, due to the success of the conjugate reduction, the final synthesis of NCME was not judged to be of sufficient value to continue developing route, in light of leads for other promising chemistry developed in the Speed group, my focus was switched to this new chemistry of the exploration of preparative routes towards reactivity of NHP precatalysts. Regarding future prospects for the crucial transformation to enable the formation of the B-ring, alternate routes could be investigated. Although I believe that the palladium-mediated direct arylation coupling was the most reasonable route given precedent in the literature, if this had continued to be futile other methods such as Suzuki-coupling could have been attempted. While these would not modify the overall strategy, they would necessitate going back to the start of the entire synthesis to incorporate the boron functional group.

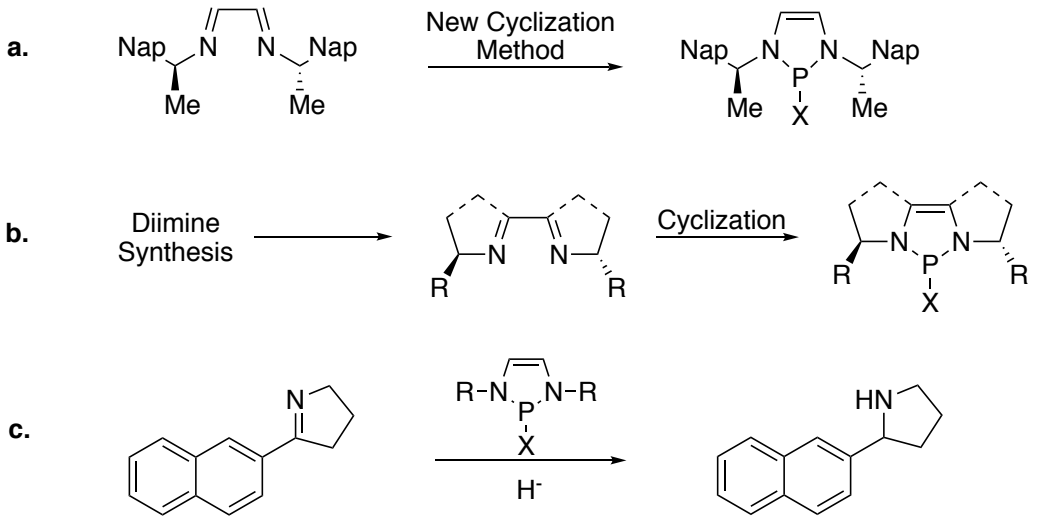
Chapter 3. Exploration of Preparative Routes and Reactivity of NHP Precatalysts

3.1 Contributions

Prof. Alexander W. H. Speed (Dalhousie University) is thanked for the initial preparation of compound **X-1**, **X-2** and **Y-3**. Blake Huchenski is thanked for the preparation of P_2 dimer. Dr. Travis Lundrigan is thanked for the optimization of compound **X-5**. Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University) is thanked for the acquisition of mass spectrometric data. Dr. Katherine Robertson (Saint Mary's University) is thanked for the acquisition of crystallographic data and solving of crystal structures.

3.2 Introduction

N-heterocyclic phosphines (NHPs) have become versatile hydride transfer catalysts. One of the many reasons behind the emerging popularity of this class of catalyst is the large degree of modularity in NHP synthesis, allowing structural and electronic variants, which may lead to unique and interesting chemical properties. To continue to develop the NHP catalytic library, efforts are continuing to explore major structural variants that have not been explored as catalysts in the scientific literature. The work in the following chapter aimed to expand NHP catalysis to motifs bearing substitution in the catalysts' backbone. Existing preparative routes for known NHPs will be summarized to give context to the investigation of new routes for access to previously unattainable complexes. This work includes development of new NHPs by new cyclization methods of previously unreported diimine ligands and the synthesis and examination of novel P(V) variants of diazaphospholenes and their reactivities.



Scheme 37. Main goals of this work (a.) investigating new phosphorus reagents for cyclization of known compounds, (b.) synthesis and optimization of novel diimines and subsequent cyclizations, and (c.) reactivity of synthesized DAPs.

3.2.1 DAP Synthesis

The reactivity of phosphorus-based catalyst was illustrated in the introductory chapter. The following chapter concerns itself with the examination and design of new preparative routes for NHP precatalysts. The following section explains the previous methods used to attain such complexes, their benefits, and their shortcomings. It is important to describe this foundation to stress the motivation of this research.

Structurally, NHPs are defined by having a ring structure consisting of some array of carbon, nitrogen and phosphorus atoms. Although this leaves opportunity for variation, the only subset of NHP used in the Speed group's research has been a five-membered ring consisting of an unsaturated carbon backbone with a phosphorus centre flanked by two nitrogen atoms, defined as diazaphospholenes (DAPs). It is known that the unsaturated carbon backbone is crucial to DAP reactivity, however new catalyst structures can be investigated by way of modifying this integral part of NHP reductive catalysts in ways that preserve the unsaturation.[36] In addition to the backbone, NHPs have several areas in which

one can apply variation to the complexes by adding new substituents to the flanking nitrogens, as well as changes to the substituents on the phosphorus centre. It is important to research these possible variants at length to investigate the potential reactivity of unfamiliar NHP catalysts.

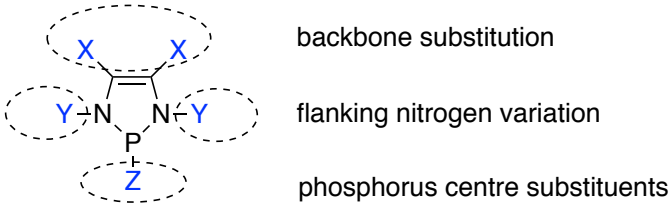
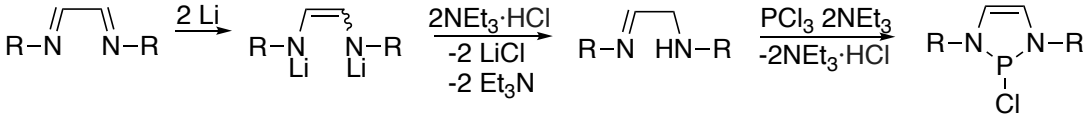


Figure 10. Areas of potential variation for DAP synthesis.

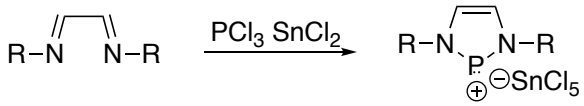
DAPs are generally synthesized by a reaction between a diimine and a phosphorus containing molecule. Development of routes towards DAPs has been a crucial area of research when designing these new and exciting organocatalysts. Early efforts found that a convenient starting point was utilizing phosphorus trihalide compounds as a convenient phosphorus sources. Demonstrated first by Kibardin and subsequently expanded by Gudat, a protocol involving initial reduction of the diimine with lithium metal, followed by addition of PCl_3 as the phosphorus source, was used to synthesize simple NHPs as seen in Scheme 38.[37]



Scheme 38. Inaugural synthesis of NHP-Cl.

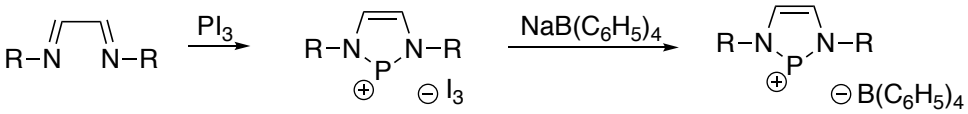
Since the reduced diimine was formed as both Z and E geometric isomers, protonation with triethylamine hydrochloride was required to produce an intermediate aminoimine which could then undergo rotation at the central sigma bond. Although this is

an effective synthesis method in many regards, there are significant issues with this protocol in terms of functional group tolerance and the harsh reaction conditions, given that lithium would be capable of reducing many substituents that may be desirable in the side-chains. Cowley and coworkers since established a milder fashion of developing NHPs through a reaction involving a diimine and PCl_3. This method used $SnCl_2$ as a reductant, the tin was incorporated as a counterion in the form of $SnCl_5^-$, ultimately yielding a phosphenium pentachlorostannate as seen in Scheme 39.



Scheme 39. Synthesis of cationic NHP-$SnCl_5$.

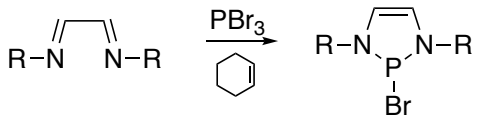
Cationic phosphorus compounds were also generated through a related synthesis involving PI_3 as shown by Cowley and coworkers, which gave products with a I_3^- counterion as seen in Scheme 40.[69] This could be exchanged for tetraphenylborate by stirring with the sodium tetraphenylborate salt. This work demonstrated further synthetic utility because it set precedent for anion-exchange reactions to form NHP salts.



Scheme 40. Synthesis of NHP-I_3 and NHP-BArF displaying anion exchange.

An important contribution to DAP synthesis was outlined by Macdonald and coworkers in which they reported a simple, one-step process using PBr_3 with cyclohexene acting as a bromine scavenger as seen in Scheme 41. Unlike previous syntheses, this approach used a mild technique that could incorporate a broad set of imines with good yields, while using inexpensive reagents. This method has is widely regarded as the most

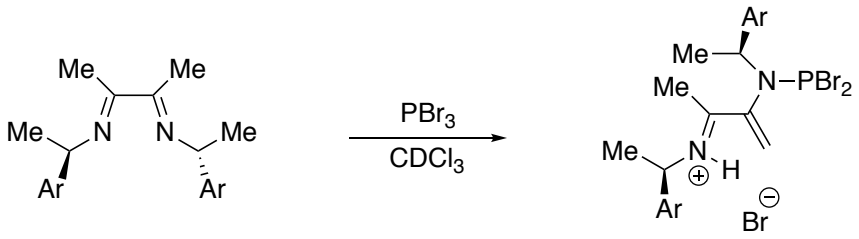
efficient and adaptable synthetic route to DAPs that has been disclosed to date, and has been used in the majority of approaches to DAP catalyst synthesis.[70]



Scheme 41. Synthesis of NHP-Br.

3.2.2 Limitations of Current DAP Synthetic Methods

Historically, phosphorus halide-based cyclization techniques have been fruitful in efforts to establish NHP precatalysts, yet more some sterically demanding or electronically rich or poor diimines don't yield the desired complexes using the established conditions. For example, previous work in the Speed group carried out by Dr. Alex Speed, showed that imines that bore steric bulk in the form of an alkyl- or aryl- substituted backbone did not cyclize like their non-substituted analogues when using each of the PBr_3/cyclohexene, PI_3 or $PCl_3/SnCl_2$ systems. Instead, these compounds decomposed to intractable product mixtures. For methyl substitution of the backbone, there was some evidence that formation of an enamine occurs during cyclization. This was established by the ^{1}H NMR spectrum of a reaction mixture with observation of the desymmetrization of signals arising from the aryl groups, the disappearance of a single methyl group in the precatalyst backbone, the appearance of a broad peak associated with a protonated imine, and appearance of two singlets with chemical shifts consistent with an enamine. This compound was not isolated, so has not been thoroughly investigated and further structural information has not been gathered.



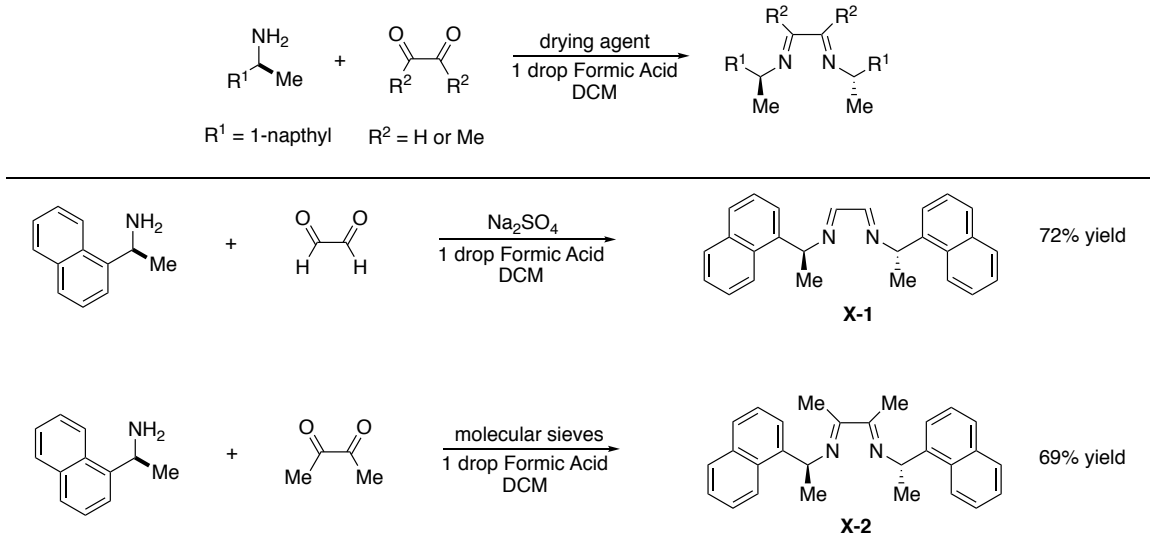
Scheme 42. Unsuccessful synthesis of methyl backbone substituted NHP-Br.

Further study of cyclization of diimines to DAPs bearing substitution on the backbone is desirable. We surmised that enhancing steric bulk in the unsaturated backbone of NHP catalysis may lead to increased catalyst selectivity by reducing the possible catalyst conformations. This hypothesis is supported by work carried out by Cramer and co-workers that used a pentacyclic DAP with greater conformational control to induce greater selectivity.[39] In Cramer's system, the fact the stereogenic centres of the catalyst are constrained in rings reduces the ability for rotation around bonds. Similarly, we observed diimines where electronic character dramatically differed from the previously cyclized diimines, such as substitution of methyl for CF_3 groups in the flanking nitrogen substituents did not exhibit formation of the desired DAPs with established cyclization reactions. Again, application of the PBr_3/cyclohexene and PI_3 methods showed no reaction while the $PCl_3/SnCl_2$ route resulted in slow decomposition.

3.2.3 Underexplored Diimines in DAP Chemistry

The aim of this work is to develop DAP precatalysts that are inaccessible using existing cyclization techniques. In doing so, diimine ligands that have not undergone reported cyclizations to DAPs were examined with the intention of accessing catalysts that are more conformationally constrained. Initial efforts in this area began by attempting to access chiral DAPs bearing substituents on the backbone. We sought to access these from diimines bearing methyl substituents. These can be accessed in a simple fashion through

modifying the general ligand synthesis by substituting glyoxal for diacetyl, and changing the drying agent as seen in Scheme 43.



Scheme 43. General diimine synthesis resulting in diimines **X-1** and **X-2**.

Cramer and coworkers' work revealing the enhanced stereoselection in reductive reactions catalyzed by polycyclic diimines in DAP catalysis also lead us to investigate a separate class of ligands that had not yet been applied to DAP synthesis, namely bisoxazolines and bisthiazolines. These ligands can be generated from amino alcohols in three and two-step synthesis respectively. Synthetic routes for bisoxazolines were well described in the literature, while there is some precedent for bisthiazoline synthesis without complete synthetic details.[71] We recognized these ligands may have strong potential for asymmetric induction due to their history of being effective C_2-symmetric chiral ligands in transition-metal catalysis. Early use of bisoxazoline ligands was demonstrated through alkene cyclopropanation and enantioselective Diels Alder reactions and they swiftly garnered popularity due the flexible synthesis of a chiral bidentate ligand.[72] Their ability to undergo cyclization with phosphorus sources was more speculative. While both bisoxazolines and bisthiazolines bear resemblance to diimines, they could be considered

far more electron-rich. Since the cyclization reaction to form DAPs results in a reduction of the diimine, this could be more challenging to accomplish with such electron rich motifs. To begin this investigation into novel precatalysts the synthesis of a library of diimines and related compounds were conducted to provide material for subsequent cyclization techniques to be tested as seen in Figure 11.

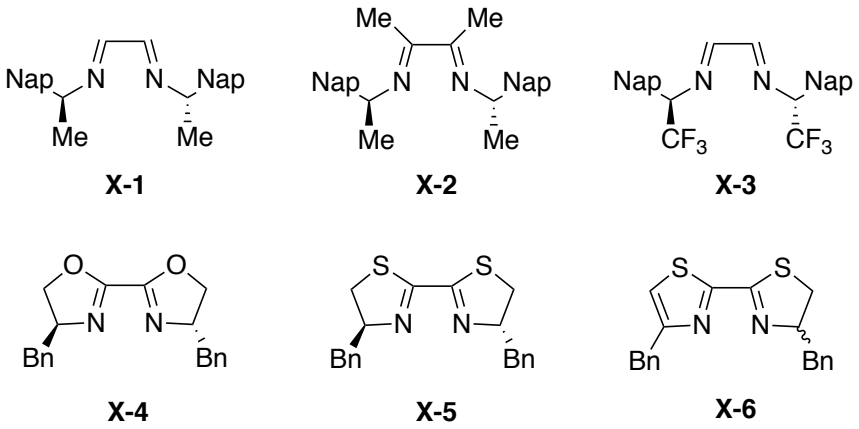


Figure 11. Diimines and related compounds synthesized for cyclization reactions.

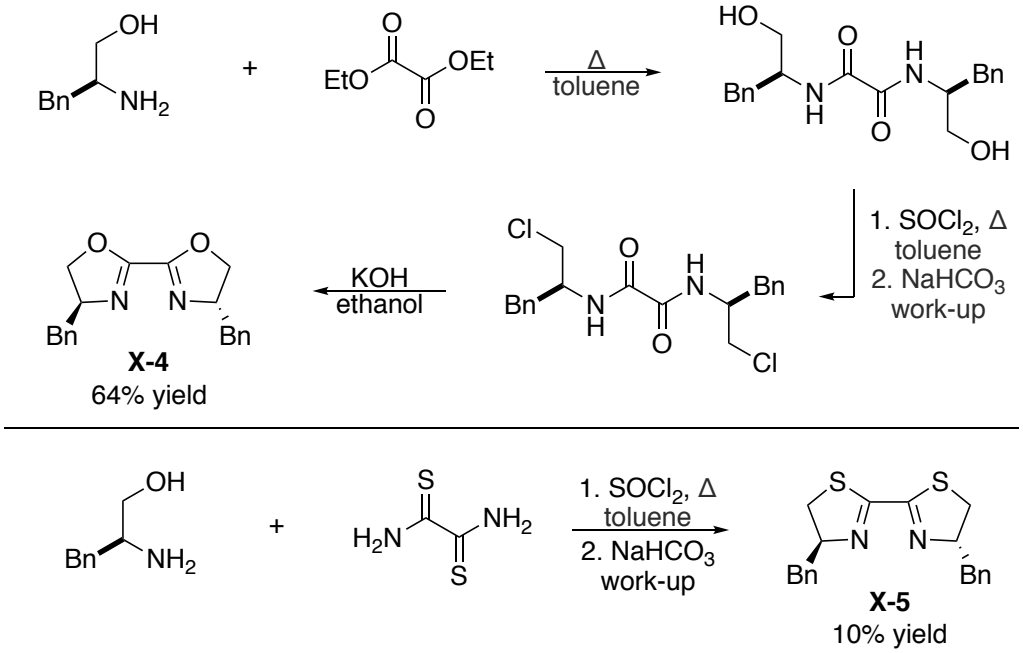
This concise set of diimine cyclization substrates lends itself to the primary focus on the cyclization reaction. Known diimine **X-1** was included in the series will be used to benchmark the new cyclization reactions moving forward. It is easily cyclized using the traditional PBr_3 synthesis and success or failure of new methods with this benchmark substrate **X-1** will give insight into the applicability of other cyclization techniques. It is likely that due to the difference between steric profiles of the diimines, some cyclization techniques may be successful with diimines that have lesser steric profiles and fail with more highly substituted ligands. This interpretation can help gauge which methods may be useful for each specific ligand. Ligand **X-2** is similar to ligand **X-1**, however it has the additional methyl substituents in the backbone. This methyl substitution is a useful starting point into further exploration of sterically demanding substitutions in the saturated

backbone. Although the methyl substitution is relatively small, reactions that are successful with this ligand may be attempted with diimines bearing bulkier substituents in the future should their synthesis be feasible. Ligand **X-3** has CF_3 groups instead of methyl groups in the flanking alkyl chains. This ligand is interesting to investigate if the strongly electron-withdrawing nature of this substitution would have a resulting impact on catalyst conformation, reactivity, and ultimately, selectivity. Ligands **X-4** and **X-5** are the previously mentioned bisoxazoline and bisthiazoline, they also provide an electron-rich counterpoint to ligand **X-3**, albeit of a relatively different structural design. Finally, ligand **X-6** is a partially oxidized version of ligand **X-5**. As will be revealed, **X-6** was an unforeseen product in the synthesis of **X-5**, however it was still investigated in cyclization reactions as it had the potential to reveal new and exciting findings upon further consideration.

3.3 Synthesis and Optimization of Diimines

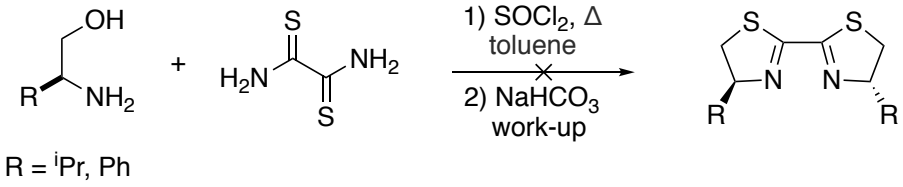
Synthesis of ligands **X-1** and **X-2** are robust and widely known in the literature. We followed the method demonstrated by the tom Dieck group.[73] This method combines glyoxal or the alternative dicarbonyl compound and the chiral amine with the drying agent Na_2SO_4 and a drop of formic acid in dichloromethane. Tom Dieck reported that formic acid was necessary as an imine condensation catalyst to obtain products of high purity. Formic acid is presumably used because of its high volatility, enabling its removal when the reaction is complete. Using this method ligands **X-1** and **X-2** were synthesized in high yields of 72% and 69% respectively. Ligand **X-3** was synthesized by Dr. Alex Speed using the same approach from the corresponding chiral amine. Because of the scarcity of the chiral amine used to prepare **X-3**, this ligand was used sparingly. Ligands **X-4** was known

to have reliable synthesis and is constructed through a reaction involving disubstituted oxalic acid derivatives and two equivalents of an amino alcohol. These starting materials are added together under basic conditions to make an oxalamide. Subsequent chlorination of the pendant alcohols is conducted, and addition of a base promotes double cyclization of the dichloride intermediate.[74] Ligand **X-4** was synthesized using this method in strong yields of 64%. Stirring amino alcohols with dithioxamides in ethanol led to the formation of a bis-thioamide, but the reaction took several days, in part due to the low solubility of the reaction partners in ethanol. Exposure of the bisthioamide to thionyl chloride, then base led to **X-5**. Literature reports for the synthesis of ligand **X-5** showed reaction schemes, but did not contain experimental details or conditions. Literature suggested the cyclization of the thiazolines did not require strong base, unlike the oxazoline cyclization. My initial attempts to develop a route led to poor yields of 10%. Efforts were employed to improve yields, such as promoting cyclization through the use of triphenylphosphine dibromide to brominate the molecules rather than using thionyl chloride. The motivation behind this was to substitute the chloride leaving group with a bromide to explore if this minor change impacted yields. This modification was unsuccessful. An alternate route was investigated using a solvent-free system with a mortar and pestle, but this was also fruitless as no product was formed. The overall synthesis was further explored by another member within the group months later, Dr. Travis Lundrigan. As previously mentioned, a partially-oxidized by-product of the synthesis of ligand **X-5** was the ligand **X-6**, again in low yields of 7% so it was also used sparingly moving forward.



Scheme 44. Synthesis of diimines **X-4** and **X-5**.

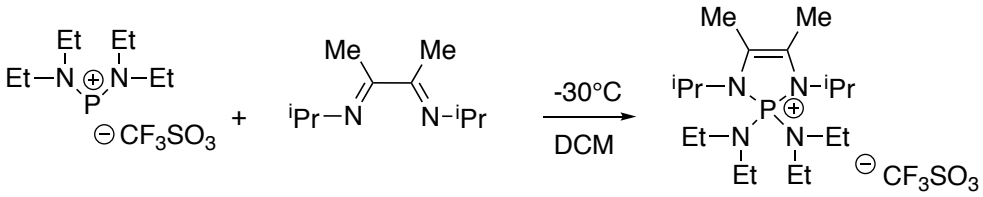
Other bisthiazoline ligands in addition to those displayed in Scheme 44 were topics of interest for this study, especially given the poor yields of **X-5**. We speculated alternate groups may allow higher-yielding syntheses. These other targets used amino alcohols with phenyl and isopropyl groups instead of the benzyl group in the primary investigation as seen in Scheme 45. However these synthesis also had long reaction times and the other bisthiazolines were not accessed. This approach was abandoned to prioritize experiments with more accessible diimines.



Scheme 45. Unsuccessful synthesis of bisthiazoline variants.

3.4 Synthesis and Optimization of Phosphenium Reagents for Diimine Cyclizations

Since previous research within the Speed group has shown that phosphorus halide based cyclization techniques have issues with some imines, there is a need to explore new methods of cyclization to access unique DAPs for catalysis. Phosphenium salts of the species R_2P^+ have been shown to react with unsaturated species such as 1,3 dienes to give five-membered rings.[75] Mazieres has shown that phosphenium cations have reacted diimines to form phosphorus heterocycles with a positive charge on the phosphorus, as seen in Scheme 46. Given the fact the two amino ligands remain on the phosphorus, the phosphorus in these species is in the (V) oxidation state, unlike the previous DAP examples with PBr_3, where a reduction occurs during the reaction.[76] Unlike the examples used in the P(III) DAPs, this mode of cyclization involved the initial synthesis of phosphenium cations prior to cyclization, which constitutes an additional step. Given the strong precedent shown by Mazieres, we elected to re-evaluate these older, two step procedures in chiral DAP synthesis as they may establish a workable approach to generating the desired backbone-substituted DAP catalysts that were yet to be thoroughly tested.



Scheme 46. Synthesis of NHP phosphoniums.

This work required phosphenium cations to be synthesized, to be used in the cyclization reactions. An assembly of five possible cyclization reagents as seen in Figure 12, bearing substituents of various sizes were considered. The phosphenium salts were prepared by abstraction of chloride from the corresponding diaminochlorophosphines with a halide-abstracting reagent such as TMS triflate.

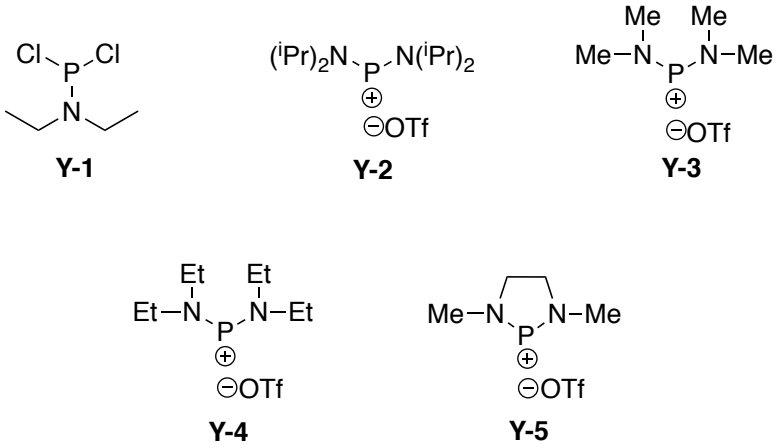


Figure 12. Library of phosphenium reagents used for cyclization reactions.

Notably, phosphorus reagent **Y-1** is not a prototypical phosphenium cation, however it was previously synthesized for another project within the group. It is accessible and still has precedent for performing the desired cyclization reactions with appropriate halide abstraction. This reagent was low-priority and was used sparingly. It was synthesized cleanly through a reaction between two equivalents of the appropriate amine and PCl_3 at -78°C and gently warmed to room temperature.[77] The chloride precursors to phosphenium reagents **Y-2**, **Y-3**, and **Y-4** were all prepared through a general method involving the reaction between one equivalent of PCl_3 and four equivalents of the necessary amine in hexanes at 0°C, however the reagents were also commercially available, and commercial sources were used.[78] I prepared the chloride precursor to heterocyclic phosphenium **Y-5** through the addition of one equivalent of PCl_3 to one equivalent of the diamine N,N'-dimethylethylenediamine with excess NEt_3 at –40°C. The chlorides of the diaminochlorophosphines are covalently bound, but are readily transformed into the ionic triflates analogues through an abstraction reaction using a single equivalent of TMSOTf, and subsequent removal of TMS chloride *in vacuo*. The resulting products were brought into a glovebox for safe keeping. While **Y-2** was a solid, that could be further purified by

triturating and washing with diethyl ether, **Y-3**, **Y-4** and **Y-5** were ionic liquids. Their immiscibility with diethyl ether, unlike their chlorophosphine precursors, was good evidence of their ionic character, but despite trituration attempts in that solvent or pentane, including sonication, they did not produce solid products.

3.5 Synthesis of Diazaphospholene Precatalysts

With a small set of diimines, as well as a series of phosphorus compounds being synthesized, the next logical step was to explore the cyclization reactions with various combination of reagents**.** A new preparative route was also investigated that makes the desired NHP phosphonium in a one-pot reaction without isolation of the intermediate phosphonium. In doing so, the diaminochlorophosphine is dissolved in dichloromethane and TMSOTf is added to form the triflate analogue without isolation. After solvent removal *in vacuo* the diimine is added in the glovebox to form the desired product. This route aims to improve the general synthetic methods of NHPs by offering a robust synthesis that eliminates the need for intermediate isolation steps.

3.5.1 Cyclizations with X-1

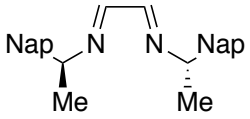


Figure 13. Diimine **X-1**.

Cyclization reactions started with benchmark diimine **X-1**. We reasoned this would be a good starting point as it is hypothesized that this ligand will be the easiest to cyclize given the relative simplicity and lower steric profile compared with the other diimines. Also, this diimine has been comprehensively researched within the group and its chemistry in DAP cyclization reactions is generally very well behaved. To a 1 dram vial of

approximately 2 mL of THF one equivalent of ligand was added to a slight excess of the phosphorus reagent. For ligand **X-1** this method was largely successful, generating the desired complexes as seen in the resulting ^{31}P NMR spectrums. Generally, when interpreting the ^{31}P NMR spectrum of these sorts of reactions, the deciding factor when determining if a reaction has precedence for further testing is the disappearance of a signal associated with the known phosphorus starting material and the appearance of a new signal that is a result of a new phosphorus environment, the DAP. As seen below in Figure 14, the signal associated with the starting material is effectively replaced by a singlet coinciding with the desired product. This methodology is used throughout this work moving forward.

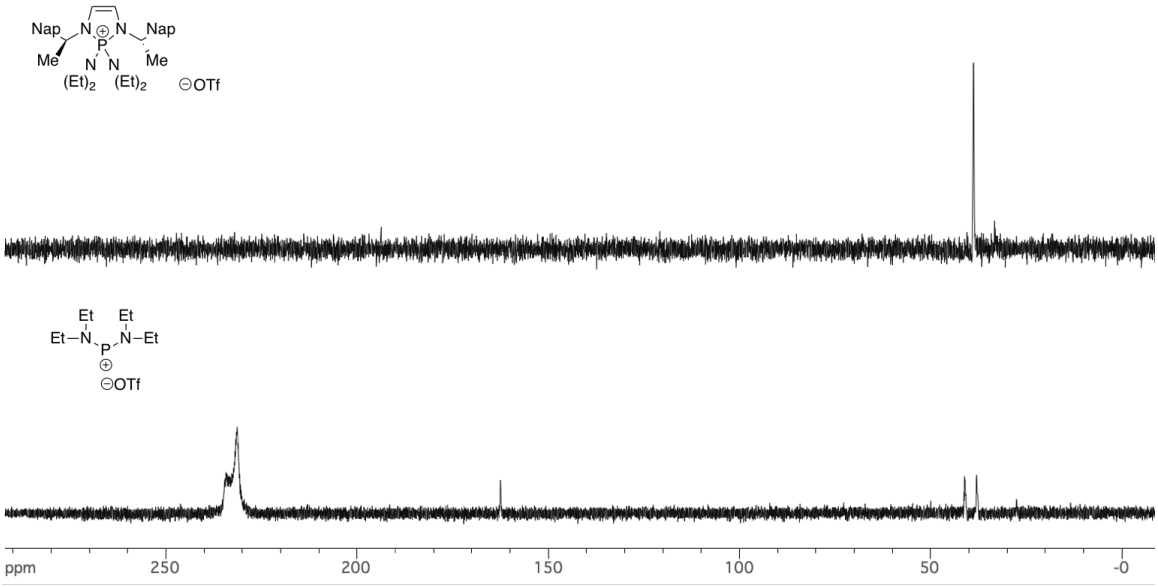
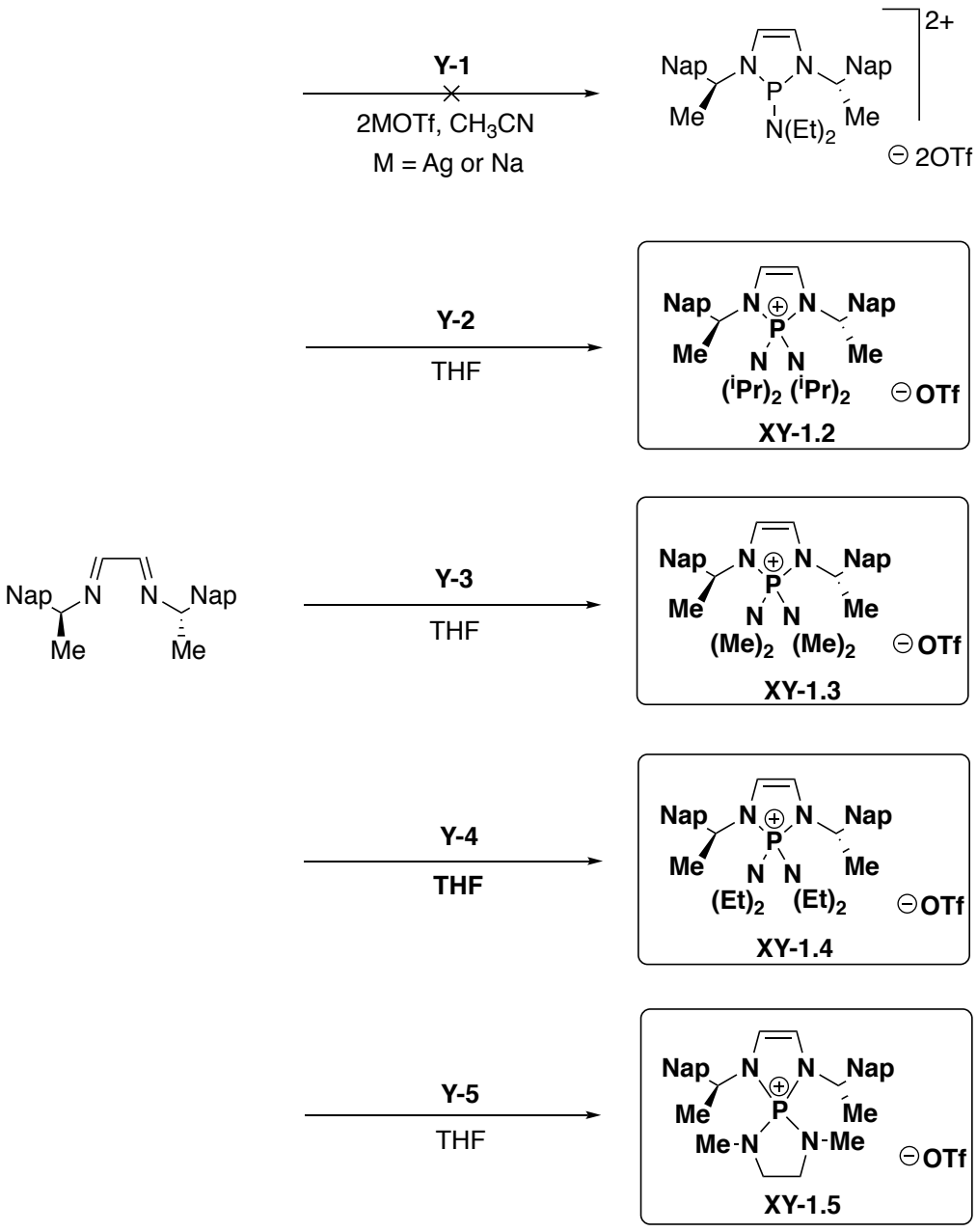


Figure 14. ^{31}P NMR spectra of compound **XY-1.4** (top) and compound **Y4** (bottom with slight impurities)

As seen in Scheme 47, each of the following complexes were synthesized and able to be used in subsequent reduction reductions. Notably, the reaction between **X-1** and phosphorus source **Y-1** was the only combination that did not furnish the desired product.



Scheme 47. Cyclization attempts using diimine **X-1**.

The precatalysts were used as catalysts for the reduction of an imine substrate and those results then indicated if the compound should be examined further. This method gave

insight into which of the many possible precatalyst combinations were most promising. The biggest takeaway from these initial reactions is that the cationic phosphenium reagents shown in Scheme 47 could go about cyclization with this benchmark chiral diimine. However, since these reactions used the least sterically demanding diimine, success with the more elaborate diimines remained to be established. While the end-goal was to use these complexes for reductions, all the other cyclizations will be discussed in this section, followed by their catalytic studies in a later segment.

3.5.2 Cyclizations with X-4

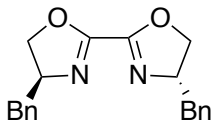


Figure 15. Bisoxazoline **X-4**.

The next ligand that was explored was **X-4** due to its ease of synthesis. The first phosphorus reagent investigated was dichloride species **Y-1**. This reaction was carried out following the reaction conditions of conventional phosphorus halide methods, but with the addition of two equivalents of metal triflates to abstract the halides. We hoped this would result in attack of the nitrogens of **X-4** on the phosphorus, giving the dicationic product, which could be formulated as a P(V) species. In the interest of rapid screening, ^{31}P NMR spectroscopy was used as the primary tool used to observe changes and determine whether a reaction was worthwhile for further investigation. We anticipated successful product formation would result in a new single signal, so multiple signals would indicate formation of multiple products. Unfortunately, reactions involving ligand **X-4** were simple to summarize as all unsuccessful. Reactions with phosphorus source **Y-1** did not yield the desired product, but primarily unreacted starting material as the ^{31}P NMR spectrum

overwhelmingly displayed a peak associated with that of **Y-1**. This reaction was run with two different metal triflates to determine whether this variable was impactful, but it was not as both NaOTf and AgOTf gave reaction mixtures of predominantly starting material. The bisoxazoline ligand was then reacted with the remaining phosphenium reagents beginning with phosphenium **Y-2**. The two components were added together in a 1 dram vial in approximately 2 mL of THF and allowed to sit overnight undisturbed. The ^{31}P NMR spectrum of the resulting reaction mixture gave mixed results. Instead of previous examples demonstrating no indication of cyclization, this case gave a spectrum containing a complex mixture of many products with several signals lying between 10ppm to -12ppm.

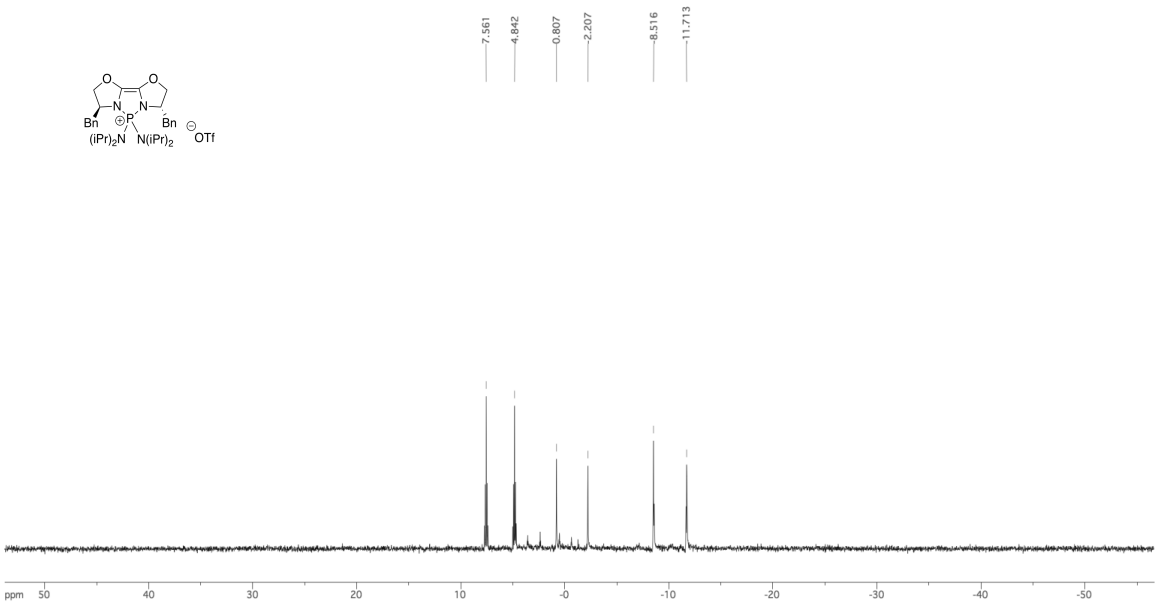
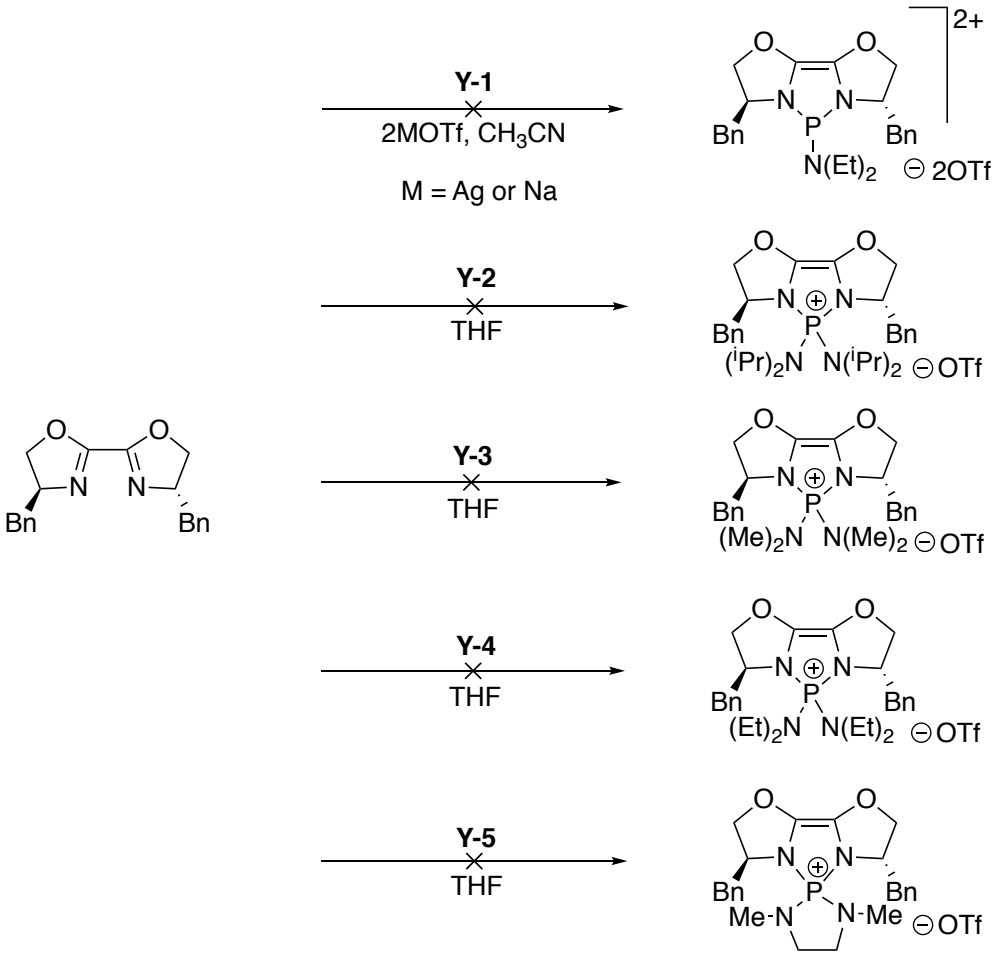


Figure 16. ^{31}P NMR spectrum showing potential decomposition of NHP.

Previous work within the group showed that this may be due to hydrolysis of the phosphorus species, however this hypothesis was not investigated further. It should be noted NMR samples of **X-4** prepared within the glovebox did not show the presence of water, or any unexplained ^{1}H NMR signals, suggesting that **X-4** was not contaminated with water. Nonetheless, the desired cyclized species was not successfully obtained using this

reagent so the following phosphorus source, **Y-3**, was next to be examined. Following the same protocol as the previous attempt, the reaction between these two species again did not furnish a cyclized product. Minor signals were present in the ^{31}P NMR spectrum displaying a mixture of potential products. One of these signals may have been the desired product, however the lack of a clean cyclization, and lack of obvious method to purify the product, was deemed too troublesome to further investigate during the outset of this project. Next, phosphorus source **Y-4** was investigated, but also did not display the pattern of the anticipated product. The final phosphorus reagent, **Y-5** was investigated. This reaction, like all other reactions with the bisoxazoline ligand, did not yield the desired product. As seen using ^{31}P NMR spectroscopy, there was no evidence of product formation through a predominant single peak in the phosphorus NMR spectrum associated with the phosphorus starting material. Reasons for the lack of cyclization of this ligand are unknown at this point. The electronic character of the ligand is a likely culprit as the since phosphorus reagents of various sizes were used.



Scheme 48. Cyclization attempts using bisoxazoline **X-4**.

3.5.3 Cyclizations with X-5

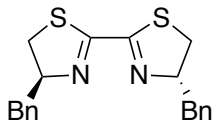
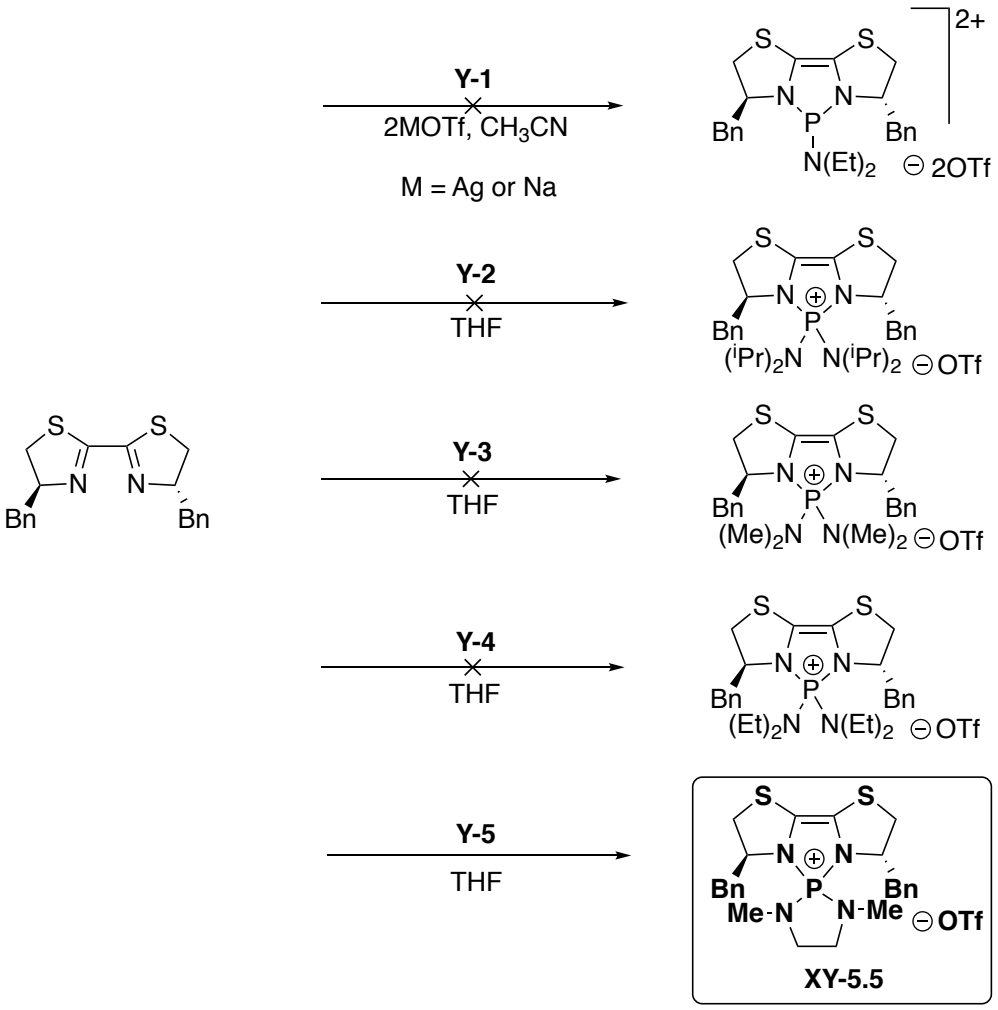


Figure 17. Bisthiazoline **X-5**.

The next ligand investigated was bisthiazoline species, **X-5**. Since the synthesis of this ligand was unoptimized for much of the duration of this project, reactions were run on a small-scale. Fortunately, some of the results with this ligand had potentially appealing outcomes as will become evident. The first phosphorus reagent used was the dichloride species **Y-1** and like the previously examined ligand, resulted in unreacted starting material

as seen in the ^{31}P NMR spectrum. This test was run using both metal triflates available, yet both had the same result. To be concise, phosphorus reagents **Y-2**, **Y-3** and **Y-4** presented no indication of product formation and solely had unreacted starting materials in their respective ^{31}P NMR spectrums. Phosphorus reagent **Y-5**, however, resulted in a potential product worth further consideration through ^{31}P NMR spectroscopy. This hypothesis is supported because previous phosphorus environments in DAP species that have been thoroughly investigated have a single peak in the 40 ppm range denoting the desired phosphorus environment. This recent example had a peak in the 20 ppm range, a slight deviation from expected results. Given the unique steric and electronic profile of the ligand combined with the unexplored space of these sorts of phosphenium cyclizations, this result was worth noting for potential future studies.



Scheme 49. Cyclization attempts using thiazoline **X-5**.

3.5.4 Cyclizations with X-6

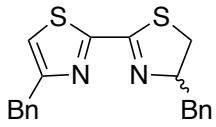
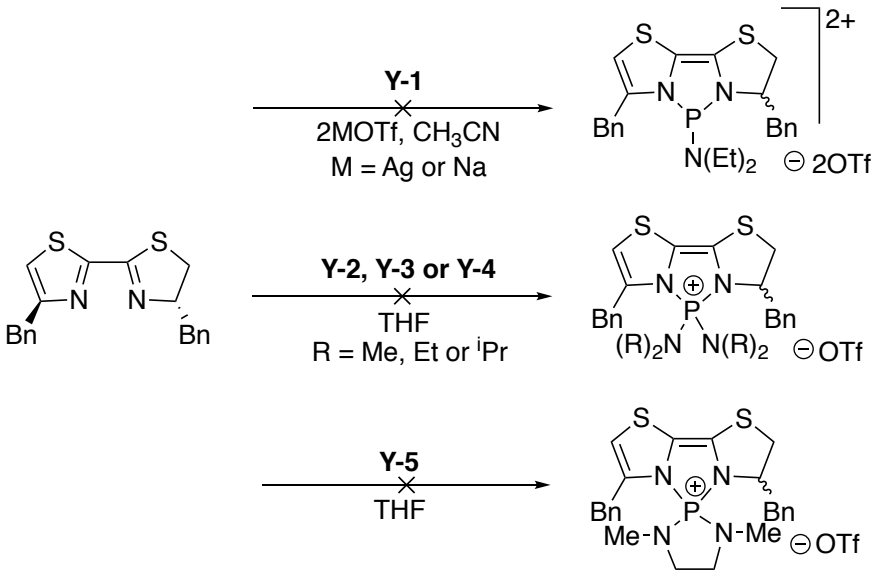


Figure 18. Diimine **X-6**.

The next ligand surveyed was **X-6**. The first reaction with phosphorus source **Y-1** was quickly deemed unsuccessful with exclusively starting material in the ^{31}P NMR spectrum. Again, to be concise, phosphorus reagents **Y-2**, **Y-3**, **Y-4** and **Y-5** all showed multiple products through ^{31}P NMR spectroscopy. Although it is possible that one of the

signals in the ^{31}P NMR spectrum is product, the lack of a clean cyclization to a single product made further investigation a low priority. Previous cyclization methods in DAP chemistry that are well adopted have been efficient cyclization methods giving single products. Tangential studies may consider the isolation of these potential products, however the main concern with this work at this point is to find methods that quickly, efficiently and cleanly synthesize desired products for reactivity studies.



Scheme 50. Cyclization attempts using compound **X-6**.

The initial outset of this project was to cyclize a variety of differing ligands through these cyclization techniques, however these heterocyclic bisoxazoline and bisthiazaoline ligands have shown very little potential through the modes of cyclization attempted thus far. As will become more evident shortly, outcomes from the backbone substituted ligands yet to be discussed showed greater potential, so given the motivations of this work to explore new motifs in catalysis, attention turned to the compounds with greater potential. It is entirely possible that the bisoxazoline and bisthiazoline ligands have potential in NHP

chemistry, however further development of cyclization chemistry will be required in order to access diazaphospholene derivatives of this compound.

3.5.5 Cyclizations with X-3

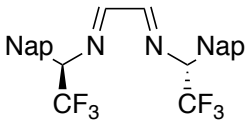
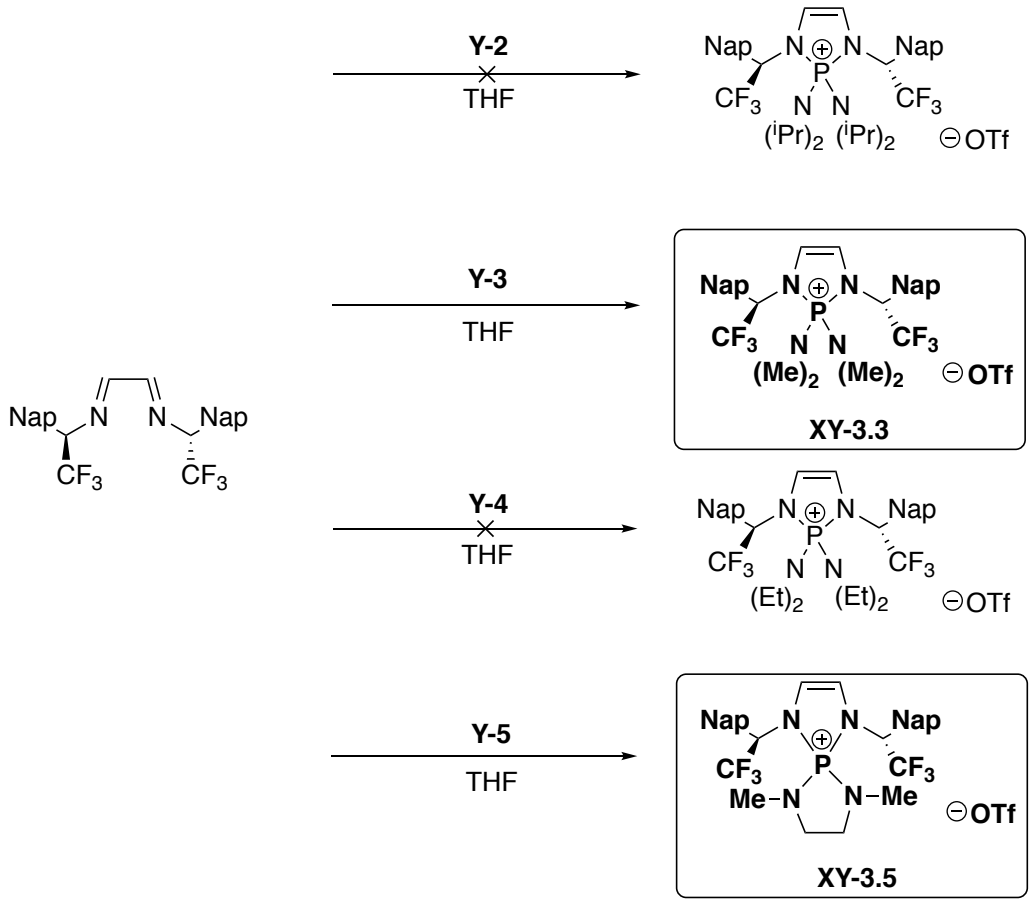


Figure 19. Diimine **X-3**.

Due to the precious nature of this CF_3 substituted diimine it was used sparingly to explore cyclization reactions. Because of the rarity of this compound, only the phosphorus sources that we believed to have the greatest potential to cyclize were attempted. In this case, the phosphorus source, **Y-1** was deemed the least likely to perform the desired transformation due to previous cyclization attempts. This concept coupled with the ease of synthesis of the remaining phosphorus reagents allowed for reactions with species **Y-2**, **Y-3**, **Y-4** and **Y-5**. Of these reactions, two showed potential to be investigated further. The two that did not show any signs of cyclization were reactions with phosphorus reagents **Y-2** and **Y-4** displayed only signals in the ^{31}P NMR spectrum associated with starting material. Interestingly, the reaction with **Y-4** seems to have potentially polymerized the THF medium in which the reaction was run. Fortunately, reactions with phosphorus reagents **Y-3** and **Y-5** showed potential cyclization as seen through new singlet phosphorus environments in their respective ^{31}P NMR spectra. It is worth noting both of these phosphenium cations are relatively sterically undemanding relative to the others that were explored. An efficient synthesis of the ligand **X-3** is yet to be established, hindering its applicability moving forward.



Scheme 51. Cyclization attempts using diimine **X-3**.

3.5.6 Cyclizations with X-2

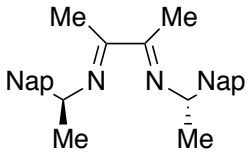
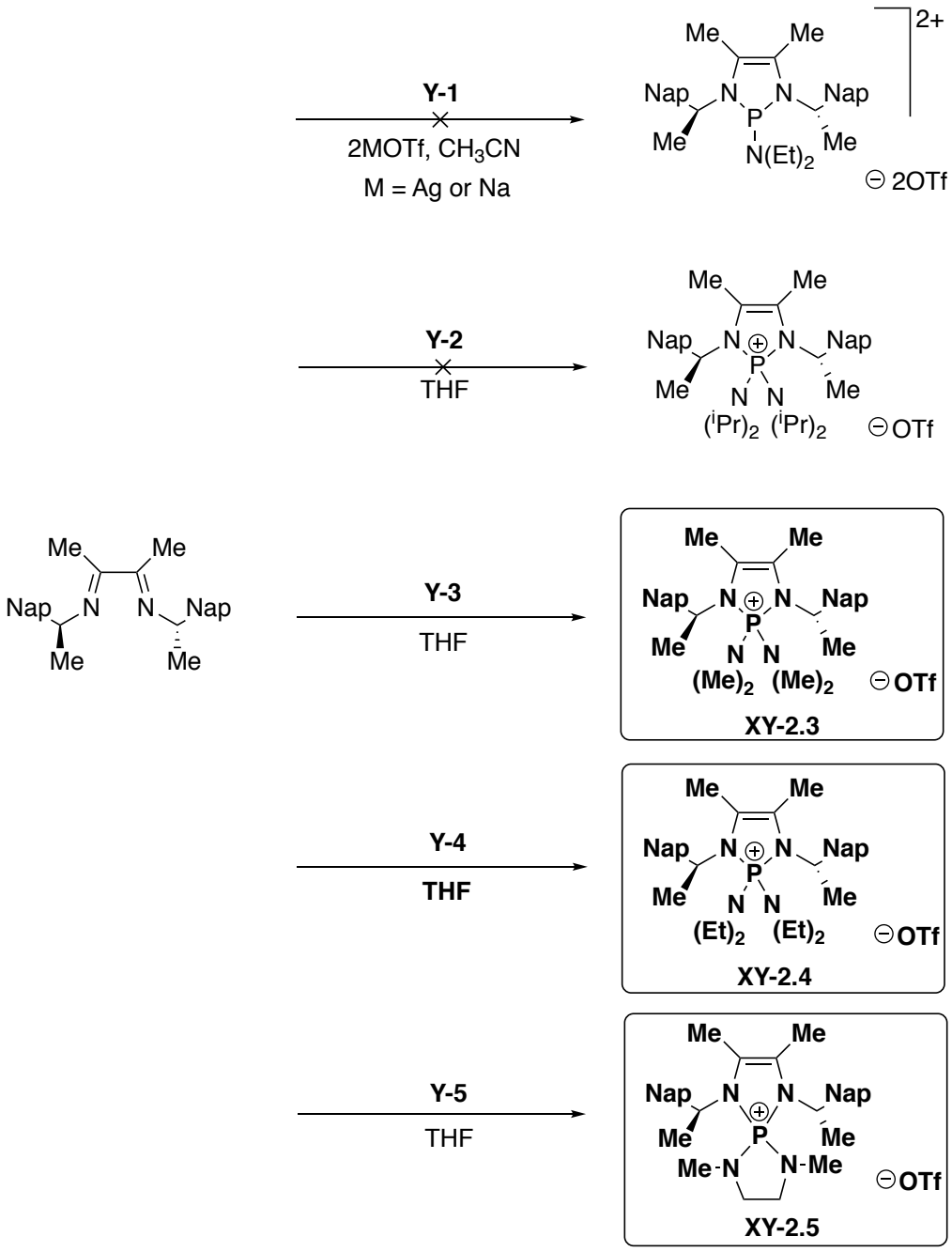


Figure 20. Diimine **X-2**.

The most intriguing ligand at the outset of this work was diimine species **X-2**. This diimine has added substitution in the backbone, without other major changes to the geometry and electronic environment of the diimine relative to the most successful glyoxal-derived diimine that was the centre of the Speed group's prior work. This diimine was allowed to react with all the available phosphorus species with positive results. Of the 5

phosphorus sources investigated, 3 were immediately successful with clean cyclizations as observed through ^{31}P NMR spectroscopy with signals at 38.6 ppm, 40.3 ppm and 30.1 ppm respectively. The successful cyclizations were accomplished using reagents **Y-3**, **Y-4** and **Y-5**, meaning reagents **Y-1** and **Y-2** were ineffective. It should be noted that **Y-2** is a rather bulky reagent compared with **Y-3**, **Y-4**, and **Y-5**. Given the increased steric demand of diimine **X-2** relative to **X-1**, the absence of cyclization with **Y-2** points to a limitation in using that reagent for cyclizations with more sterically demanding diimines.



Scheme 52. Cyclization attempts using diimine **X-2**.

The aim of this project is to synthesize DAPs and ultimately test their reductive capabilities. At this point, the success of these syntheses has been ascertained using spectroscopic data to determine if any clean reactivity occurred in the cyclization reaction. Although this information shows potential product formation, based on Mazieres'

precedent, we felt it was important to obtain further structural information about the adduct to ensure our assignment of the structure of the product was correct. This is especially important when researching potential catalysts as a correct understanding of the structure is necessary to gain insight into the inner workings of potential catalytic cycles and catalyst conformation. We made the acquisition of crystallographic data for derivatives of **X-2** a top priority moving forward. Compound **XY-2.4** was subjected to multiple conditions to promote crystal growth. The cyclization reactions to this point were predominantly run in relatively dilute THF, however to get the desired crystals, the reaction times, temperatures and solvent systems were the variables that needed to be manipulated. Many trials of this reaction were run investigating other solvents such as acetonitrile and dichloromethane to see the product would crystallize from the reaction mixture at ambient temperatures. Unfortunately, this was not the case as the product remained in solution. The next step was to run these reactions and subsequently cool them to –33^{o}C and see if this would encourage the formation of crystals, but again this was unsuccessful as the product remained in solution. What ultimately proved to be a successful method was simply slow evaporation from the original solvent used, THF. Suitable crystals were grown over approximately 2 weeks using this technique. This result is crucial to this thesis, demonstrating that the synthesis of chiral DAP phosphonium cations was successful. The crystal structure seen in Figure 21 was acquired and solved by Dr. Katherine Robertson at Saint Mary's University which satisfyingly aligned with our initial hypothesis. This structure also further supports the synthesis of the other complexes which have similar ^{31}P NMR spectroscopic diagnostic features. Now that we correctly identified one of the proposed DAP products from spectral data and the crystallographic studies support these claims, it only reassures that our other

assumptions based on ^{31}P NMR spectroscopy for other examples are likely correct. Since one crystal structure was obtained, we next prioritized reactivity studies, rather than attempting crystallize the other potential products precatalysts as complex **XY-2.4** was already the most intriguing finding thus far. Nonetheless, it is entirely possible that other precatalysts could be crystallized using similar methods to those used for this example.

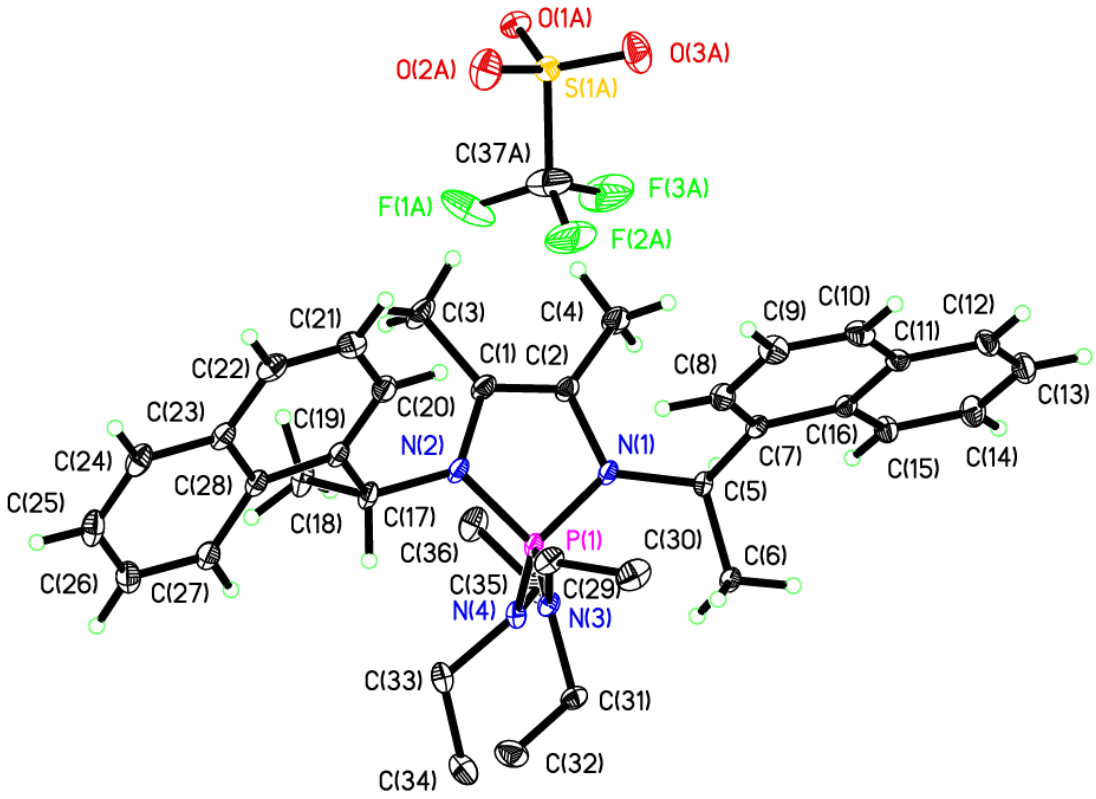
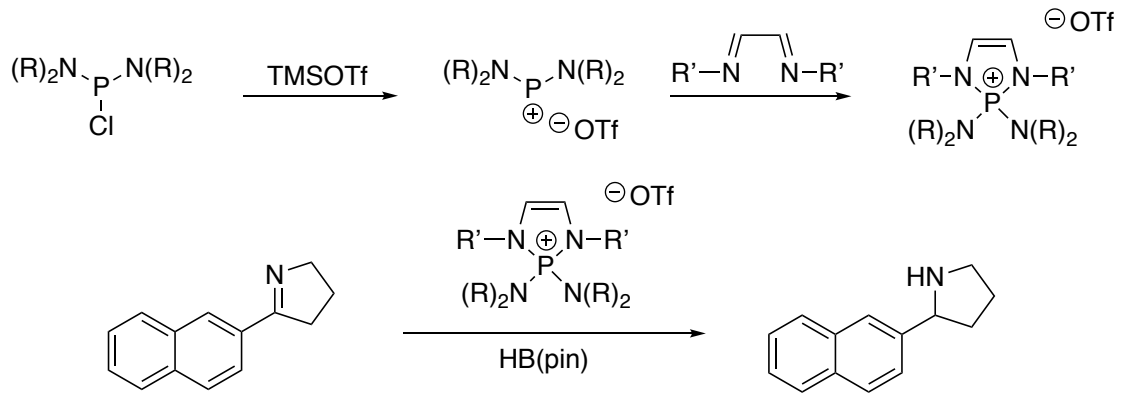


Figure 21. Single crystal X-ray structure of **XY-2.4**.

The identification of compound **XY-2.4** has shown that the preparative route displayed in this work has successfully synthesized new NHPs. A more efficient synthesis of **XY-2.4** was developed as a single pot procedure without isolation of the intermediate phosphenium, which is an ionic liquid. The appropriate chlorophosphine is treated with TMSOTf to create a cationic phosphenium reagent. This reagent, without isolation, is combined with the appropriate diimine to generate the desired NHP through cyclization.

This compound can then be isolated without removal of the TMSCl *in vacuo*, and can be used as a precatalyst for the reduction of imines. Due to the one-pot nature of this method, it should also be noted that the TMSCl byproduct that is formed in the synthesis does not interfere with cyclization.

This is the most important contribution to the NHP field investigated in this work. A new robust route has been developed with the potential to ease future synthesis as it incorporates mild reaction conditions and eliminates the need for isolation of the phosphenium cation intermediate prior to cyclization. Avoiding lengthy separation and purification processes are essential in developing strategies to improve the efficiency of chemical reactions.



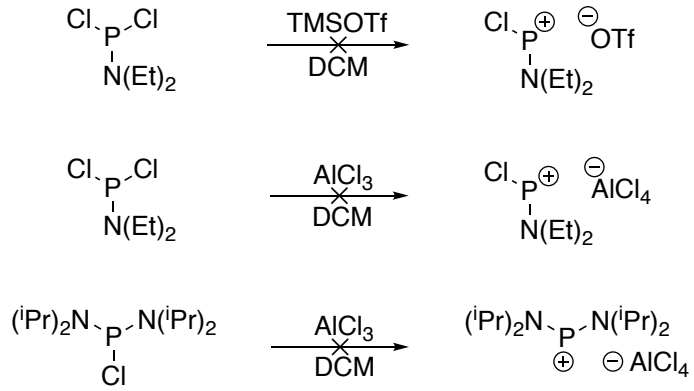
Scheme 53. One-pot synthesis of NHP precatalysts.

3.6 Exploration of other Counterions for the Phosphenium

At this point in the project, each ligand has been tested with each of the phosphorus sources in initial cyclization attempts. Notably, phosphorus source **Y-1** was the least successful reagent for cyclization, with no positive results with any ligand. An attempt to prepare and isolate a phosphenium cation from **Y-1**, before adding diimines was made. The compound, as seen in Scheme 53, was reacted with either TMSOTf and $AlCl_3$ in an attempt

to abstract chloride ions, which could perhaps lead to solid phosphenium cations as has precedent in the literature.

The reactions, however, were fruitless as the reaction with TMSOTf resulted in solely starting material and the reaction with $AlCl_3$ appeared to result in decomposition, even when repeated at –78°C. bis-diisopropyl phosphenium, **Y-2**, was also reacted with the $AlCl_3$, however with no product formation, solubility was likely a contributing factor in this case. This is still a potential area of expansion moving forward but showed that this area was not as accessible as anticipated.



Scheme 54. Chloride ion abstraction attempts on phosphenium reagents **Y-1** and **Y-2**.

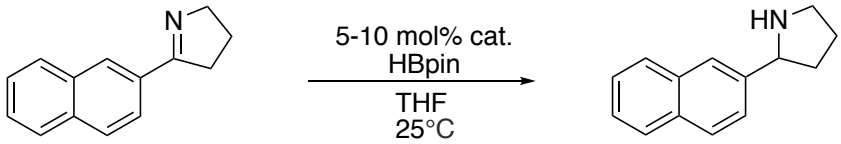
The one-pot synthetic route utilized in these efforts generated many of the desired products without the need for intermittent isolation, as intended. Abstraction of the chloride from the diaminochlorophosphines with TMSOTf was accomplished easily prior to diimine addition. This route contributes a simple and general route, easing synthesis of these compounds overall.

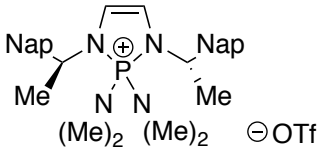
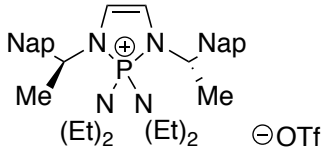
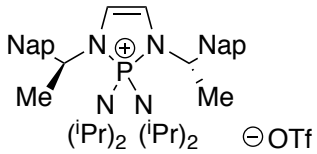
3.7 Reactivity of Synthesized Diazaphospholenes

Several novel cationic diazaphospholenes bearing phosphorus in the (V) oxidation state were synthesized and characterized in work leading up to this point. The formulation was confirmed for one example with X-ray crystallography. Subsequently it was important

to test their reactivity. The initial DAPs tested in this section were those prepared from the benchmark diimine, **X-1**. We sought to examine the effect of the amine substituents about the phosphorus centre and compare it with the well precedented structure of the same scaffold in the P(III) oxidation state (the phosphenium triflate). Next, the more elaborate ligand, **X-2**, was tested in enantioselective reduction. This is a completely new scaffold in reductive DAP chemistry. Finally, a few individual cases of other DAPs were tested on a less thorough basis and as will be revealed, yielded unexciting results. I have tested many of the synthesized DAP with one substrate shown in the following tables, 3-1 and 3-2. This was one of the better substrates in the Speed group's previous chiral phosphenium catalysis and is both readily separated and analyzed by chiral HPLC analysis.

Table 1. Summary of reactivity of NHPs with diimine **X-1**.

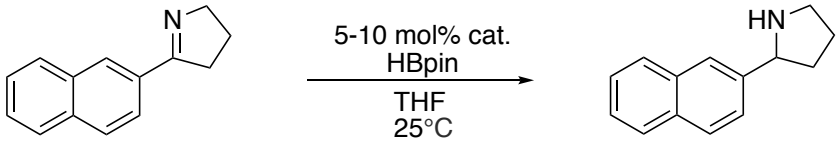


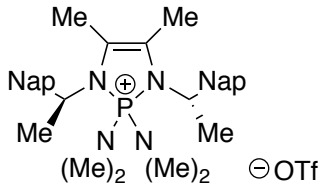
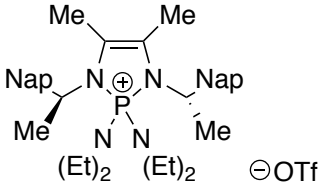
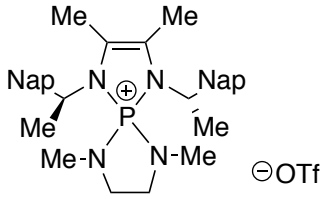
Entry	Catalyst	Conversion	Selectivity
1		> 90%	32:68
2		> 90%	39:61
3		> 90 %	14:86

These results notably indicate that the identity of the substituents on the phosphorus have a profound influence on the stereochemistry of the reactions, despite all of the examples being produced from a common diimine backbone. The highest selectivity was observed for entry 3. In this case, it appears the bulkiest of the phospheniums had the greater impact on selectivity, aligning with the initial hypothesis that perhaps the increased steric profile results in fewer possible catalyst conformations. The sense of induction was determined by the HPLC elution times, in relation to results of known configuration from the Speed group's earlier work with phosphenium cations. The sense of induction for these

catalysts was the same as the phosphenium catalyst. Next, the DAPs derived from methyl substituted diimine **X-2** were tested.

Table 2. Summary of reactivity of NHPs with diimine **X-2**.

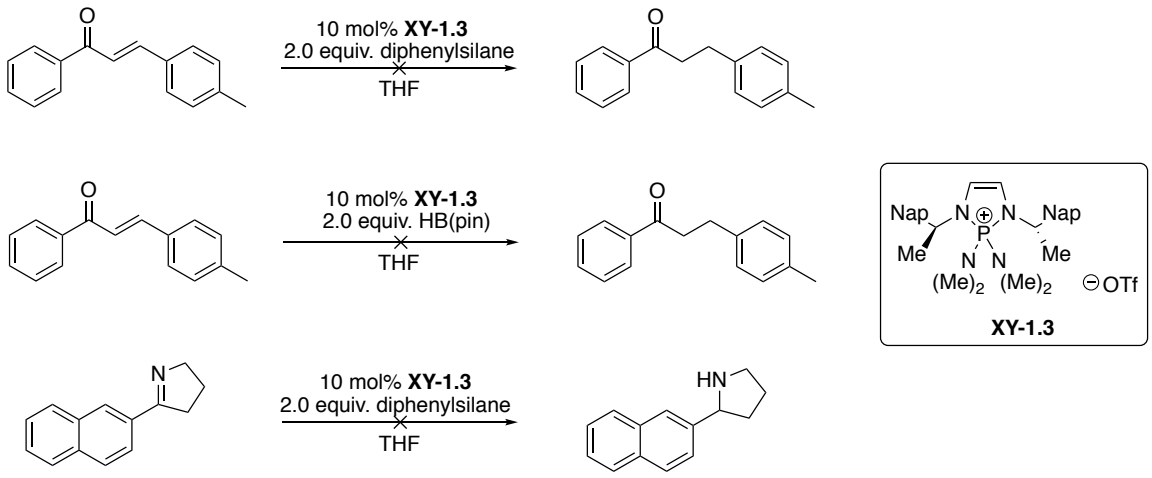


Entry	Catalyst	Conversion	Selectivity
1		> 90%	18:82
2		> 90%	12:88
3		64%	50:50

An example prepared with diimine **X-2** and the phosphenium derived from diethylamine were the examples with the greatest enantioinduction of these novel compounds examined so far. This entry, 2, is also the same compound that was characterized through X-ray crystallography.

The remaining DAPs that were successfully synthesized and had their reactivity tested all had a combination of poor conversions and no selectivity. At this point most of

the reactivity studies were limited to one specific imine with only HBpin as a reductant. Another area of interest was to investigate other saturated species as well as utilizing different reductants such as diphenylsilane. This potential area was looked at briefly with the following reactions utilizing a previously synthesized chalcone.



Scheme 55. Reactivity of NHP **XY-1.3** with varying saturated species and reductants.

These inaugural reactions did not yield promising results as it appeared that in entry a, incorporating diphenylsilane resulted in no reduction whatsoever and trial b, yielded minimally reduced product as seen in Figure 22. Trial c, which used the previously investigated imine substrate, also did not result in the reduced product. Although this area was not investigated thoroughly, incorporating different reducing agents and different saturated substrates is a good avenue to investigate moving forward.

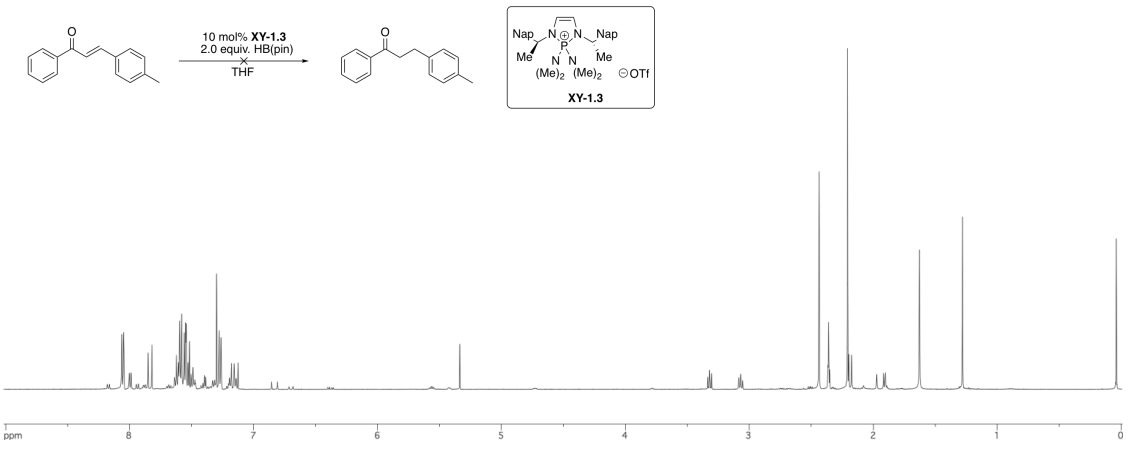


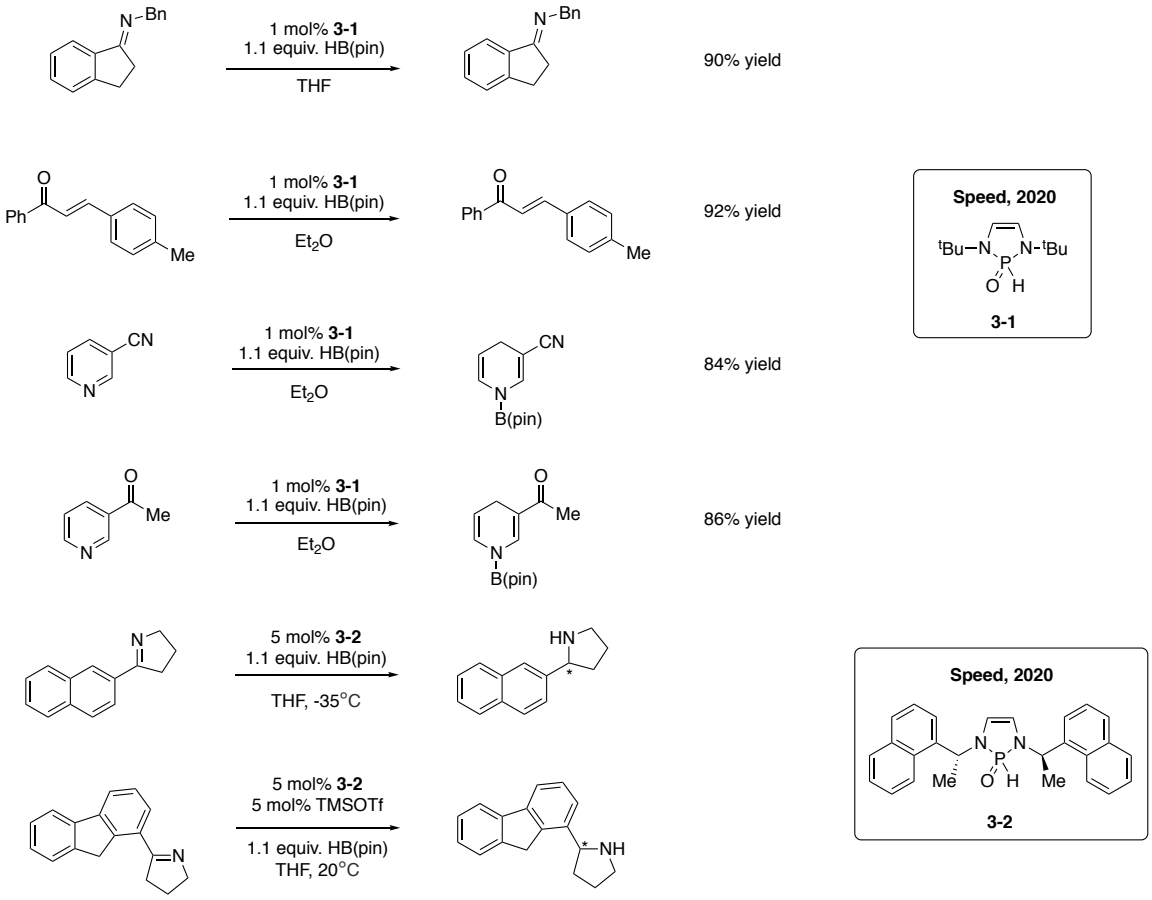
Figure 22. Partial reduction of chalcone with compound **XY-1.3**.

In its totality, the imine reductions had some successful findings with the highlight being entry 2 of Table 3-2 with a selectivity of 12:88. One topic of note is the potential to change the enantioinduction of the catalysts. We hypothesize that there may be a conformational difference in the active catalyst displayed in this work and previous DAPs investigated within the group. The Speed group has recently shown interest in secondary phosphine oxides (SPOs) as DAP catalysts. An appropriate next step in this work is to transform the most successful catalyst in this work into its SPO analogue. If this transformation is successful, perhaps the modified phosphorus substituents would result in decreased steric bulk about the phosphorus centre. This could potentially change the catalyst conformation and have a resulting impact on the sense of induction of the imine substrate reduction.

3.8 Heterocyclic Secondary Phosphine Oxides

The Speed group has recently published work on the synthesis and reactivity of moisture-stable secondary phosphine oxides precatalysts (SPOs).[43] Previous diazaphospholenes have hydrolyzed to SPOs incidentally due to their high moisture

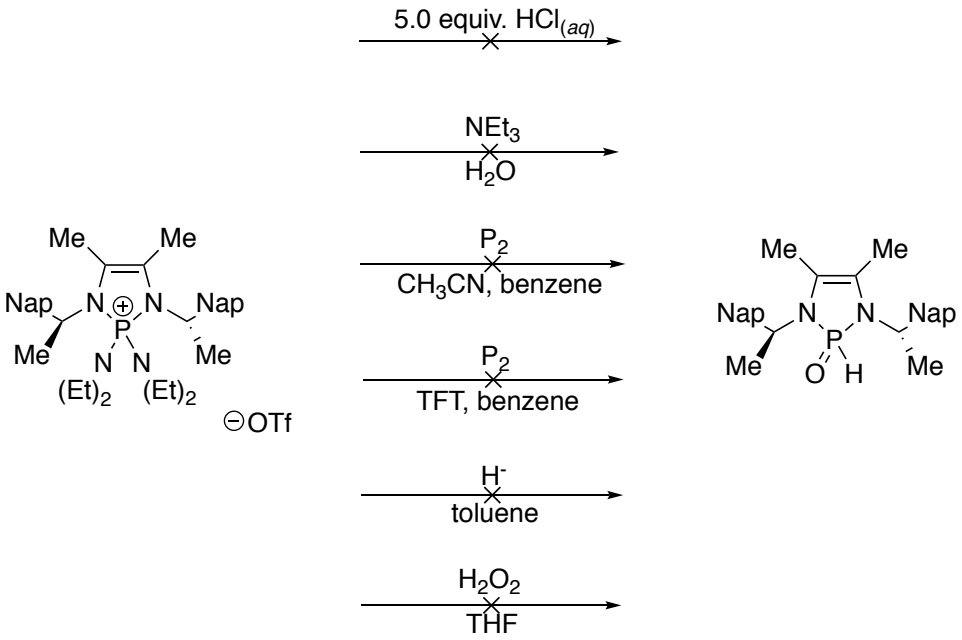
sensitivity, however it was observed that this change occurred more slowly in the presence of HB(pin). These air stable SPOs are formed directly from diazaphospholene bromides and provide an interesting development in the continued effort to increase the accessibility of these catalysts for synthetic uses. This work successfully went about the same transformation that the more sensitive catalysts previously developed within the group were also able facilitate. Notably, SPO **3-2** had high selectivity for the substrate previously investigated in this work. SPOs are yet another potential area of investigation for my work. The hypothesis that steric demand about the phosphorus centre plays a pivotal role in selectivity of my catalysts, substantially changing the coordination environment about the phosphorus centre may give insight into catalyst conformation. Additionally, the straightforward synthesis may allow for previously inaccessible NHP precatalysts. The target for this area was to use my current best catalyst with respect to selectivity and try to transform it into the SPO derivative.



Scheme 56. Substrates reduced by achiral **SPO 3-1** and chiral **SPO 3-2** by other members in the Speed group.

Initial thoughts for this process was to treat the precatalyst with an excess of concentrated hydrochloric acid to create either the phosphine oxide or a trichloride species which would then readily be hydrolyzed into the desired SPO or phosphoric acid derivative. This method was markedly unsuccessful as the treatment with such a harsh reagent resulted in no SPO formation. Next, the prototypical route for this transformation, treatment with NEt_3 and water, was investigated with no trace of SPO formation through ^{31}P NMR spectroscopy. Other avenues were immediately investigated, the next route considered being an ongoing project within the group in which a DAP dimer (P_2) may ultimately cleave the amine groups from the phosphorus centre. This technique, however,

was also unsuccessful with resulting complex ^{31}P NMR spectrums. Additional trials were run, one in the presence of blue light which has been shown to promote reactivity and another swapping out the acetonitrile solvent for trifluorotoluene because different solvent polarities may affect reaction outcome. These adjustments resulted in a complicated ^{31}P NMR spectrum and there was no indication of SPO formation of the desired complex. This next route investigated was treatment with a "superhydride" (sodium triethylborohydride) also used for other projects within the group. This test would hypothetically result in the DAP hydride, which could then likely be transformed into the desired SPO. This method, however, was again unsuccessful in generating the desired complex. A final reaction to generate the desired SPO was treatment of the **XY-2.4** with H_2O_2 in DCM to promote solubility. This test, like all the other trials preceding it, was unsuccessful. Although these initial tests did not give the wanted results, it does demonstrate the strong air and moisture stability of this novel compound which could be useful in other areas such as chiral phase transfer catalysis.



Scheme 57. Oxidation attempts of **XY-2.4**.

This compound, although the prioritized target of these efforts, is likely more challenging to transform due to the increased steric demand about the phosphorus centre making it less accessible than other synthesized NHPs. The potentially less challenging methyl analogue, **XY-2,3**, was next to be explored as it would ultimately result in the same product. In summary, this species was treated with all the same reagents unsuccessfully: HCl, P_2, NEt_3/H_2O and H_2O_2. New routes were also investigated, such as an attempt incorporating CsF as well as an attempt using LiH, however both efforts were fruitless and starting material was maintained. Treatment with sat. LiOH had the most appealing results through ^{31}P NMR with potential SPO conversion, but is yet to be confirmed through other characterization methods and will not be reported in this work.

3.9. Summary

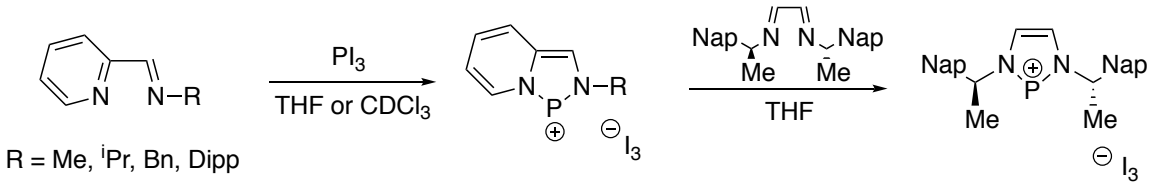
I believe this work to have contributed to the broadening of DAP reductive chemistry. I was able to synthesize novel chiral P(V) complexes using a new and unique

route to chiral phosphenium cations, and subsequently test their reactivity. This synthetic route eliminates previously necessary isolation steps for the intermediate phosphenium ions, providing a simple method to access previously unexplored NHPs. In terms of reactivity, the NHPs I have developed do not compete with the best catalysts in the field. To the best of my knowledge, many previously inaccessible NHPs were able to be successfully synthesized and subsequently have their reactivity investigated. I believe the work I have done may lead into further investigations into DAP with substituted backbones and their reactivity. The robust air and moisture sensitivity of my many of my compounds may also lead to other applications, such as phase-transfer catalysis. I believe the appropriate next steps are to take the positive results of some of the complexes designed here and apply them to reductions of other imine substrates. Understanding the relationship between the selectivity of the reductions and the substrates on the phosphorus within the same imine family will be an important development.

Chapter 4. Conclusions and Future Work

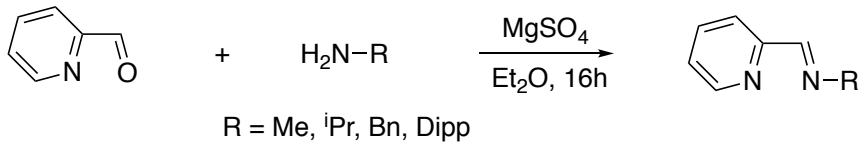
The total synthesis of NCME was not accomplished in chapter 2. Although the desired final product remains elusive, a unique NHP-mediated conjugate reduction step was implemented for the first time in the total synthesis of colchinoid molecules. This step demonstrated the sensitivity of our catalytic system as is seen through the aryl bromide remaining intact throughout the entirety of the synthetic route.

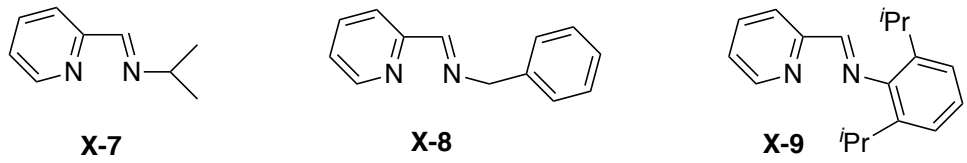
In terms of chapter 3, I demonstrated a new synthesis method towards accessing previously unexplored NHPs. In addition to the route, through this work it became evident that the substituents about the phosphorus in phosphonium catalysts likely play a role in catalyst conformation, as is seen through the changes in selectivity. A method of accessing phosphorus (III) compounds with the substituted backbones still remains inaccessible. One possibility involves use of phosphenium cyclizations where the original ligand could then undergo a reductive elimination from the phosphorus (V) product. A potential strategy is to explore phosphenium cations derived from de-aromatized species. Pyridyl imines can be prepared from pyridine aldehydes, and Gudat has shown these undergo cyclization with PI_3 resulting in dearomatization of the pyridine ring. If these species could undergo cyclization with diimines, we anticipate a retrocyclization could occur, releasing the pyridine imine and a phosphorus (III) compound. The driving force for this reaction would be restoration of the pyridine aromaticity, and alleviation of steric clash in the original P(V) cyclization product.



Scheme 58. General cyclization strategy from de-aromatized species.

Of the 4 imines attempted, 3 were synthesized to a degree that they could be used for further cyclizations. The only compound that was not formed was the methyl pyridyl diimine where the reaction mixture was composed of primarily starting materials. We thought it likely that higher temperatures and reaction times to generate this desired diimine, but these modifications had a negligible impact on product formation. The methods used to justify this synthesis was primarily ^{1}H NMR spectroscopy, paying special attention to the peak associated with the aldehyde hydrogen. Initial cyclization reactions were run in an attempt to generate the desired compounds, however unfortunately, due to time constraints, especially related with limited working hours due to the COVID-19 epidemic, further investigation in the project was limited.





X-7 **X-8** **X-9**

Scheme 59. Attempted synthesis of diimines **X-7** to **X-9**

Should this project be successful, it may allow access to backbone-substituted NHPs with phosphorus in the (III) rather than (V) oxidation state. This would allow a direct comparison of stereoselectivity between existing phosphorus (III) reduction

catalysts without backbone substitution, and new derivatives with backbone substitution. While the phosphorus (V) species had intriguing stereoinduction that should be further investigated, they appear to be less reactive than the Speed group's previously reported phosphorus (III) catalysts in reactions such as conjugate reduction. Accordingly access to backbone-substituted diazaphospholenes in the P(III) oxidation state remains a worthy and un-met goal.

Appendix

Experimental Section

Unless stated otherwise all reactions were carried out in oven dried Schlenk glassware under N_2 atmosphere. Hydroboration reductions were carried out under a nitrogen atmosphere in scintillation vials in a 2001 issue IT Glovebox. ^{1}H, ^{13}C, ^{31}P, and ^{13}F NMR spectra were acquired at 300K on Bruker AV-500 MHz and AV-300 MHz NMR spectrometers. Standard NMR tubes and caps were used. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR spectra are referenced to residual non-deuterated NMR solvent ($CHCl_3$ = 7.26 ppm or CH_3CN = 1.94 ppm). ^{13}C NMR spectra are referenced to the central $CDCl_3$ peak (77.16 ppm) or CD_3CN peak (1.32 ppm). Mass spectrometric data were acquired by Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University). Crystal structure obtained from Dr. Katherine Robertson at St. Mary's University. High Performance Liquid Chromatography (HPLC) data was acquired on a Varian Prostar instrument, equipped with detection at λ = 254 nm, using either Astec Cellulose DMP, or Chiralpak ADH columns. A 99:1 hexanes/isopropanol solvent mixture was used as the eluent, with a flow rate of 0.5 mL/min.

Solvents

Hexanes were used as received and distilled before use for HPLC

Ethyl Acetate was used as received

Pentane for reactions was deoxygenated and dried by sparging with nitrogen gas, followed by passage through a double-column solvent purification system from mBraun Inc. The solvents were stored over activated 3 Å molecular sieves in the glovebox.

Diethyl ether for purification (ACS grade) was purchased from Fisher and used as received. Diethyl ether for reactions was distilled from a purple solution of benzophenone/sodium ketyl and stored over activated 3 Å molecular sieves in the glovebox.

Tetrahydrofuran (Anhydrous >99%, inhibitor free) was purchased in a Sure/SealTM container from Aldrich and used as received for lithiation reactions. For reaction screenings in the glovebox, the bottle was brought into the glovebox through the antechamber with nitrogen purge, the septum was removed from the bottle, and activated 3 Å molecular sieves were added for long term storage.

Dichloromethane (ACS grade) was purchased from Fisher and distilled from calcium hydride immediately before for reactions

Deuterochloroform (Cambridge Isotopes) was stored over activated 3 Å molecular sieves but otherwise was used as received.

Reagents

Glyoxal solution was purchased from Aldrich as 40 wt. % in water solution.

Triethylamine was purchased from Aldrich in a Sure/Seal® bottle and used as received.

Trimethylsilyl triflate was purchased from Oakwood Chemical and distilled at 10 torr before use.

Pinacolborane was purchased from Oakwood Chemical stored at ambient temperature in the glovebox, and otherwise used as received. Distillation of pinacolborane gave no improvement for enantioselecivity.

Phosphorus (III) Bromide was purchased as the 99% purity grade from Aldrich in a Sure/Seal® bottle and used as received.

Phosphorus (III) Chloride was purchased as the 99% purity grade from Aldrich in a Sure/Seal® bottle and used as received.

Crystallographic Solution and Refinement Details (provided by Dr. Katherine

Robertson).

The crystal chosen was attached to the tip of a MicroLoop with Paratone-N oil. Measurements were made on a Bruker D8 VENTURE diffractometer equipped with a PHOTON III CMOS detector using monochromated Mo Kα radiation (λ = 0.71073 Å) from an Incoatec micro-focus sealed tube at 150 K [1]. The initial orientation and unit cell were indexed using a least-squares analysis of the reflections collected from a 180° phi-scan, 2 seconds per frame and 1° per frame. For data collection, a strategy was calculated to maximize data completeness and multiplicity, in a reasonable amount of time, and then implemented using the Bruker Apex 3 software suite [1]. The crystal to detector distance was set to 4.0 cm. Cell refinement and data reduction were performed with the Bruker SAINT [2] software, which corrects for beam inhomogeneity, possible crystal decay, Lorentz and polarisation effects. A multi-scan absorption correction was applied (SADABS [3]). The structure was solved using SHELXT-2014 [4] and was refined using a full-matrix least-squares method on F^2 with SHELXL-2018 [4]. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to carbon were included at geometrically idealized positions and were not refined. The isotropic thermal parameters of these hydrogen atoms were fixed at $1.2U_{eq}$ of the parent carbon atom or $1.5U_{eq}$ for methyl hydrogens. Data was collected to maximum θ angle of 39.94° (0.55 Å resolution). However, the high angle data was very noisy above 0.70 Å. The data was cut off at this value during refinement using a SHEL instruction. The triflate anion was found to be disordered. It was split into two parts which were made equivalent using a SAME command to apply appropriate restraints. In addition the thermal parameters of all of the disordered oxygen and fluorine atoms were separately restrained to have similar thermal

parameters. Separate RIGU commands were also placed over each part of the disordered triflate anion to restrain the 1,2 and 1,3 distances. The occupancies of the two parts were refined to total one giving a final ratio of 77.3(3) and 22.6 % for the two parts. The molecule was found to crystallize in the chiral space group $P2_12_12_1$, with R chirality at C5 and C17. The absolute structure of the molecule was reliably determined. Using the program Platon [5] the refined structure was calculated to have a Flack parameter of 0.03(3), a Parsons parameter of 0.03(3) and a Hooft parameter of 0.01(3). These values agree with the Parson's value calculated by the program SHELXL, 0.029(29) from 3673 selected quotients.

Table S 1. Crystal data and structure refinement details

Identification code	AS019	
Empirical formula	$C_{37}H_{48}F_3N_4O_3PS$	
Formula weight	716.82	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.362(4) Å	✔= 90°
	b = 17.434(6) Å	= 90°
	c = 22.377(8) Å	= 90°
Volume	3652(2) $Å^3$	
Z	4	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.189 mm^{-1}	
F(000)	1520	
Crystal size	0.226 x 0.030 x 0.025 mm^3	
Theta range for data collection	2.163 to 30.508°	
Index ranges	-13<=h<=13, -24<=k<=24, -30<=l<=31	
Reflections collected	150229	
Independent reflections	11161 [R(int) = 0.1137]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7364 and 0.6717	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11161 / 161 / 523	

Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.1008
R indices (all data)	R1 = 0.0598, wR2 = 0.1094
Absolute structure parameter	0.03(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.305 and -0.287 e.$Å^{-3}$

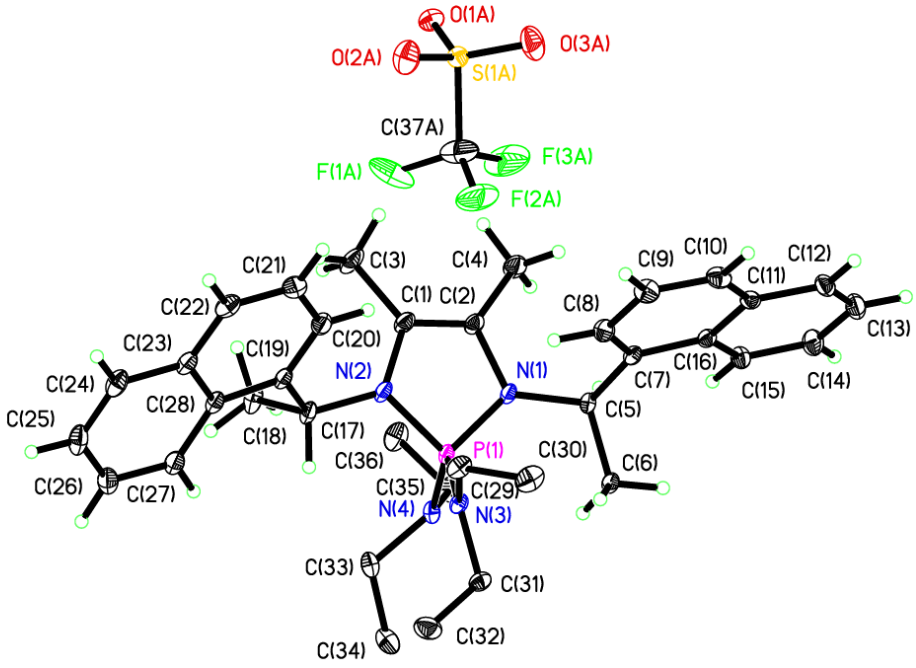


Figure E1. Structural diagram of compound **XY-2,4**. Thermal ellipsoids have been drawn at the 30% probability level to lessen overlap. Hydrogen atoms on the ethyl groups are removed for clarity. Only one part of the disordered anion is shown

General Procedure for the Synthesis of Diimines

The appropriate enantiopure amine (1-2 equiv.) was dissolved in a flask containing a stirbar with dichloromethane (5-15 mL) followed by the addition of Na_2SO_4 (4 equiv.), and either glyoxal solution (40 wt. % in H_2O, 1 equiv.) or diacetyl (1 equiv.) and a drop of formic acid under open air. The solution stirred for 2-4h as required, the reaction may be monitored by obtaining ^1H NMR spectrum of aliquots (no work-up of the aliquot was conducted, the withdrawn sample was directly diluted with $CDCl_3$ and measured). The

Na_2SO_4 was filtered and washed with dichloromethane and the filtrate was concentrated to give the desired diimine which was used without further purification.

General Procedure for the Synthesis of of Phosphenium Triflate Reagents

A solution of the appropriate amine (1-2 equiv.) in DCM (5-25 mL) was added to a 250 mL Schlenk flask and cooled (as low as –40°C). To this flask PCl_3 (1 equiv.) in DCM (5-10 mL) was added, rinsing with further solvent to complete the transfer and the solution was stirred for 2h. Trimethylsilyl triflate (1.1 equiv.) was added to the solution over 2 min and was stirred for 1h. The DCM was removed in vacuo, the tube is backfilled with nitrogen, sealed and brought into the glovebox for one of two following situations:

Situation 1: The resulting oil or foam is triturated with diethyl ether and a metal spatula to form a powder in some cases. The suspension is transferred to a Schlenk filter, filtered, and washed with further diethyl ether. The compound was then held under vacuum until a constant weight was achieved.

Situation 2: If the compound is an ionic liquid and has not been able to be turned into a solid in previous attempts it may be used directly in cyclization reactions without isolation.

General Procedure for the Synthesis of N-Heterocyclic Phosphenium Triflates

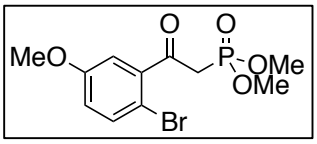
The desired diimine (1 equiv.) and phosphenium triflate reagent (1 equiv.) were sequentially added to THF (2-4 mL) in a 1 dram vial, rinsing with further THF to complete the transfer. The solution is left at ambient temperature for 2-18h and followed by one of two situations:

Situation 1: In some cases, the THF is removed in vacuo and the vial is backfilled with

nitrogen, NMR spectra were obtained. In specific cases the reaction mixture was left within the glovebox partially covered to allow for gentle evaporation of solvent on a small-scale. Solid may form during this time and the excess solvent is decanted. NMR spectra of the solid were obtained.

Situation 2: The compound may be directly used for imine reduction without isolation.

Compound 2-1:



Dimethyl methyl phosphonate (1.30 mL, 12.0 mmol, 4 equiv.) was added to a 100 mL Schlenk flask containing THF (30 mL) and cooled to –78°C. n-Butyllithium (5.04 mL, 12.6 mmol, 4.2 equiv.) was added to the flask over 1 minute. After 15 minutes, 2-bromo-5-methoxybenzoate (0.48 mL, 3.00 mmol, 1.0 equiv.) was added to the flask and stirred for an additional 45 minutes. The resulting solution was poured into an Erlenmeyer flask containing $NH_4Cl_{(aq)}$ and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude brown liquid was purified by column chromatography (1:1EtOAc/hex) resulting in compound **2-1** as a light brown oil (0.86 g, 2.55 mmol, 85% yield).

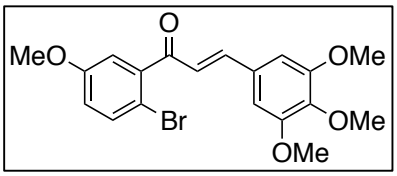
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J*= 9.0Hz, 1H), 7.12 (d, *J*= 3.0Hz, 1H), 6.91 (dd, *J*= 9.0, 3.0 Hz 1H), 3.85 (s, 3H), 3.82 (d, *J*= 11.5Hz, 6H), 3.80 (s, 3H), 3.74 (d, *J*= 22.5Hz**,** 2H), 1.62 (s, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 158.9, 141.4, 134.4, 118.7, 114.7, 109.1, 55.7, 53.1 (d, *J*=25Hz), 41.0 (d, *J*= 14Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ 21.8

HRMS(ESI): calculated $(M+Na)^+$ $[C_{11}H_{14}BrNaO_5P]$: 358.9660; found: 358.9657

Compound 2-2: Cesium carbonate (1.06 g, 3.30 mmol, 2.2 equiv.) was added to a 100 mL



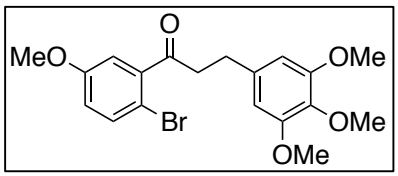
Schlenk flask containing 20 mL of THF. To this flask, Compound **2-1** (0.50 g, 1.50 mmol, 1 equiv.) was added. In another 250 mL Schlenk flask 3,4,5-trimethoxybenzaldehyde was dissolved in 20 mL of THF. The contents of these two flasks were combined in the Schlenk flask and stirred overnight at 40°C. The resulting solution was quenched with $NH_4Cl_{(aq)}$ and the aqueous layer was extracted with DCM (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude yellow solid was purified by column chromatography (1:2 EtOAc/hex) resulting in compound **2-2** as a yellow solid (0.61 g, 0.98 mmol, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J*= 9.0Hz, 1H), 7.36 (d, 1H), 7.01 (d, *J*= 16Hz, 1H), 6.98 (d, *J*= 3.0Hz, 1H), 6.93 (dd, *J*= 9.0, 3.0Hz, 1H), 6.82 (s, 2H), 3.92 (s, 9H), 3.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 158.9, 153.5, 146.9, 142.0, 140.9, 134.2, 129.8, 125.4, 117.5, 114.3, 109.7, 105.9, 61.0, 56.2, 55.7.

HRMS(ESI): calculated $(M+Na)^+$ $[C_{19}H_{19}Br_1Na_1O_5]$ 429.0308; found 429.0297.

Compound 2-3: Compound **2-2** (0.44 g, 1.01 mmol, 1 equiv.) was added to a 1 dram glass



vial containing approximately 1 mL of THF. To this vial precatalyst **1-19** (0.32 g, 0.10 mmol, 0.1 equiv.) was added followed by HB(pin) (0.21 g, 1.58 mmol, 1.5 equiv.) and left to sit undisturbed overnight. The reaction mixture was made acidic using $NH_4Cl_{(aq)}$ and confirmed using pH indicator strips followed by being made basic with

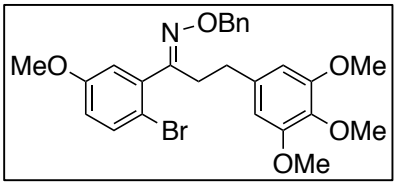
$NaHCO_{3(aq)}$ using the same indicator strips. The aqueous layer was extracted with DCM (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude yellow solid was purified by column chromatography (1:1 EtOAc/hex) resulting in compound **2-3** as a yellow solid. (0.35 g 0.87 mmol, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J*= 9.0Hz, 1H), 6.87 (dd, *J*= 9.0, 3.0Hz 1H), 6.83 (d, *J*= 3.0Hz, 1H), 6.47 (s, 2H), 3.87 (s, 6H), 3.82 (s, 3H), 3.81 (s, 3H), 3.27 (t, *J*= 7.0Hz, 2H), 3.03 (t, *J*= 7.0Hz, 2H), 1.27 (s, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 158.7, 153.2, 142.5, 136.5, 134.4, 117.6, 113.9, 108.7, 105.4, 60.8, 56.1, 55.6, 44.28, 30.6, 24.9.

HRMS(ESI): calculated $(M+Na)^+$ $[C_{19}H_{21}Br_1Na_1O_5]$: 431.0465; found 431.0465

Compound 2-4: Compound **2-3** (0.22 g, 0.55 mmol, 1 equiv.) was added to a 100 mL round-bottomed flask containing 20 mL of deionized water and a drop of THF. To this flask O-benzylhydroxylamine hydrochloride (0.10 g, 0.66 mmol, 1.2 equiv.) and sodium acetate (0.06 g, 0.66 mmol, 1.2 equiv.) were added and stirred overnight at 40°C. The resulting solution was extracted with DCM (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude yellow solid was purified by column chromatography (1:1 EtOAc/hex) resulting in compound **2-4** as a brown oil (0.18g, 0.34 mmol, 62% yield).

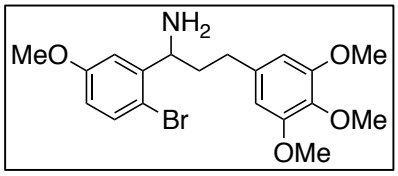


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.30 (m, 5H), 6.79 (dd, *J*= 9.0, 3.0Hz, 1H), 6.56 (dd, *J*= 11.5, 3.0Hz, 1H), 6.32 (s, 2H), 3.83 (s, 3H), 3.78 (s, 6H), 3.75 (s, 3H), 3.13 (t, *J*= 7.0Hz, 2H), 2.77 (t, *J*= 7.0Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 158.7, 156.9, 153.1, 133.6, 128.4, 128.1, 127.6, 116.3, 116.1, 115.4, 114.3, 105.3, 76.3, 75.9, 60.8, 56.1, 55.4, 36.4, 31.7, 31.4 (I should see 21 signals)

HRMS(ESI): calculated $(M+Na)^+$ $[C_{26}H_{28}Br_1N_1Na_1O_5]$: 536.1043; found 536.1033.

Compound 2-5: Compound **2-4** (0.56 g, 1.10 mmol, 1 equiv.) was added to a 100 mL



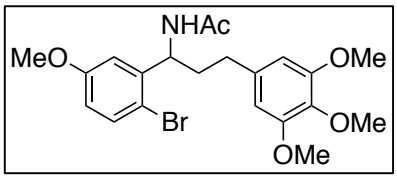
round-bottomed flask containing 20 mL of THF. To this flask borane-dimethyl sulfide (0.40 mL, 4.52 mmol, 4 equiv.) was added and stirred overnight at room temperature. The reaction mixture was made acidic using $NH_4Cl_{(aq)}$ and confirmed using pH indicator strips followed by being made basic with $NaHCO_{3(aq)}$ using the same indicator strips. The resulting solution was extracted with DCM (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude yellow solid was purified with column chromatography (100% EtOAc) resulting in compound **2-5** as a brown oil (0.14 g, 0.34 mmol, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J*= 9.0Hz, 1H), 7.09 (d, *J*= 3.0Hz, 1H), 6.71 (dd, *J*= 9.0, 3.0Hz, 1H), 6.44 (s, 2H), 4.36 (t, *J*= 7.0Hz, 1H), 3.87 (s, 6H), 3.86 (s, 3H), 3.84 (s, 3H), 2.70 (m, 2H), 2.01 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 153.1, 146.1, 137.5, 136.2, 133.4, 114.0, 113.8, 113.1, 105.4, 60.9, 56.1, 55.5, 54.2, 39.4, 33.2

HRMS(ESI): calculated $(M+Na)^+$ $[C_{26}H_{25}Br_1N_1Na_1O_4]$: 410.0961; found 410.0964

Compound 2-6: Compound **2-5** (0.14 g, 0.34 mmol, 1 equiv.) was added to a round-



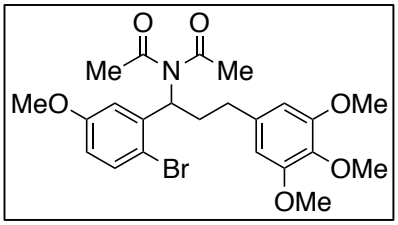
bottomed flask containing 15 mL of DCM. To this flask triethylamine (0.07 mL, 0.51 mmol 1.5 equiv.) and acetyl chloride (0.03 mL, 0.38 mmol, 1.1 equiv.) were added and stirred overnight at room temperature. The resulting solution was poured into an Erlenmeyer flask containing $NaHCO_{3(aq)}$ and the aqueous layer extracted with DCM (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4 then concentrated. The crude yellow liquid was purified with column chromatography (1:1 EtOAc/hex) resulting in compound **2-6** as a white solid (0.09 g, 0.20 mmol 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J*= 9.0Hz, 1H), 6.84 (d, *J*= 3.0Hz 1H), 6.73 (dd, *J*= 9.0, 3.0Hz 1H), 5.89 (d, *J*= 7.5Hz, 1H), 5.31 (t, *J*= 7.0Hz, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H), 2.65 (m, 2H), 2.19 (m, 2H), 2.00 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 154.7, 153.2, 145.0, 141.7, 140.2, 134.2, 115.0, 113.6, 105.4, 101.0, 60.8, 56.1, 55.5, 53.7, 36.5, 33.1, 23.4

HRMS(ESI): calculated $(M+Na)^+$ $[C_{21}H_{26}Br_1N_1Na_1O_5]$: 474.0887; found 474.0887

Compound 2-7: Compound **2-**7 was obtained in some cases following the same procedure

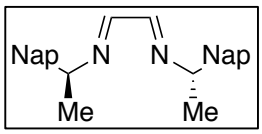


outlined for compound **2-6.**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, 1H), 6.76 (d, 1H), 6.73 (dd, 1H), 5.89 (d, 1H), 4.95 (t, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H), 2.65 (td, 2H), 2.53 (td, 2H), 2.25 (s, 6H)

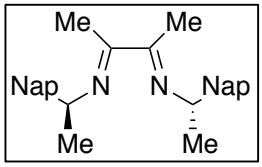
HRMS(ESI): calculated $(M+Na)^+$ $[C_{23}H_{28}Br_1N_1Na_1O_6]$: 516.0992; found 516.0993.

Compound X-1



(*R*)-1-Naphthylethylamine (4.69 mL, 29.2 mmol, 2 equiv.) was dissolved in DCM (50 mL) under N_2 and stirred with Na_2SO_4. To this solution glyoxal (1.67 mL, 14.6 mmol, 1 equiv.) and formic acid (0.05 mL, 1.46 mmol, 0.1 equiv.) were added and stirred for 16 h. The mixture was filtered over celite, and the solvent was removed *in vacuo*. The solid obtained was washed with EtOH (25 mL) and product was collected by suction filtration as a white solid (3.80 g, 72%). Spectral data are in accordance with literature values.[39] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.18 (s, 2H) 7.85 - 7.80 (m, 7H), 7.53-7.46 (m, 7H), 4.73 (q, *J*= 6.7Hz, 2H), 1.71 (d, *J*=6.7 Hz, 6H).

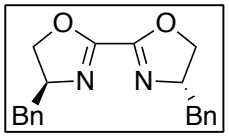
Compound X-2



R)-1-Naphthylethylamine (8.25 mL, 50.6 mmol, 2.2 equiv.) was dissolved in DCM (50 mL) under N_2 and stirred. To this solution diacetyl (1.96 mL, 23.2 mmol, 1 equiv.) and formic acid (2 drops) were added and stirred for 16 h. The mixture was filtered over celite, and the solvent was removed *in vacuo*. The solid obtained was washed with EtOH (25 mL) and product was collected by suction filtration as a white solid (6.27 g, 16 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (2, *J*= 8.5Hz, 2H), 7.89 (d, *J*= 8.5Hz, 2H), 7.79 (d, *J*= 7Hz, 2H), 7.75 (d, *J*= 8Hz, 2H), 7.45-7.55 (m, 6H), 5.78 (q, *J*= 6.5Hz, 2H), 2.31 (s, 6H), 1.69 (d, *J*= 6.5Hz, 6H)

Compound X-4

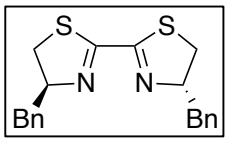


L-phenylalaninol (10.0 g, 66.0 mmol, 2 equiv.) was dissolved in 60 mL of toluene in a 250 mL round-bottomed flask. To this flask ethyl oxalate

(4.48 mL, 33.0 mmol, 1 equiv.) was added and refluxed overnight. After cooling, thionyl chloride (7.18 mL, 99.0 mmol, 3 equiv.) was added and heated to 90°C for 4h. The reaction mixture was cooled to room temperature and poured into an Erlenmeyer flask containing a cold solution of 20% $KOH_{(aq)}$ and the aqueous layer was extracted with DCM (2 x 45 mL). The mixture was washed with brine and the organic layers were combined and dried over Na_2SO_4. The crude white precipitate was purified by column chromatography (1:1 EtOAc/hex) resulting in compound **X-4** as a white solid (6.81 g, 21.0 mmol, 64% yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 - 7.24 (m, 10H), 4.68-4.63 (m, 2H), 4.41 (t, *J*= 9Hz, 2H), 4.21 (t, *J*= 9Hz, 2H), 3.31 (dd, *J*= 13.5, 2.5Hz, 2H), 2.75 (dd, *J*= 18, 9.5Hz, 2H)

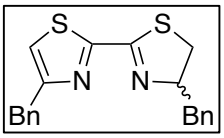
Compound X-5



L-phenylalaninol (2.52 g, 16.6 mmol, 2 equiv.) was dissolved in 45 mL of toluene in a 250 mL round-bottomed flask. To this flask ethanedithioamide (1.00g, 8.32 mmol, 1 equiv.) was added and refluxed overnight. After cooling, thionyl chloride (1.81 mL, 24.97 mmol, 3 equiv.) was added and heated to 90°C for up to 48 hours. The mixture was cooled and washed with brine and the aqueous layer was extracted using DCM (2 x 30mL). The organic layers were combined and dried over Na_2SO_4. The crude white precipitate was purified with column chromatography (1:1 EtOAc/hex) resulting in compound **X-5** as a white solid (0.28 g, 0.80 mmol, 10% yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 10H), 4.90 (m, 2H), 3.35 - 3.32 (m, 4H), 3.18 (dd, *J*= 11.5, 6.5Hz, 2H), 2.86 (dd, *J*= 10, 9.5Hz, 2H)

Compound X-6 Following the same procedure outlined for compound **X-5**, compound **X-**



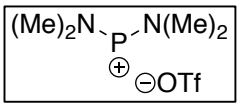
6 was obtained in some cases.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 - 7.29 (m, 10H), 6.93 (s, 1H), 4.98 (m, 2H), 4.24 (3, 3H), 3.42- 3.28 (m, 4H), 3.23 (dd, *J*= 12, 11.5Hz, 2H), 2.89 (dd, 12.5, 9Hz, 2H), 2.21 (s, 1H), 1.57 (s, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 129.4, 129.1, 128.7, 128.6, 126.6, 126.5, 118.3, 78.5, 77.3, 40.1, 37.9, 37.1.

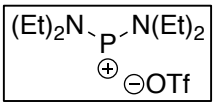
HRMS(ESI): calculated $(M+Na)^+$ $[C_{20}H_{18}N_2Na_1S_2]$: 373.0804; found 373.0813

Compound Y-3: a solution of dimethylamine (2.00 mL, 30.0 mmol, 4 equiv.) was added



to a Schlenk flask containing 20 mL of hexanes and cooled to 0°C. To this PCl_3 (2.62 mL, 15.0 mmol, 1 equiv.) was added and warmed to room temperature for 1h. The reaction mixture was then refluxed for 48 h. The resulting solvent was removed *in vacuo*. The phosphenium chloride and added to a Schlenk flask containing 20 mL of DCM and cooled to 0°C. To this flask TMSOTf (2.85 mL, 15.8 mmol, 1.05 equiv.) was added and stirred for 1h. The resulting product was concentrated using Schlenk techniques and collected as a viscous yellow liquid.**^{1}H NMR (500MHz, $CDCl_3$):** δ 3.24 (d, *J*= 10.5Hz, 12H) **^{31}P NMR (202MHz, $CDCl_3$)** δ 259.1

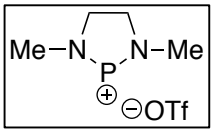
Compound Y-4: a solution of diethylamine (2.00 mL, 19.3 mmol, 4 equiv.) was added to



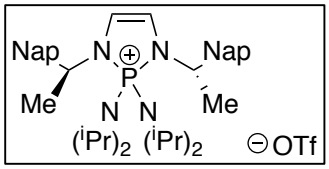
a Schlenk Flask containing 20 mL of hexanes and cooled to 0°C. To this PCl_3 (1.72 mL, 9.85 mmol, 1 equiv.) was added and warmed to room temperature for 1h. The reaction mixture was then refluxed for 48h. The resulting solvent was removied *in vacuo*. The phosphenium chloride was added to a Schlenk flask containing

20 mL of DCM and cooled to 0°C. To this flask TMSOTf (1.87 mL, 10.34 mmol, 1.05 equiv.) was added and stirred for 1h. The resulting product was concentrated using Schlenk techniques and collected as a viscous yellow liquid. **^{1}H NMR (500MHz, $CDCl_3$):** δ 1.36 (q, *J*= 7Hz, 8H),1.24 (m, 12H). **^{31}P NMR (202MHz, $CDCl_3$)** δ 231.6

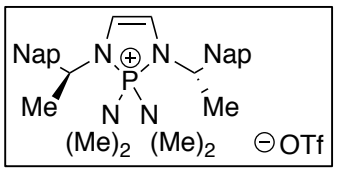
Compound Y-5: N,N'-diethylethylenediamine (2.00 mL, 18.5 mmol, 1 equiv.) was added



to a Schlenk flask containing 20 mL of DCM and cooled to -15°C. To this flask a solution of PCl_3 (1.64 mL, 9.25 mmol, 1 equiv.) in DCM (15 mL) was added and warmed to room temperature for 1h. To this solution NEt_3 (5.36 mL, 38.5 mmol, 2.1 equiv.) was added and stirred for 1h. The resulting solvent was removed *in vacuo* and the phosphenium chloride was added to a Schlenk flask containing 20 mL of DCM and cooled to -15°C. To this flask TMSOTf (1.79 mL, 9.9 mmol, 1.05 equiv.) was added and stirred for 1h. The resulting product was concentrated using Schlenk techniques and collected as a viscous yellow liquid. **^{1}H NMR (500MHz, $CDCl_3$):** δ 3.65 (t, *J*= 5Hz, 4H), 3.17 (dd, J = 12, 4Hz, 6H) **^{31}P NMR (202MHz, $CDCl_3$)** δ 252.3

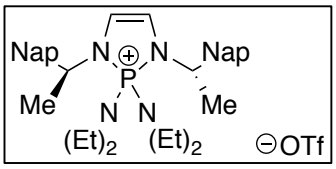


Compound XY-1.2: The general synthesis for NHP triflates afforded compound **XY-1.2** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500Mhz, $CDCl_3$):** δ 8.12-7.23 (m, 14H), 7.03 (d, 21.5Hz, 2H), 3.81 (m, 4H), 1.93 (d, *J*= 6.5Hz, 6H), 4.18 (m, 2H), δ 1.15 (dd, *J*= 21.5, 6.5Hz, 24H). **^{31}P NMR (202MHz, $CDCl_3$)** δ 41.8

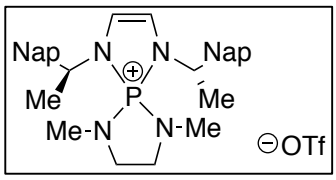


Compound XY-1.3: The general synthesis for NHP triflates afforded compound **XY-1.3** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500MHz, $CDCl_3$):** δ

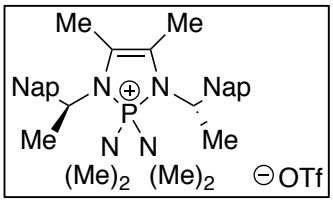
8.16- 7.30 (m, 14H), 6.84 (d, *J*= 24Hz, 2H), 5.52 (m, 2H), 2.17 (d, *J*= 11.5Hz, 12H), 1.90 (d, *J*= 7Hz, 6H). **^{31}P NMR (202Hz, $CDCl_3$)** δ 39.2



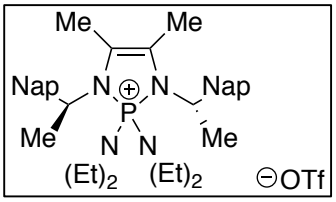
Compound XY-1.4: The general synthesis for NHP triflates afforded compound **XY-1,4** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500Mhz, $CDCl_3$):** δ 7.91 - 7.52 (m, 14H), (d, *J*= 18Hz, 2H), 5.47 (m, 2H), 2.80 (m, 8H), 1.89 (d, *J*= 7Hz, 6H), 0.76 (t, *J*= 7Hz, 12H). **^{31}P NMR (202Hz, $CDCl_3$)** δ 38.8



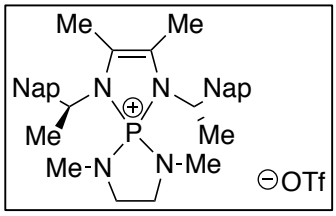
Compound XY-1.5: The general synthesis for NHP triflates afforded compound **XY-1.5** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500MHz, $CDCl_3$):** δ 8.06 - 7.51 (m, 14H), 6.65 (d, *J*= 23Hz, 2H), 5.56 (q, *J*= 7.5Hz, 2H), 2.45 (m, 2H), 2,12 (m, 2H), 1.85 (d, J= 7Hz, 6H), 1.53 (d, *J*=11Hz, 6H) **^{31}P NMR (202MHz, $CDCl_3$)** δ 31.5



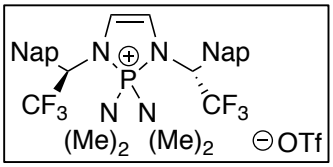
Compound XY-2.3: The general synthesis for NHP triflates afforded compound **XY-2.3** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.06 – 7.47 (m, 14H), 5.63 (q, J= 7Hz, 2H), 2.14 (d, J= 12Hz, 12H), 2.34 (s, 6H), 1.92 (d, J= 7Hz, 6H). **^{31}P NMR (202MHz, $CDCl_3$)** δ 38.6



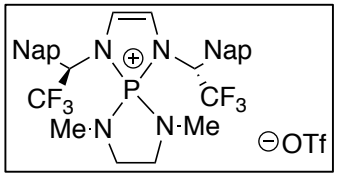
Compound XY-2.4: The general synthesis for NHP triflates afforded compound **XY-2.4** as a crystalline orange solid (58% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.05 - 7.29 (m, 14H), 5.56 (m, 2H), 3.09 (m, 8H), 2.24 (s, 6H), 2.00 (s, 6H), 0.94 (s, 12H) **^{31}P NMR (202MHz, $CDCl_3$)** δ 41.5



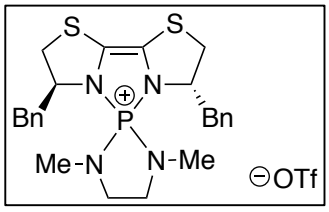
Compound XY-2.5: The general synthesis for NHP triflates afforded compound **XY-2.5** as a yellow liquid with residual starting material (without attempted crystallization). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 2.46 (s, 6H), 2.04 (s, 6H), 1.70 (d, *J*= 7Hz, 6H), **^{31}P NMR (X202MHz, $CDCl_3$)** δ 249.1



Compound XY-3.3: The general synthesis for NHP triflates afforded compound **XY-3.3** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.31- 7.48 (m, 14H), 7.20 (s, 2H), 6.86 (s, 2H), 2.10 (d, *J*= 11Hz, 12H). **^{31}P NMR (202MHz, $CDCl_3$)** 40.3



Compound XY-3.5: The general synthesis for NHP triflates afforded compound **XY-3.5** as a yellow liquid (without attempted crystallization). **^{1}H NMR (500 MHz, $CDCl_3$):** 8.17-7.48 (m, 14H), 6.92 (d, *J*= 27.5Hz, 2H), 6.16 (m, 2H), 2.85 (m, 2H), 2.67 (m, 2H), 1.46 (d, *J*= 6.5Hz, 6H). **^{31}P NMR (202MHz, $CDCl_3$)** δ 35.1. **^{19}F NMR (470MHz, $CDCl_3$):** -78.2, -68.8



Compound XY-5.5: The general synthesis for NHP triflates afforded compound **XY-5.5** as a yellow liquid with residual starting material (without attempted crystallization). **^{31}P NMR (202MHz, $CDCl_3$):** δ 23.1

NMR Spectra

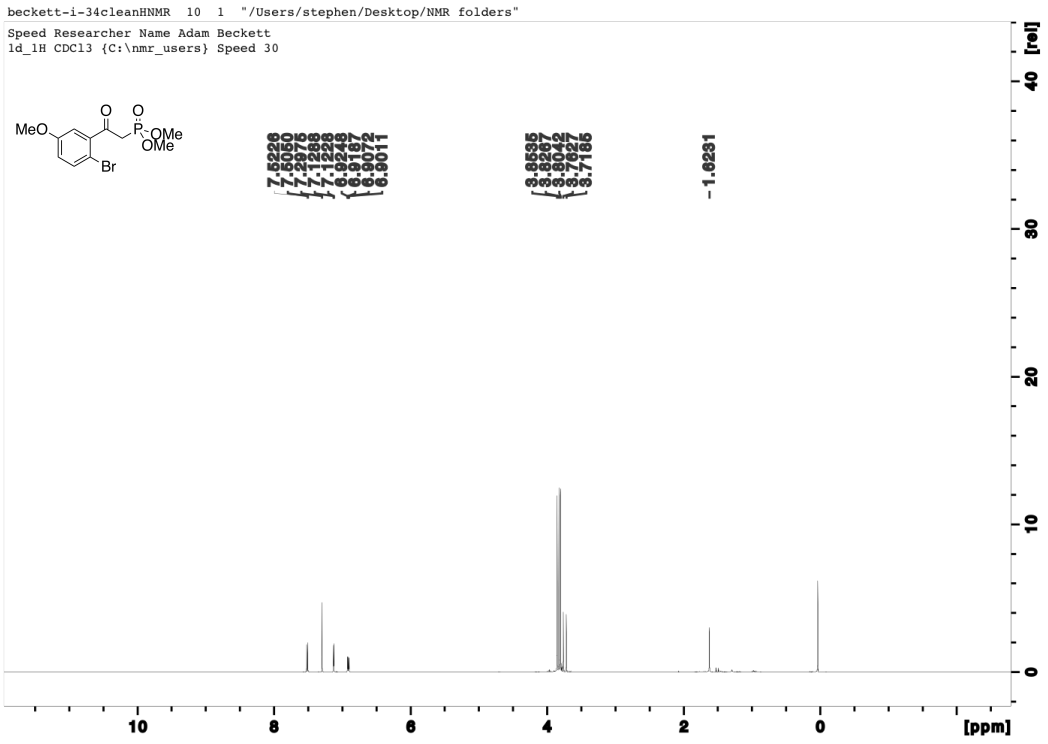


Figure S1. ^{1}H NMR spectrum of **2-1** (500MHz, $CDCl_3$)

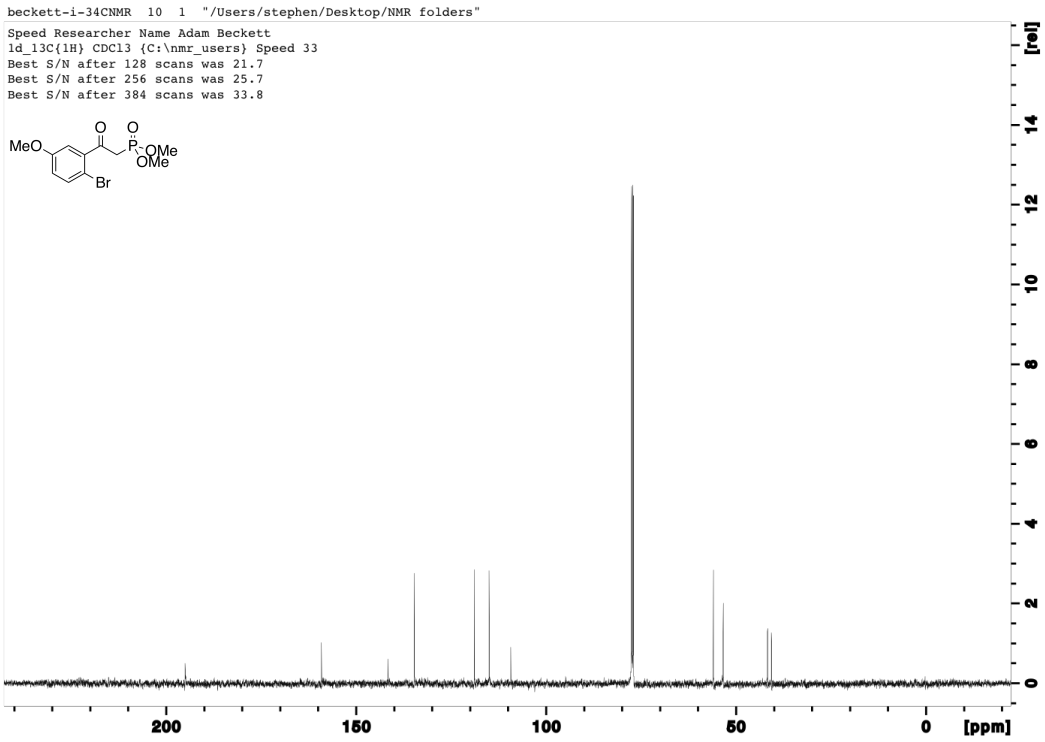


Figure S2. ^{13}C NMR spectrum of **2-1** (500MHz, $CDCl_3$)

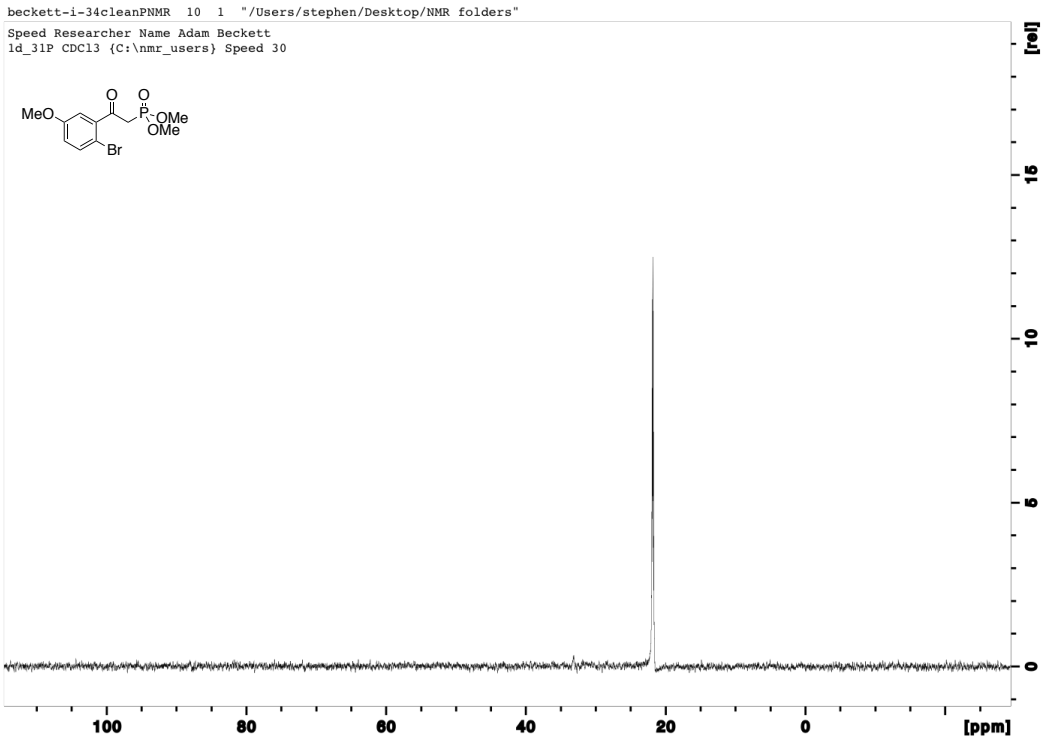


Figure S3. ^{31}P NMR spectrum of **2-1** (202MHz, $CDCl_3$)

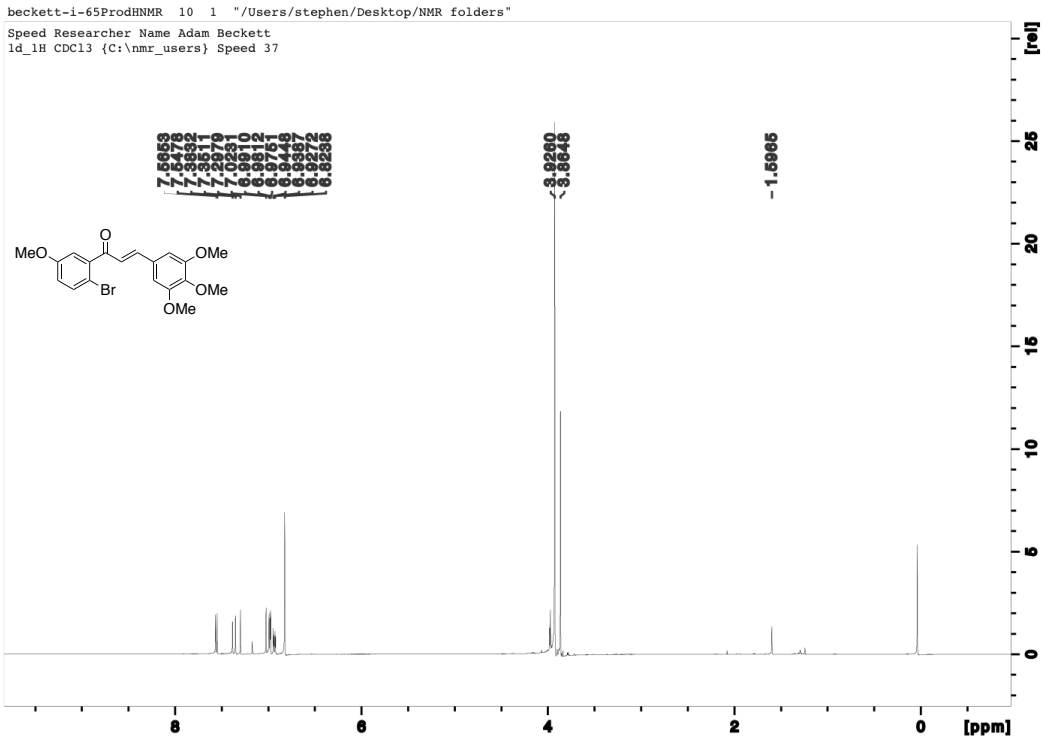


Figure S4. ^{1}H NMR spectrum of **2-2** (500MHz, $CDCl_3$)

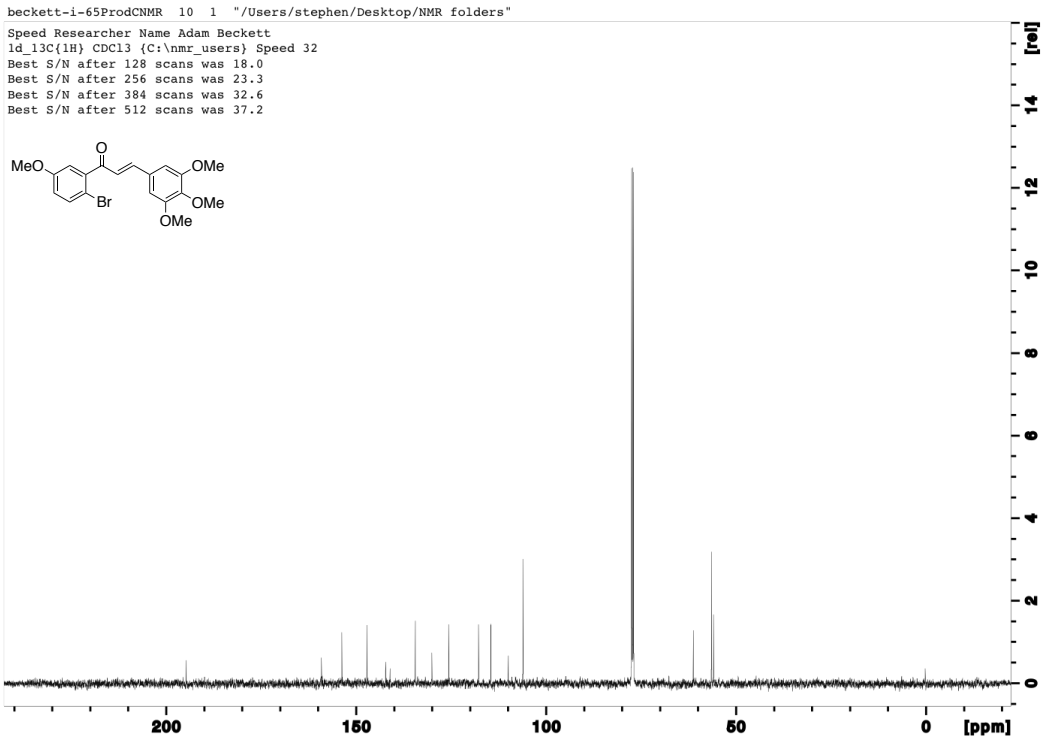


Figure S5. ^{13}C NMR spectrum of **2-2** (500MHz, $CDCl_3$)

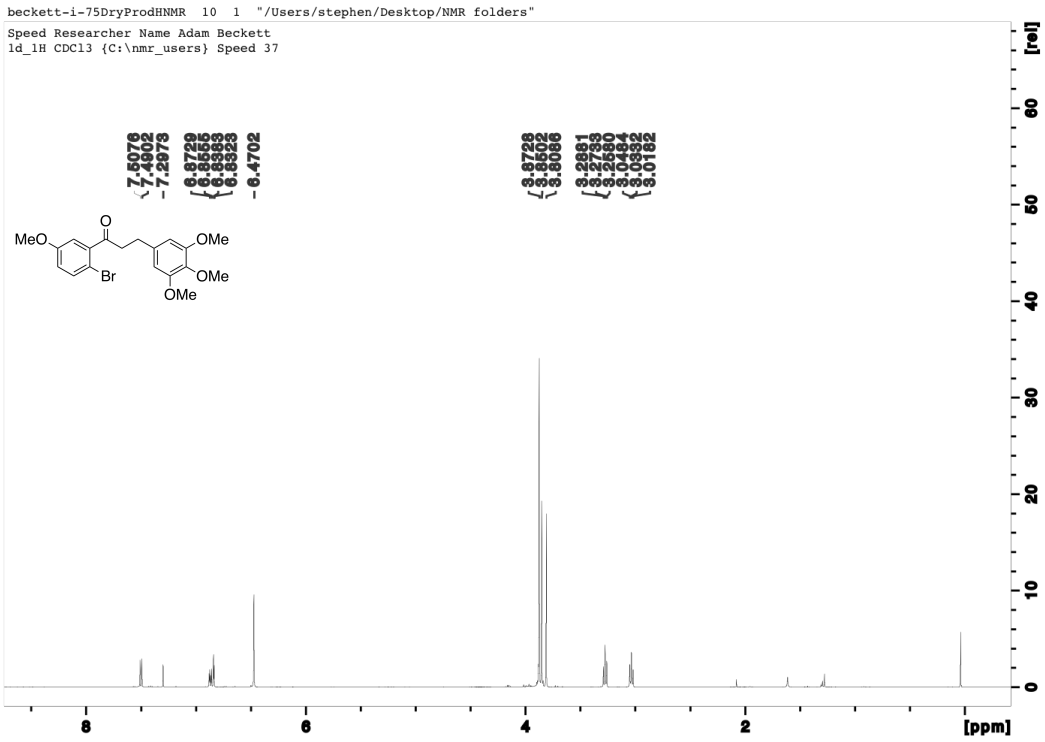


Figure S6. ^{1}H NMR spectrum of **2-3** (500MHz, $CDCl_3$)

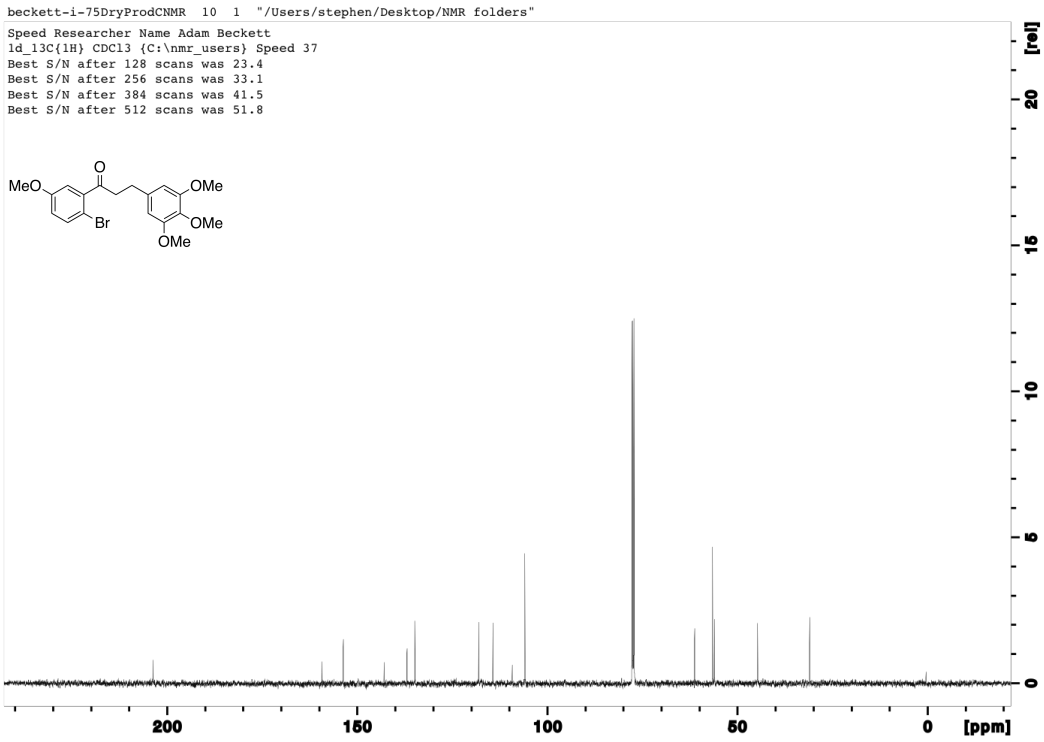


Figure S7. ^{13}C NMR spectrum of **2-3** (500MHz, $CDCl_3$)

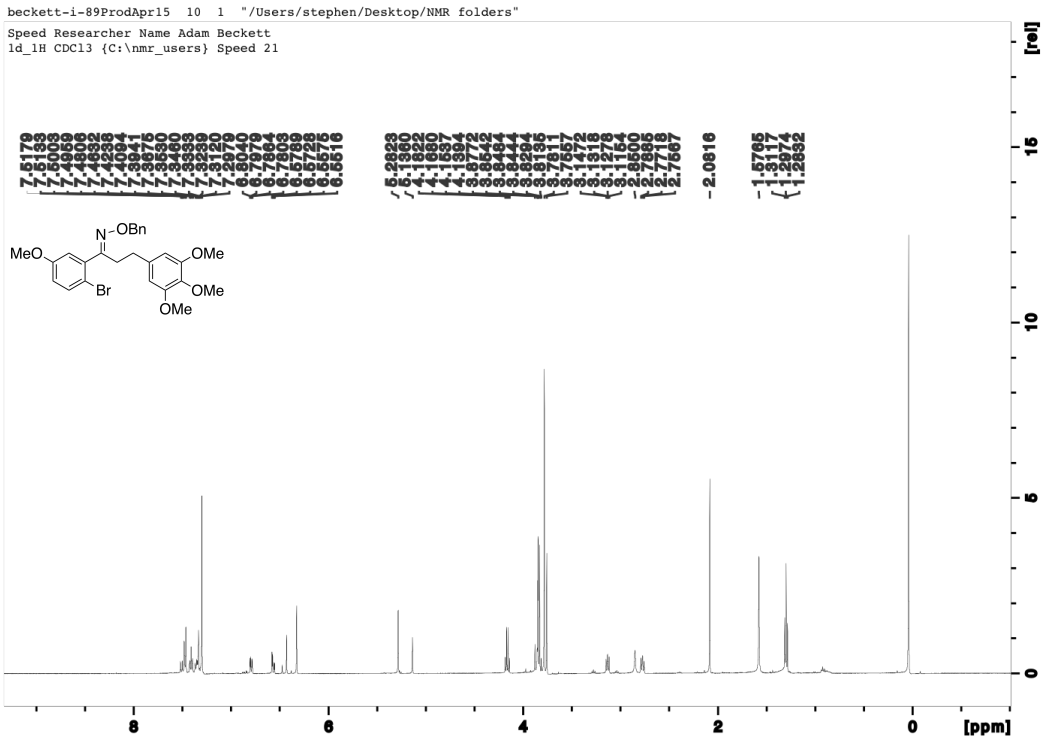


Figure S8. ^{1}H NMR spectrum of **2-4** (500MHz, $CDCl_3$)

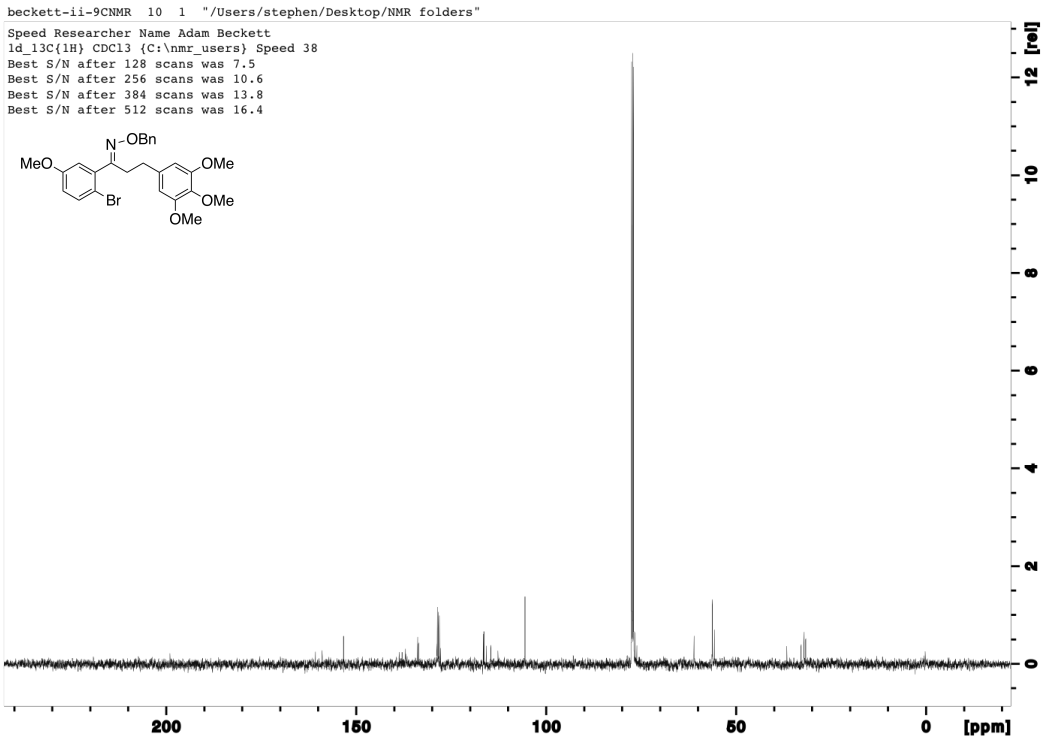


Figure S9. ^{13}C NMR spectrum of **2-4** (500MHz, $CDCl_3$)

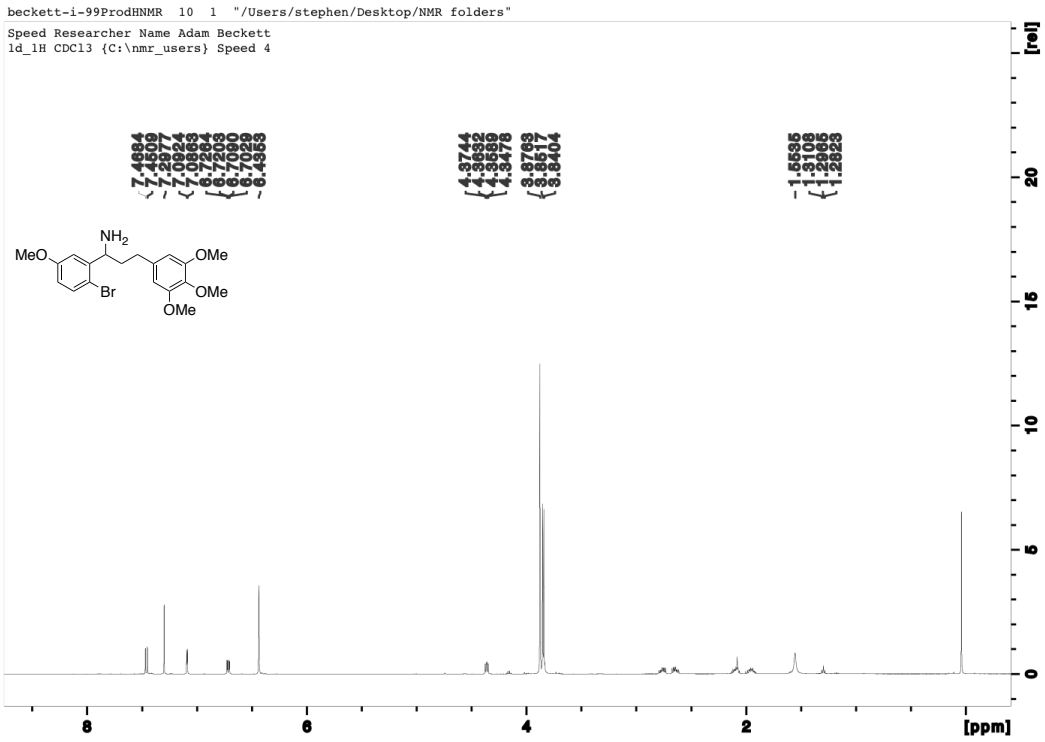


Figure S10. ^{1}H NMR spectrum of **2-5** (500MHz, $CDCl_3$)

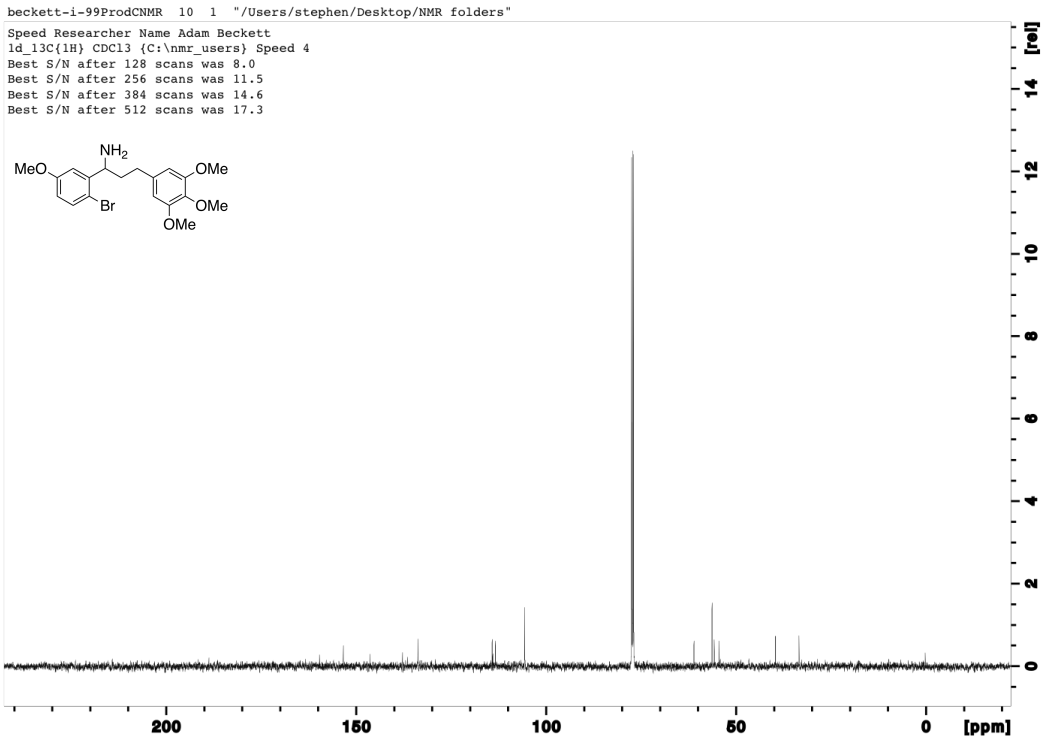


Figure S11. ^{13}C NMR spectrum of **2-5** (500MHz, $CDCl_3$)

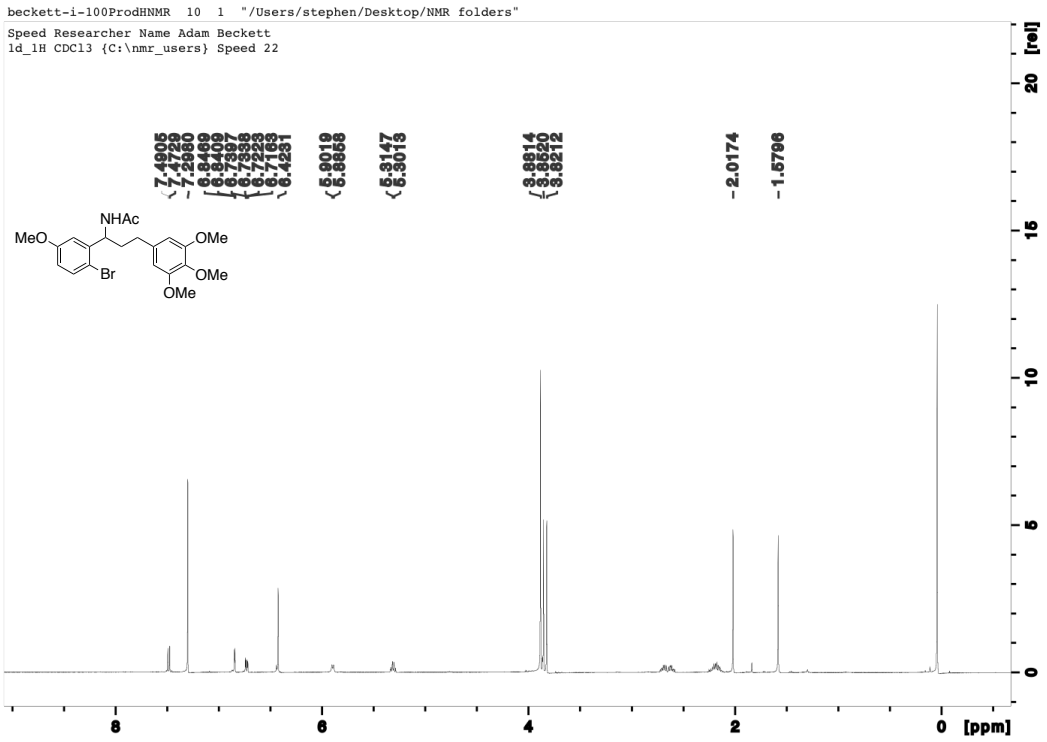


Figure S12. ^{1}H NMR spectrum of **2-6** (500MHz, $CDCl_3$)

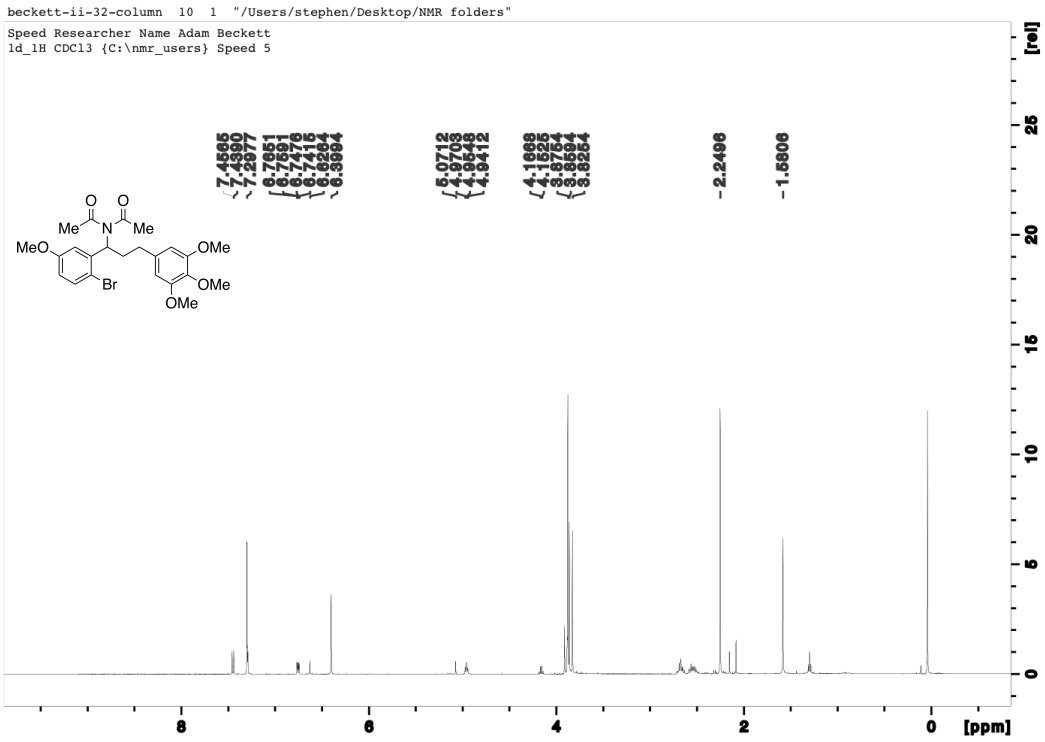


Figure S13. ^{1}H NMR spectrum of **2-7** (500MHz, $CDCl_3$)

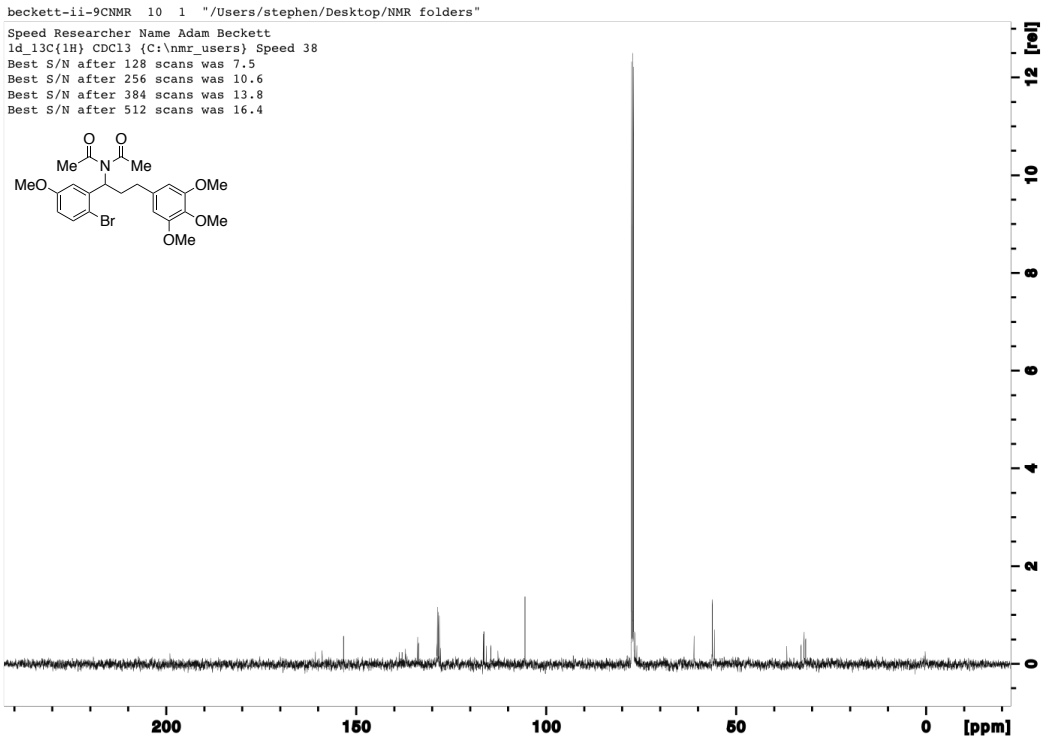


Figure S14. ^{13}C NMR spectrum of **2-7** (500MHz, $CDCl_3$)

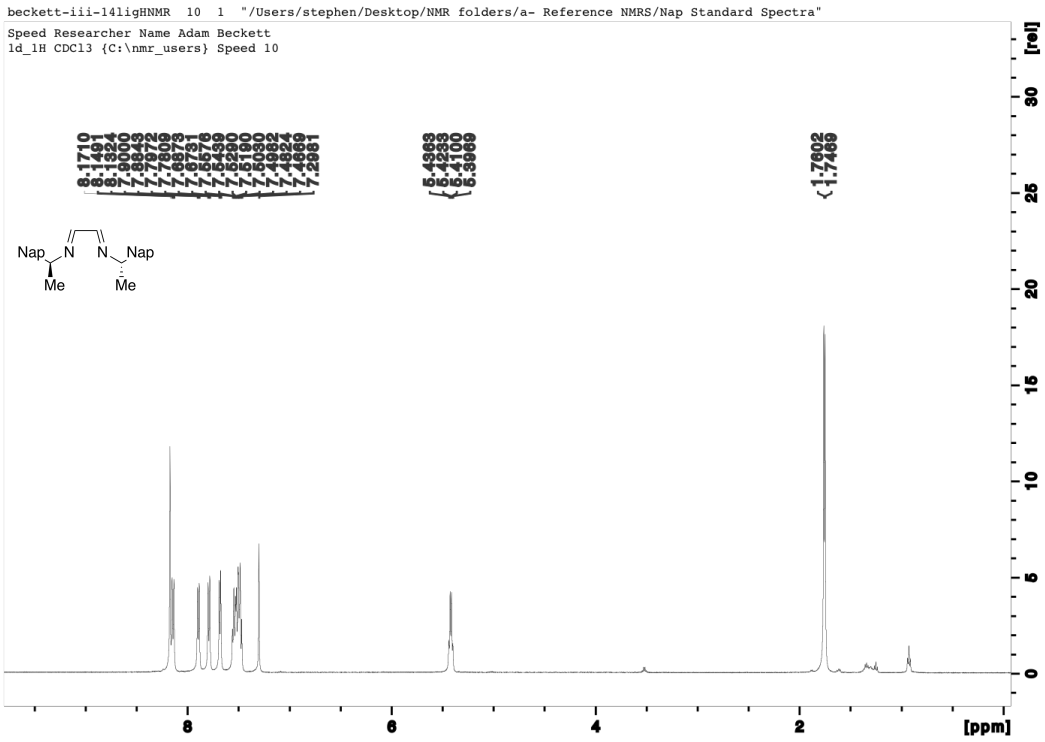


Figure S15. ^{1}H NMR spectrum of **X-1** (500MHz, $CDCl_3$)

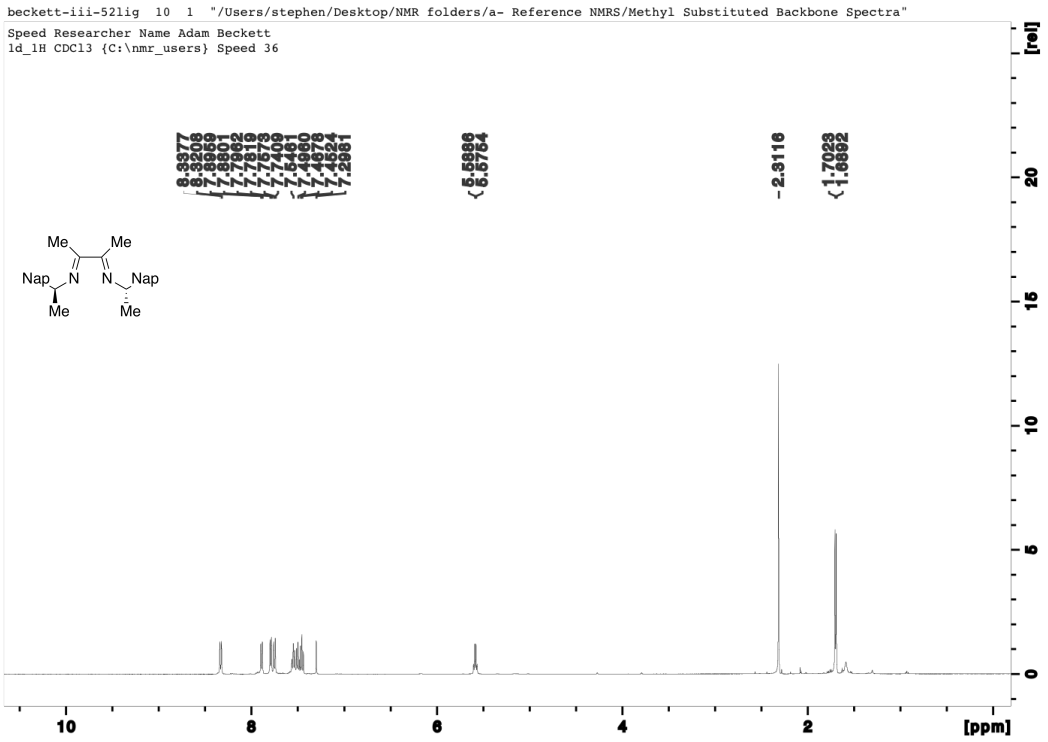


Figure S16. ^{1}H NMR spectrum of **X-2** (500MHz, $CDCl_3$)

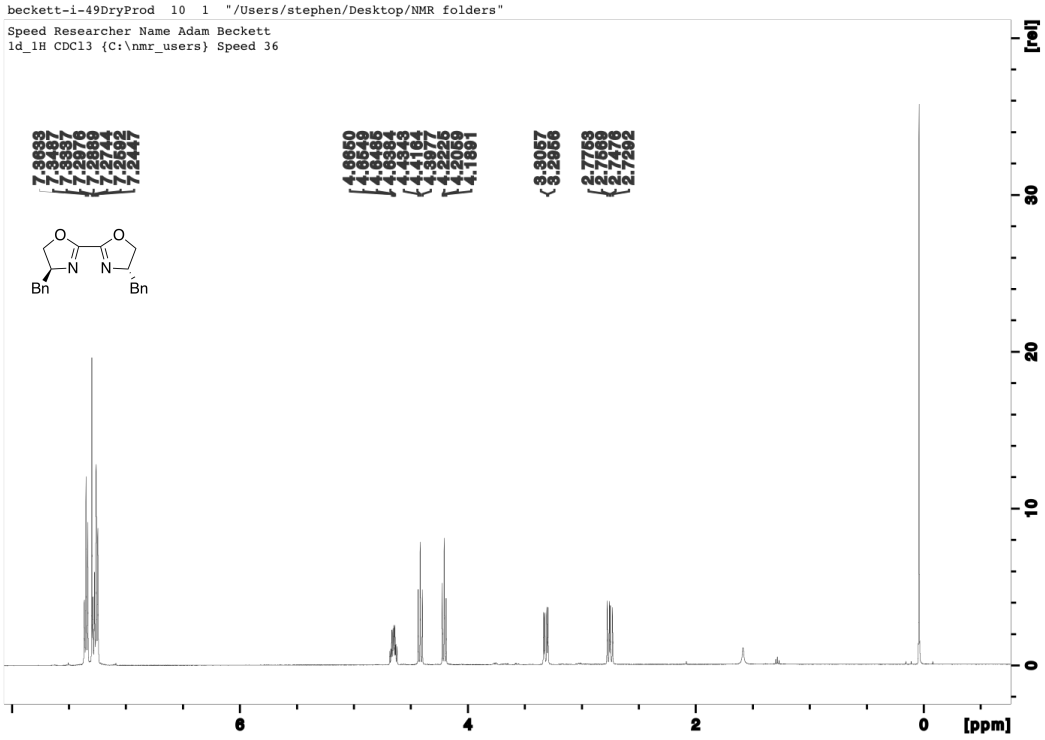


Figure S17. ^{1}H NMR spectrum of **X-4** (500MHz, $CDCl_3$)

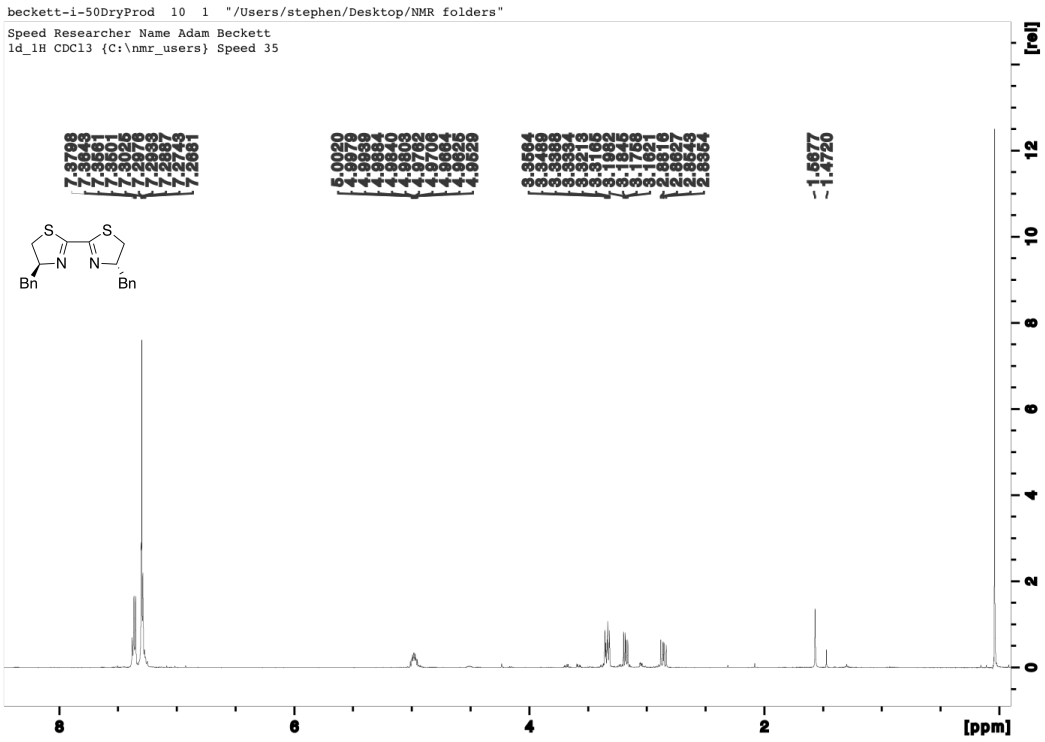


Figure S18. ^{1}H NMR Spectrum of **X-5** (500MHz, $CDCl_3$)

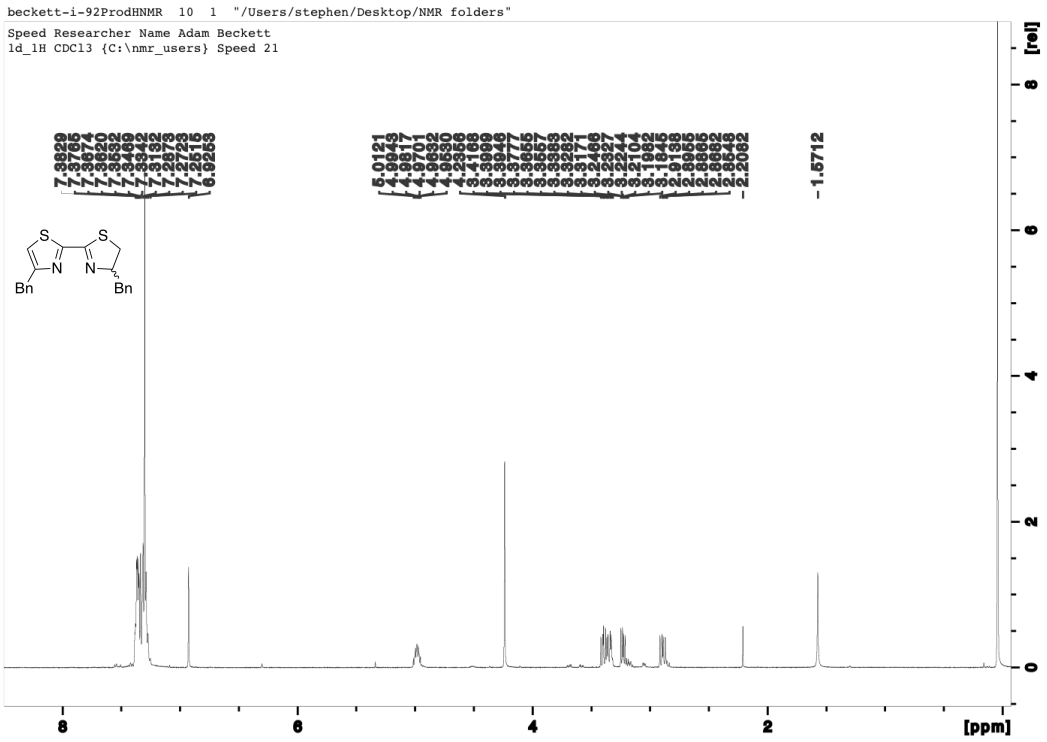


Figure S19. ^{1}H NMR spectrum of **X-6** (500MHz, $CDCl_3$)

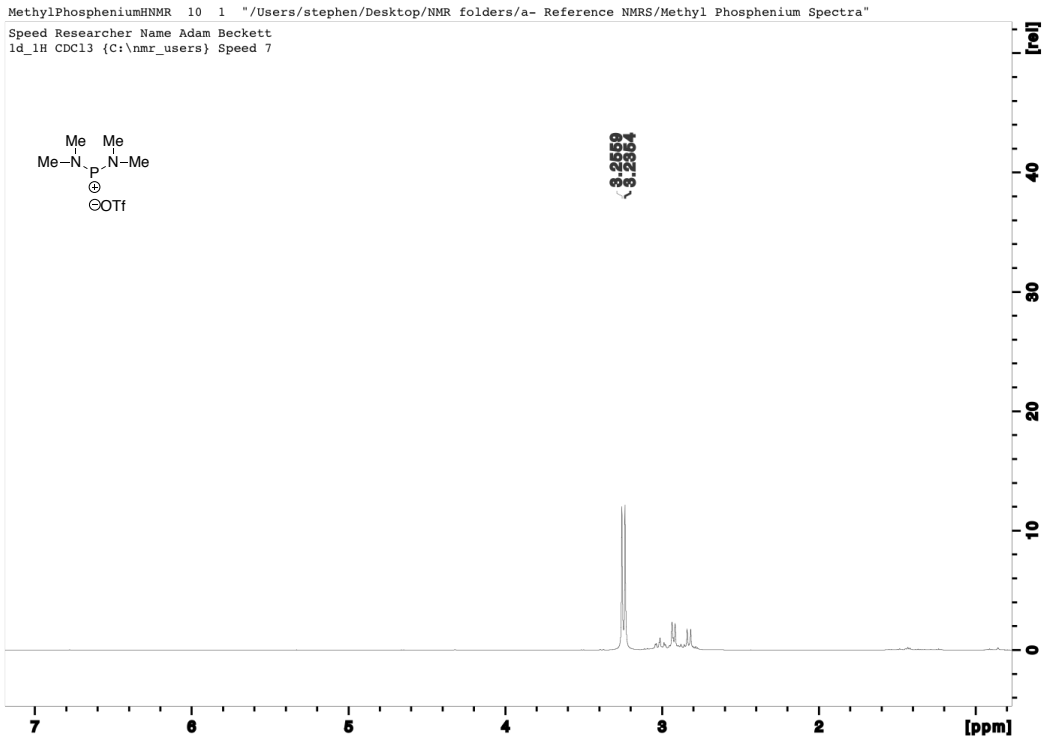


Figure S20. ^{1}H NMR spectrum of **Y-3** (202MHz, $CDCl_3$)

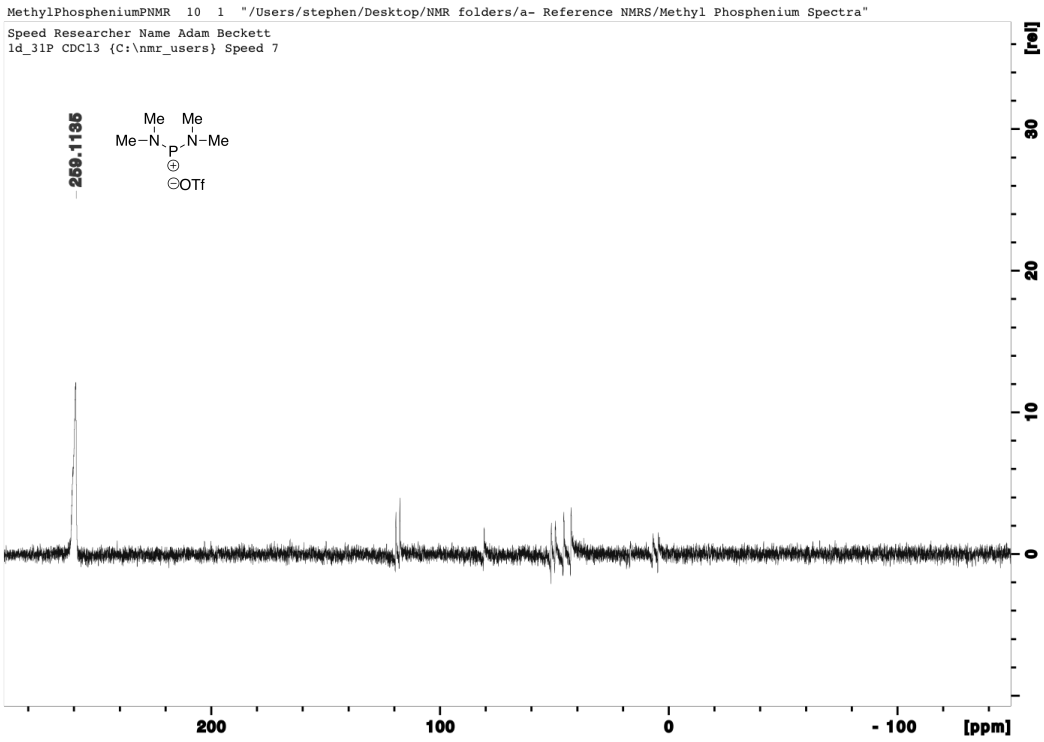


Figure S21. ^{31}P NMR spectrum of **Y-3** (202MHz, $CDCl_3$)

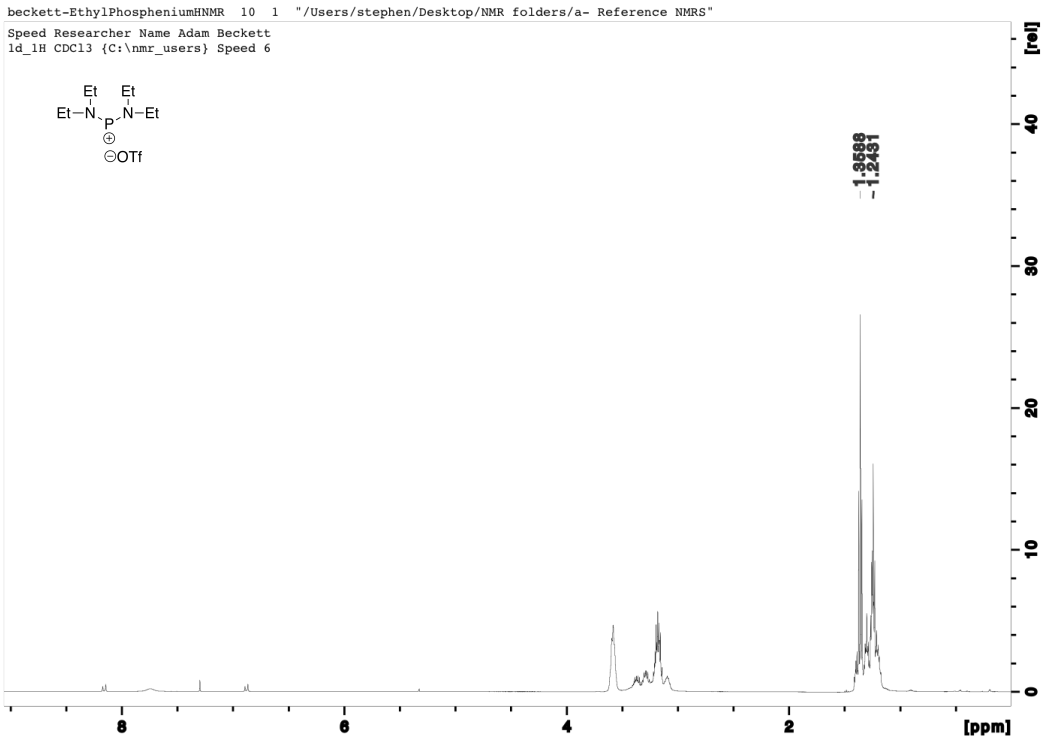


Figure S22. ^{1}H NMR spectrum of **Y-4** (500MHz, $CDCl_3$)

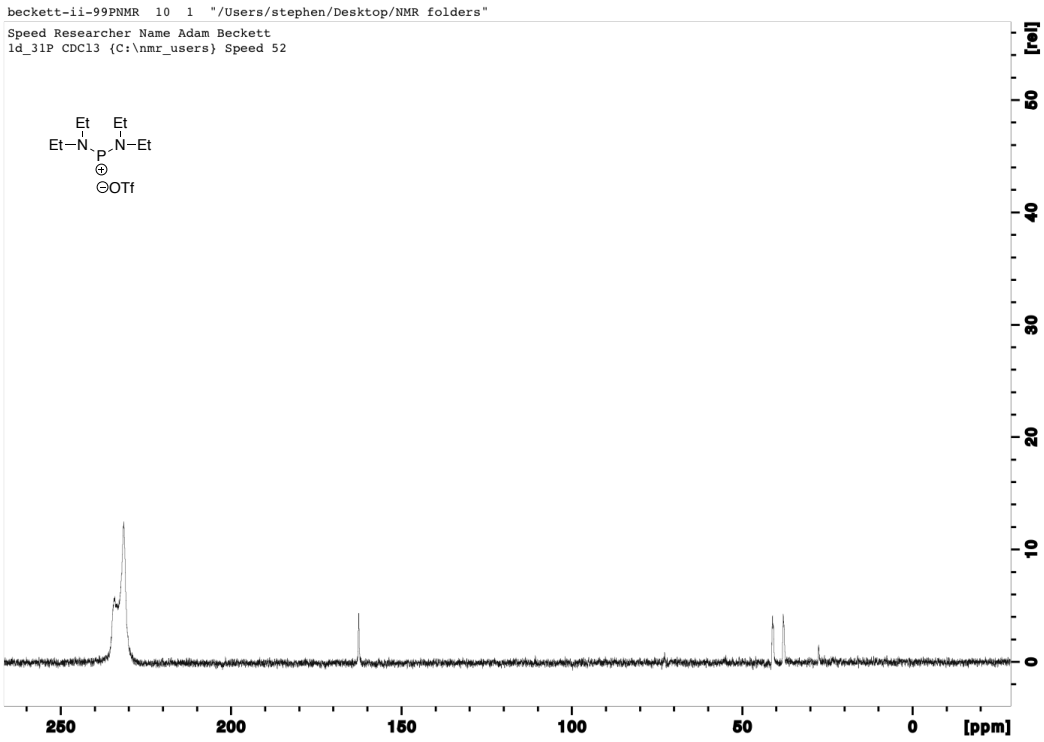


Figure S23. ^{31}P NMR spectrum of **Y-4** (202MHz, $CDCl_3$)

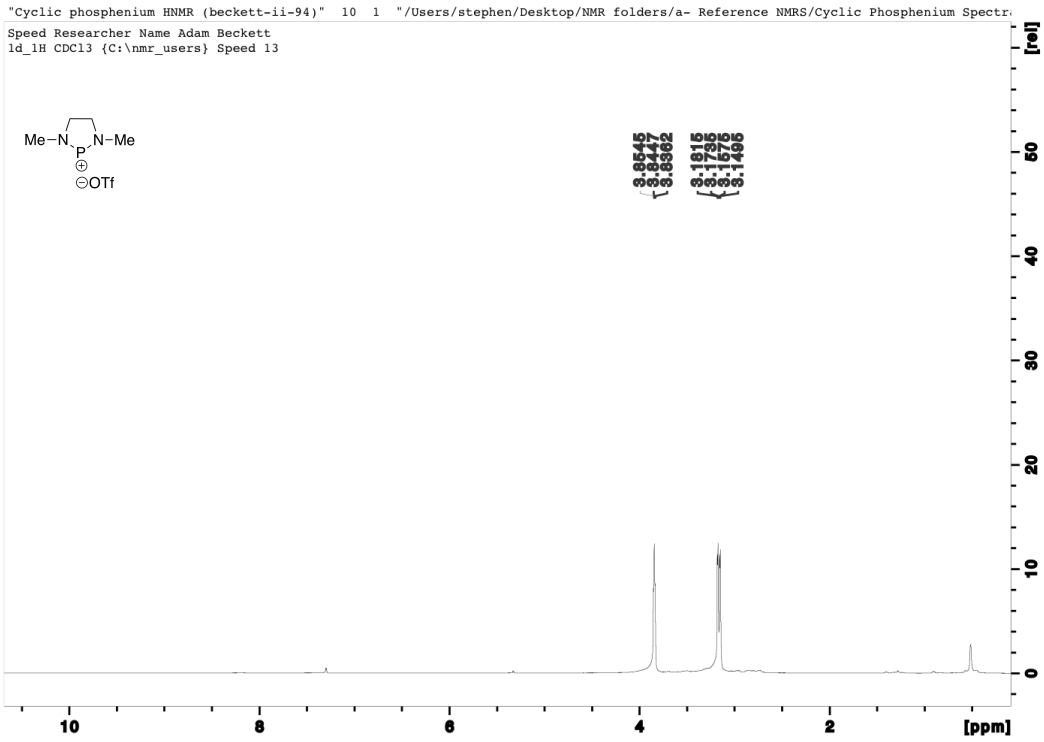


Figure S24. ^{1}H NMR spectrum of **Y-5** (500MHz, $CDCl_3$)

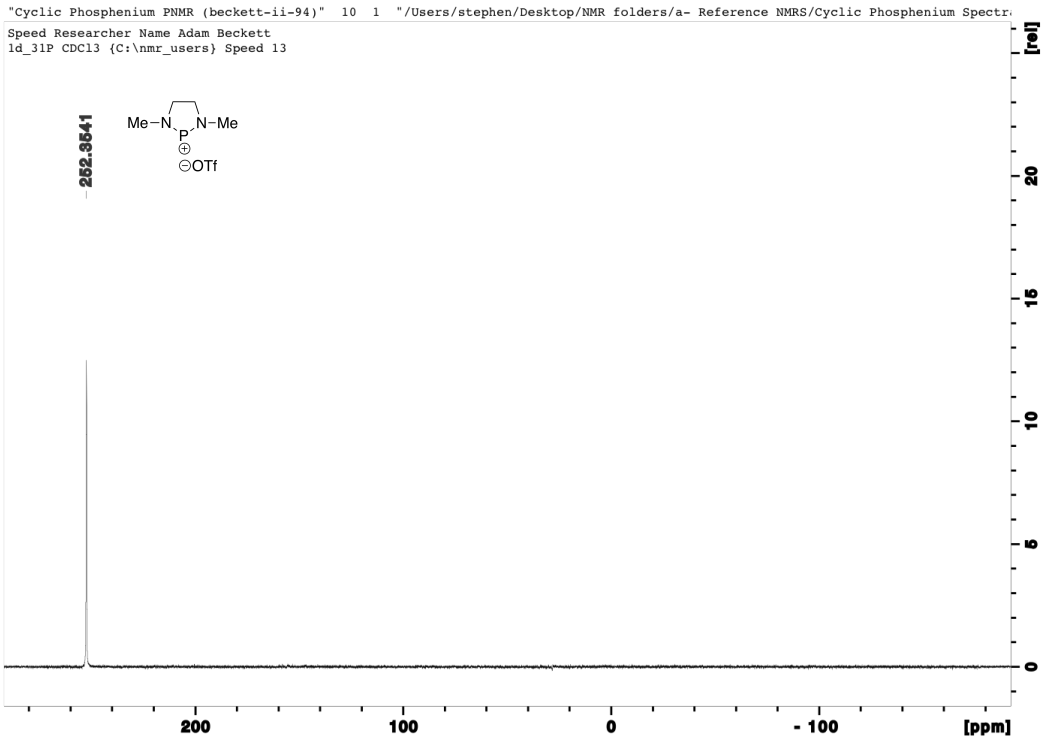


Figure S25. ^{31}P NMR spectrum of **Y-5** (202MHz, $CDCl_3$)

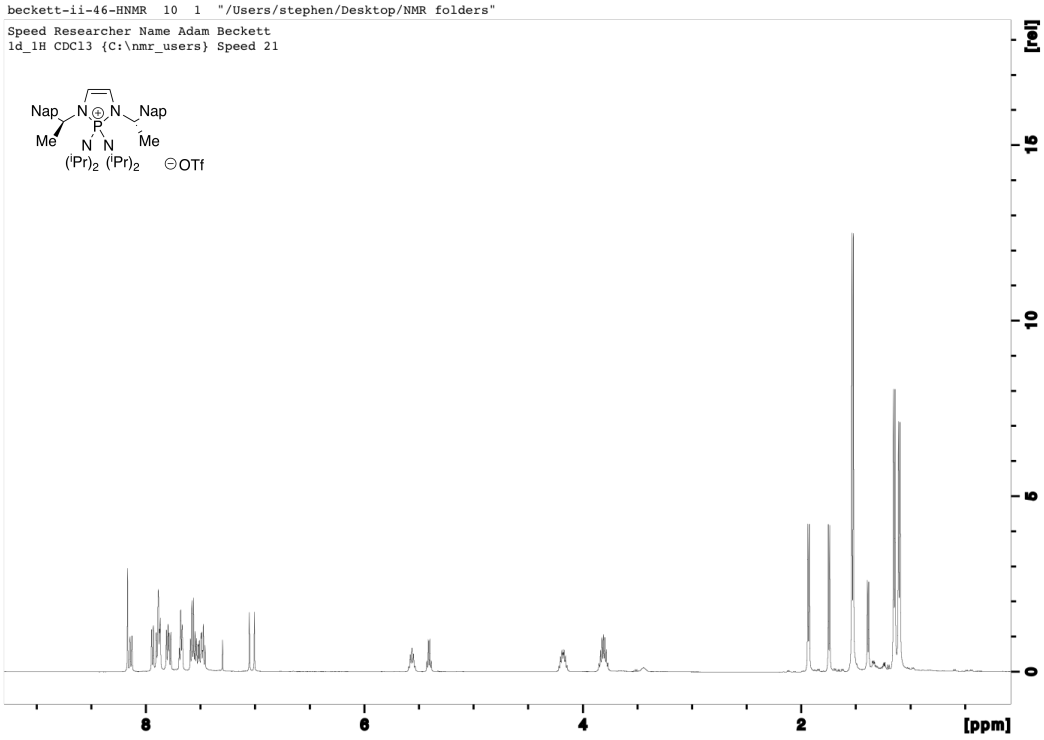


Figure S26. ^{1}H NMR spectrum of **XY-1.2** (500MHz, $CDCl_3$)

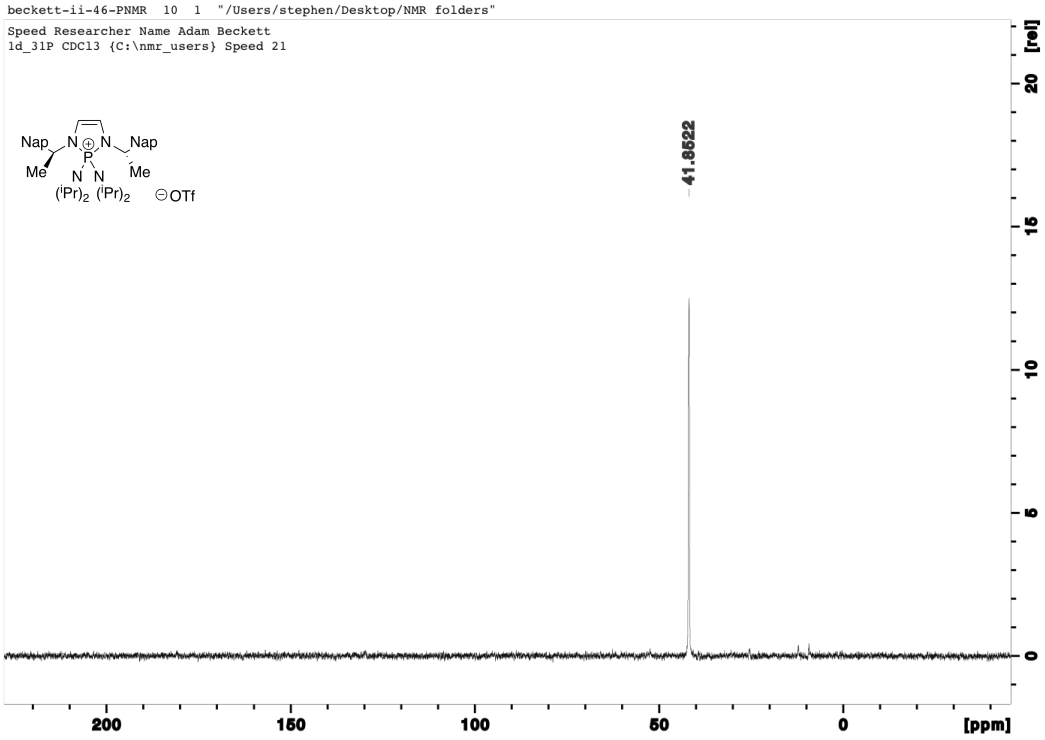


Figure S27. ^{31}P NMR spectrum of **XY-1.2** (202MHz, $CDCl_3$)

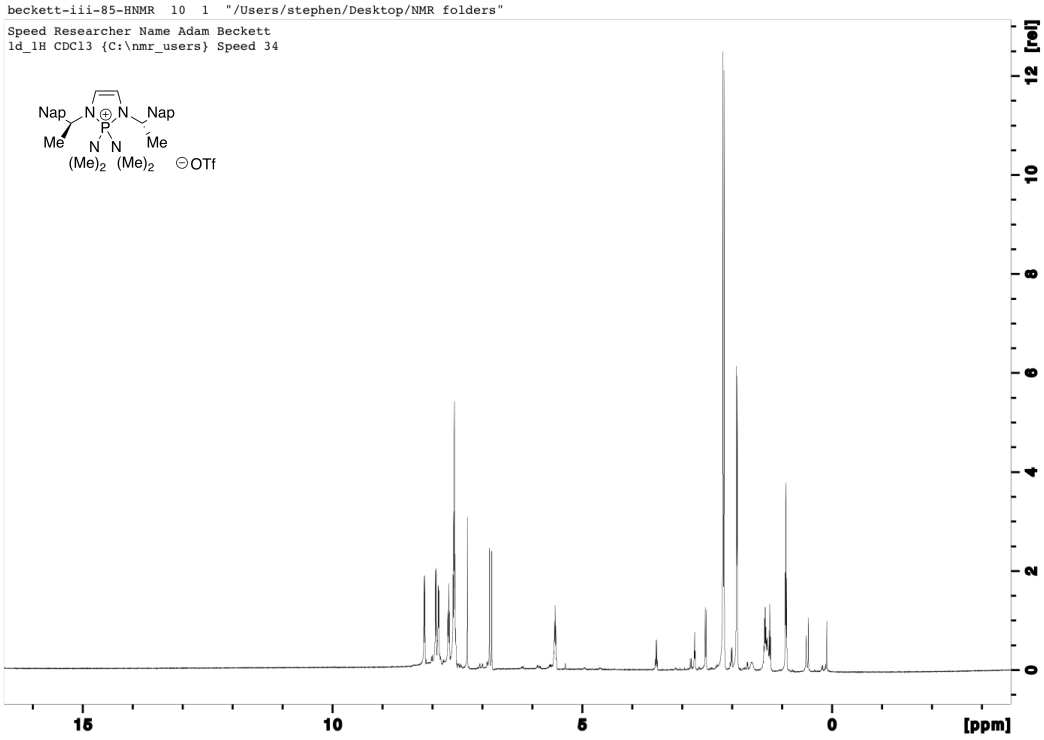


Figure S28. ^{1}H NMR spectrum of **XY-1.3** (500MHz, $CDCl_3$)

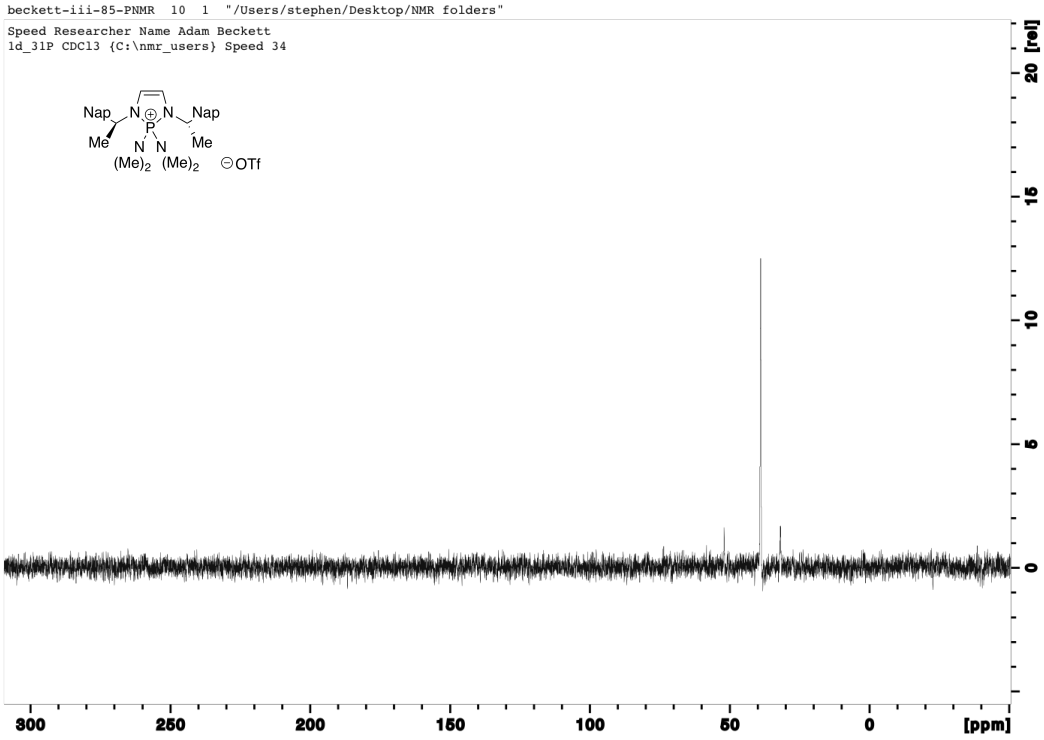


Figure S29. ^{31}P NMR spectrum of **XY-1.3** (202MHz, $CDCl_3$)

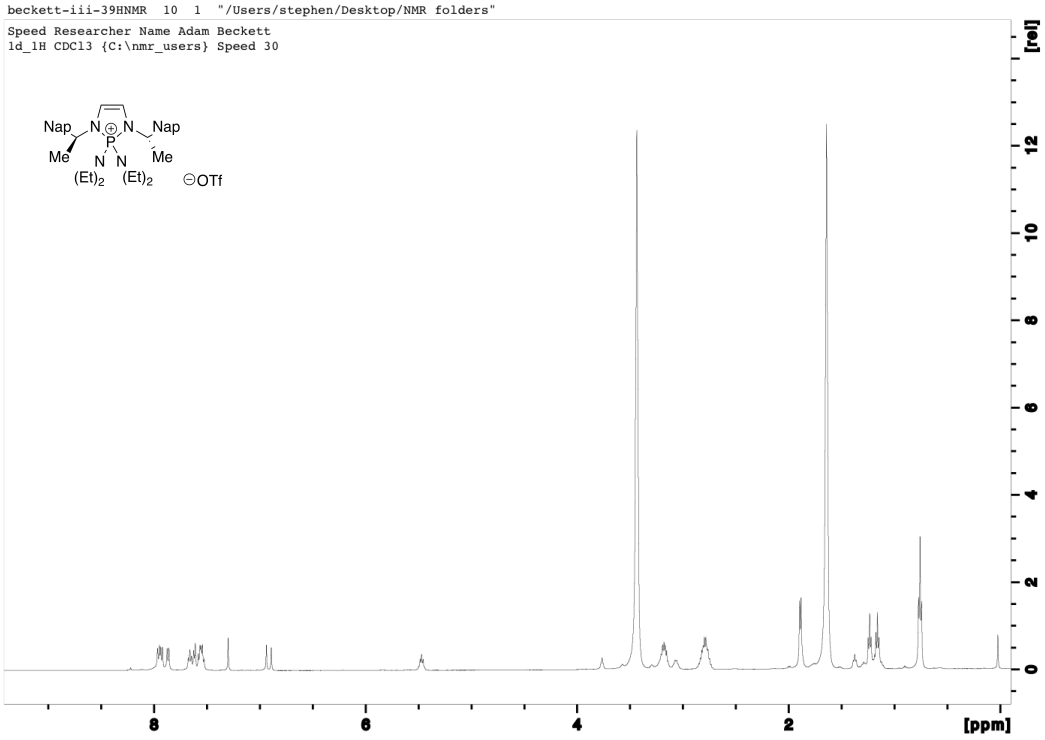


Figure S30. ^{1}H NMR spectrum of **XY-1.4** (500MHz, $CDCl_3$)

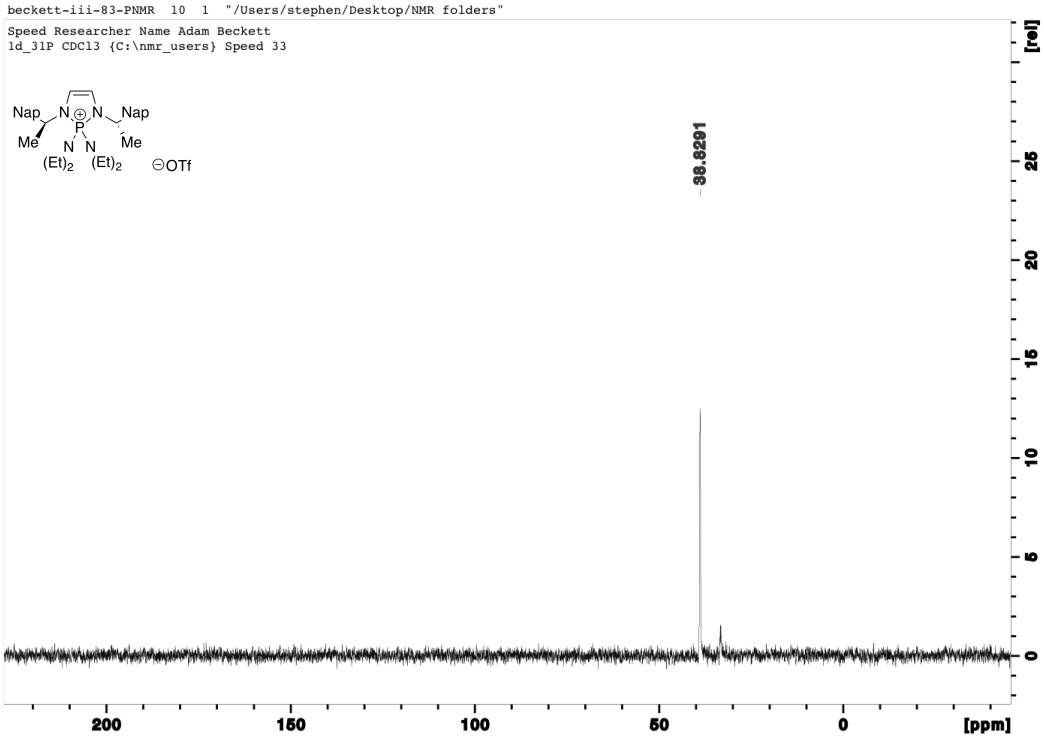


Figure S31. ^{31}P NMR spectrum of **XY-1.4** (202MHz, $CDCl_3$)

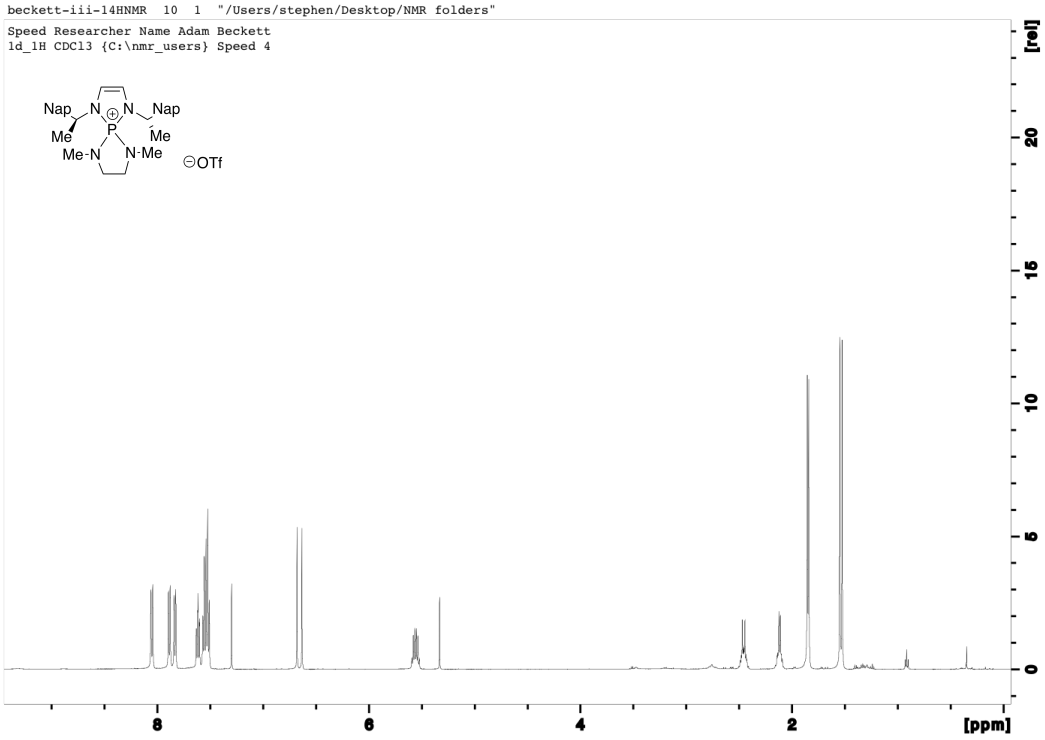


Figure S32. ^{1}H NMR spectrum of **XY-1.5** (500MHz, $CDCl_3$)

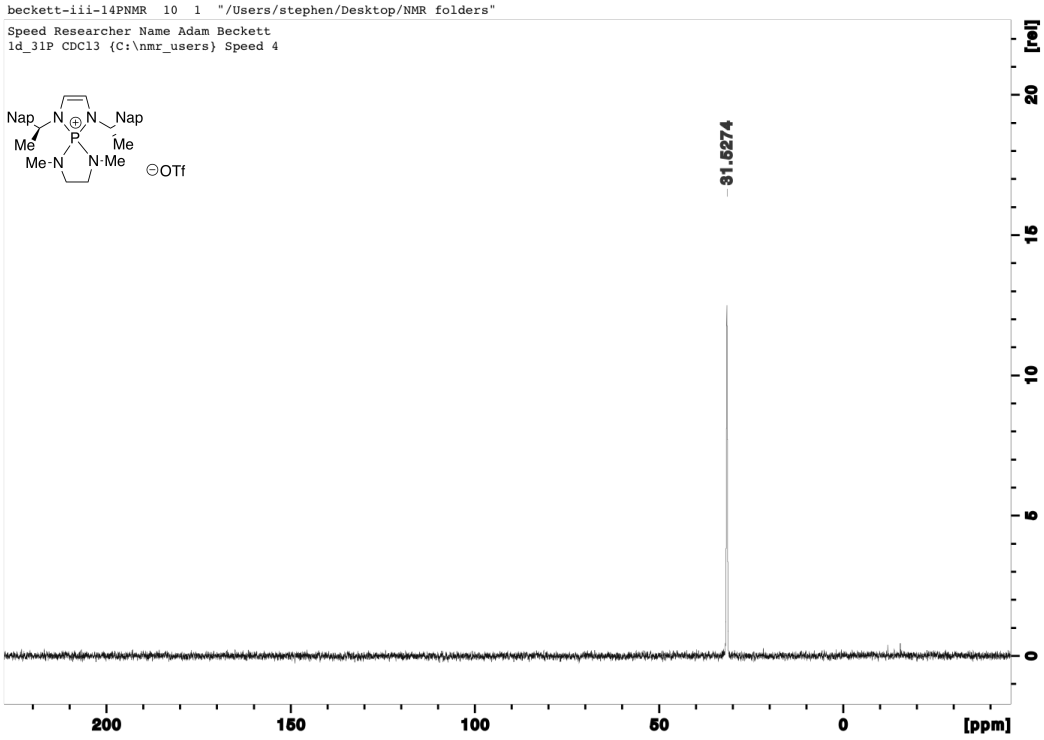


Figure S33. ^{31}P NMR spectrum of **XY-1.5** (202MHz, $CDCl_3$)

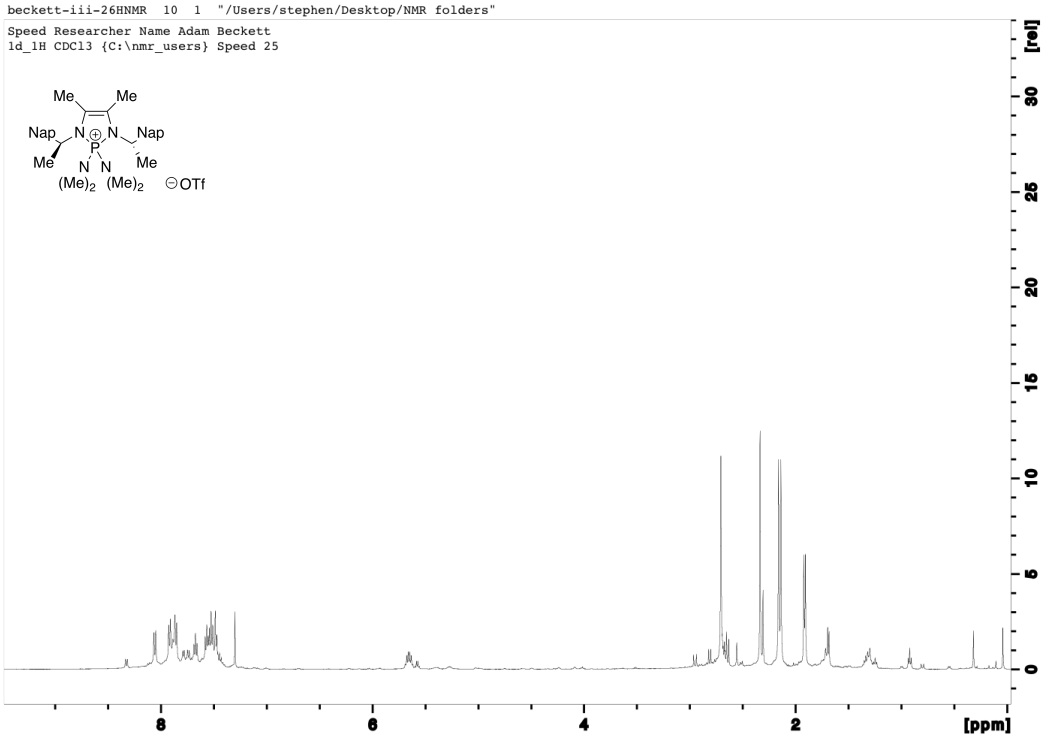


Figure S34. ^{1}H NMR spectrum of **XY-2.3** (500MHz, $CDCl_3$)

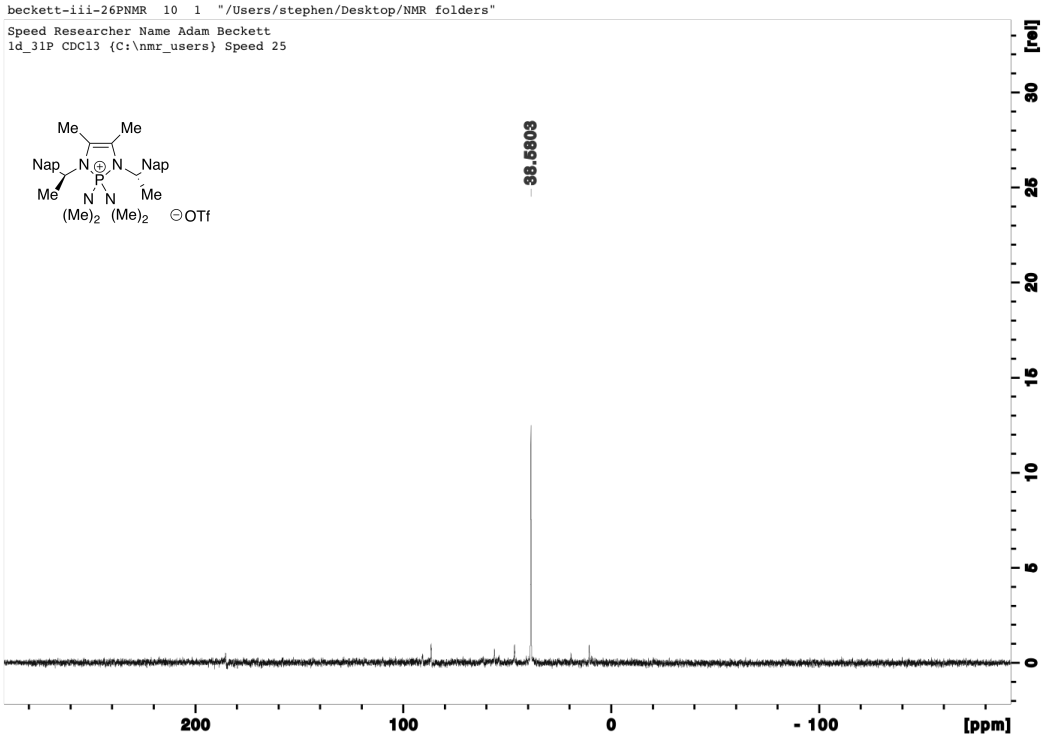


Figure S35. ^{31}P NMR spectrum of **XY-2.3** (202MHz, $CDCl_3$)

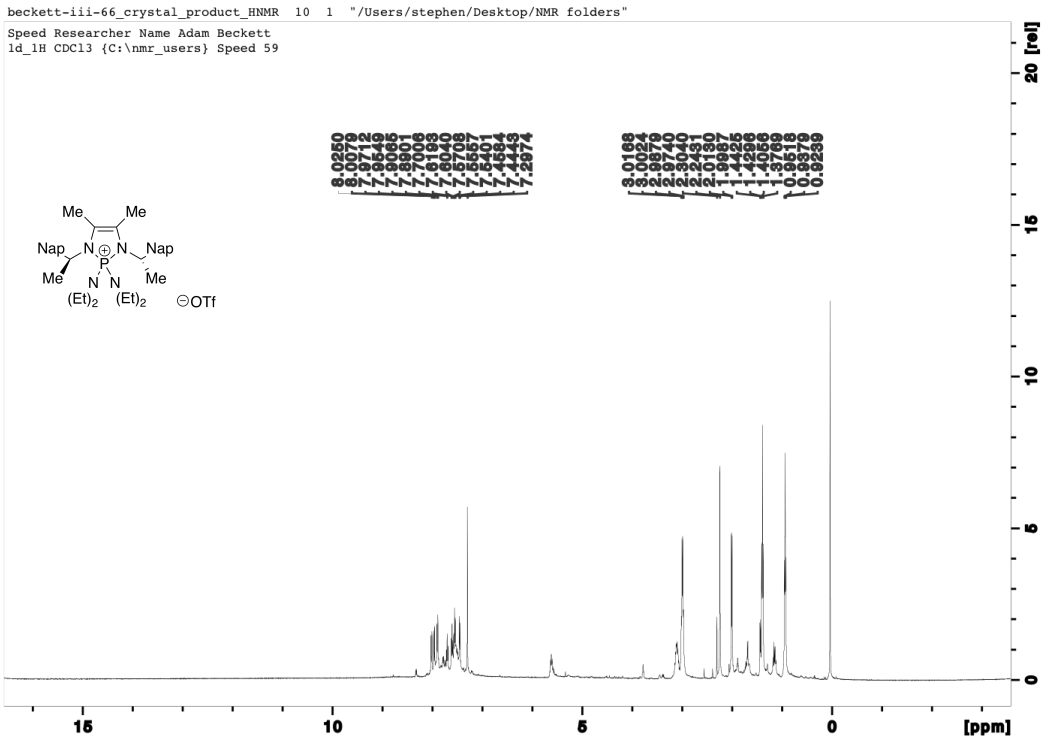


Figure S36. ^{1}H NMR spectrum of **XY-2.4** (500MHz, $CDCl_3$)

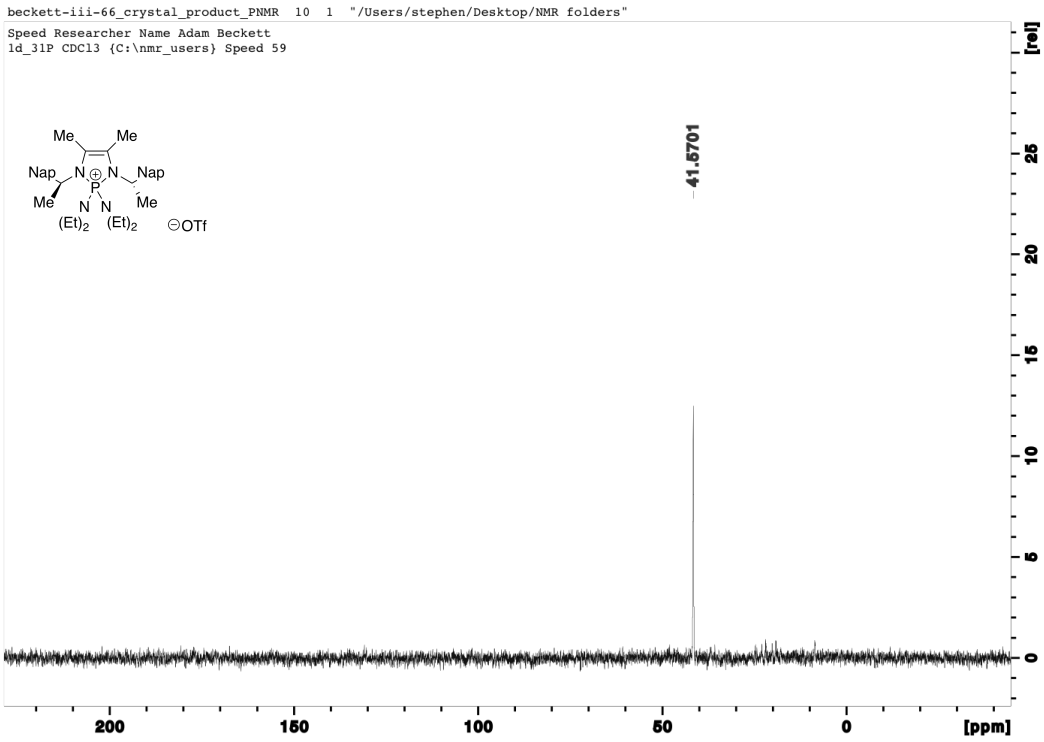


Figure S37. ^{31}P NMR spectrum of **XY-2.4** (202MHz, $CDCl_3$)

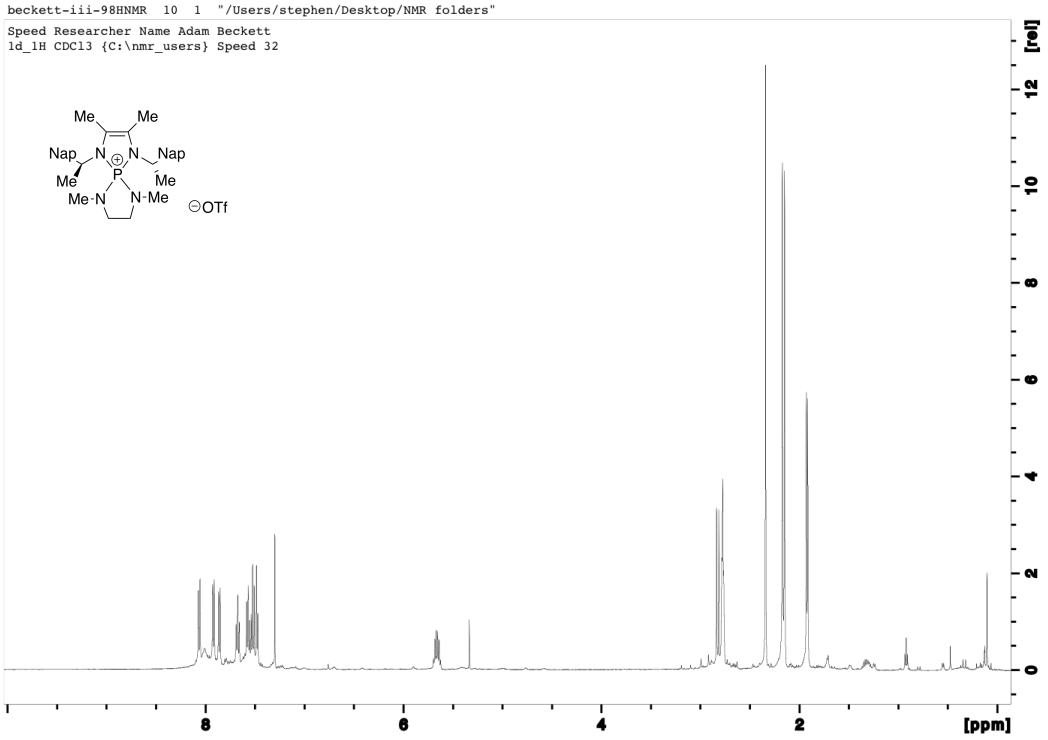


Figure S38. ^{1}H NMR spectrum of **XY-2.5** (500MHz, $CDCl_3$)

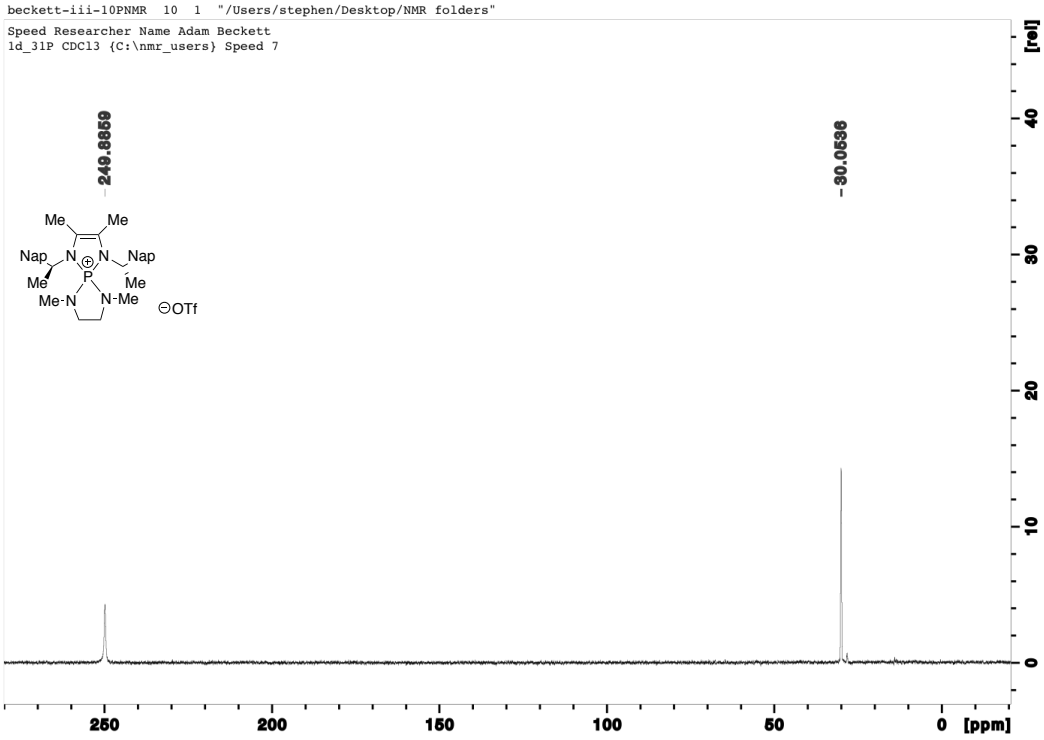


Figure S39. ^{31}P NMR spectrum of **XY-2.5** (202MHz, $CDCl_3$)

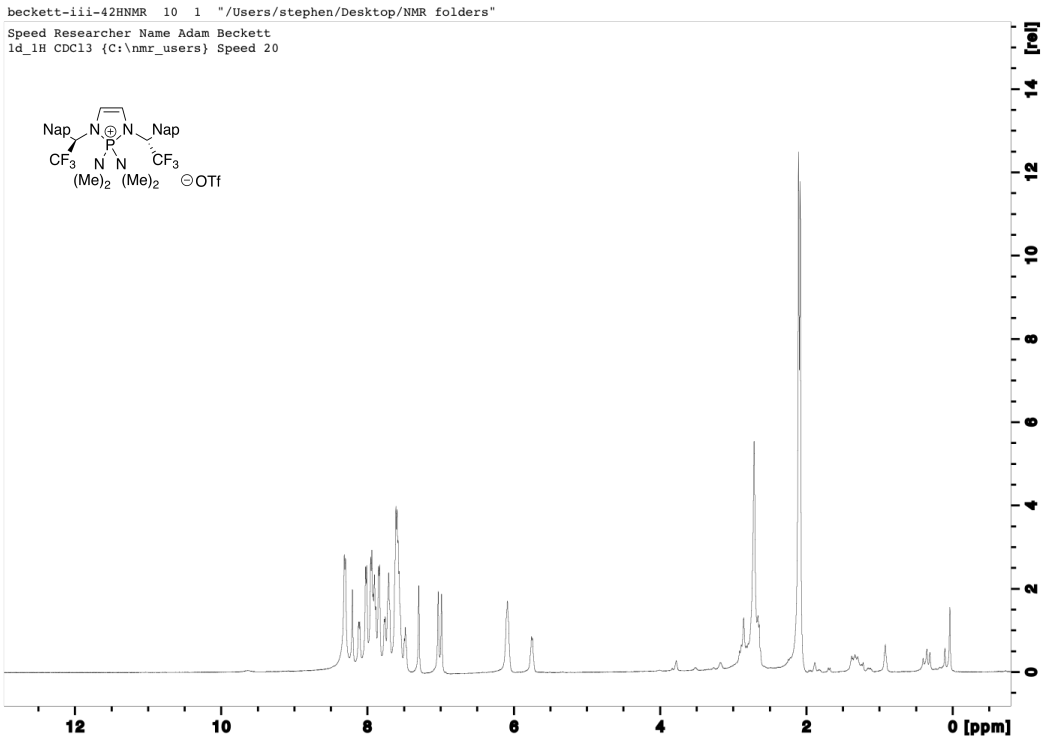


Figure S40. ^{1}H NMR spectrum of **XY-3.3** (500MHz, $CDCl_3$)

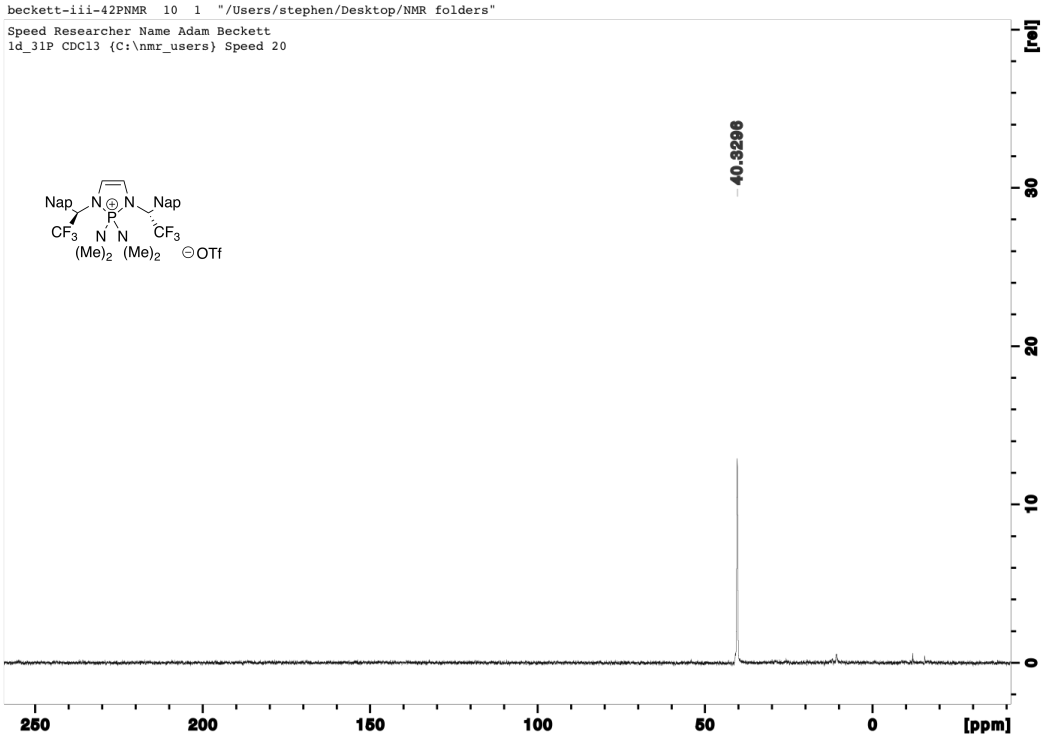


Figure S41. ^{31}P NMR spectrum of **XY-3.3** (202MHz, $CDCl_3$)

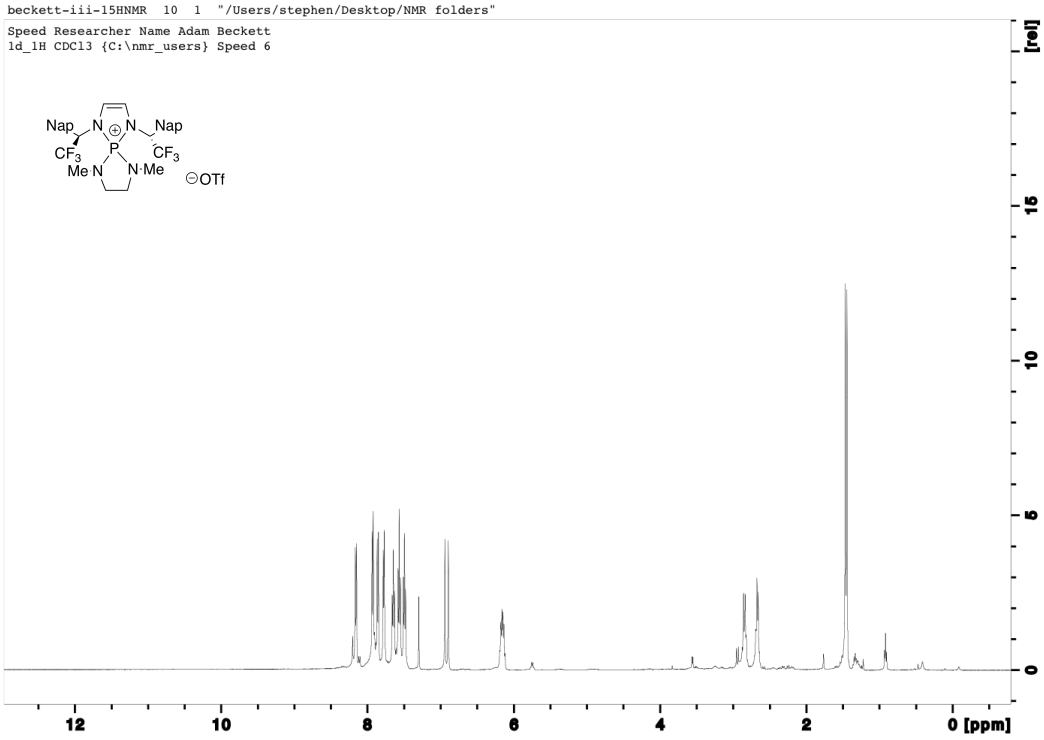


Figure S42. ^{1}H NMR spectrum of **XY-3.5** (500MHz, $CDCl_3$)

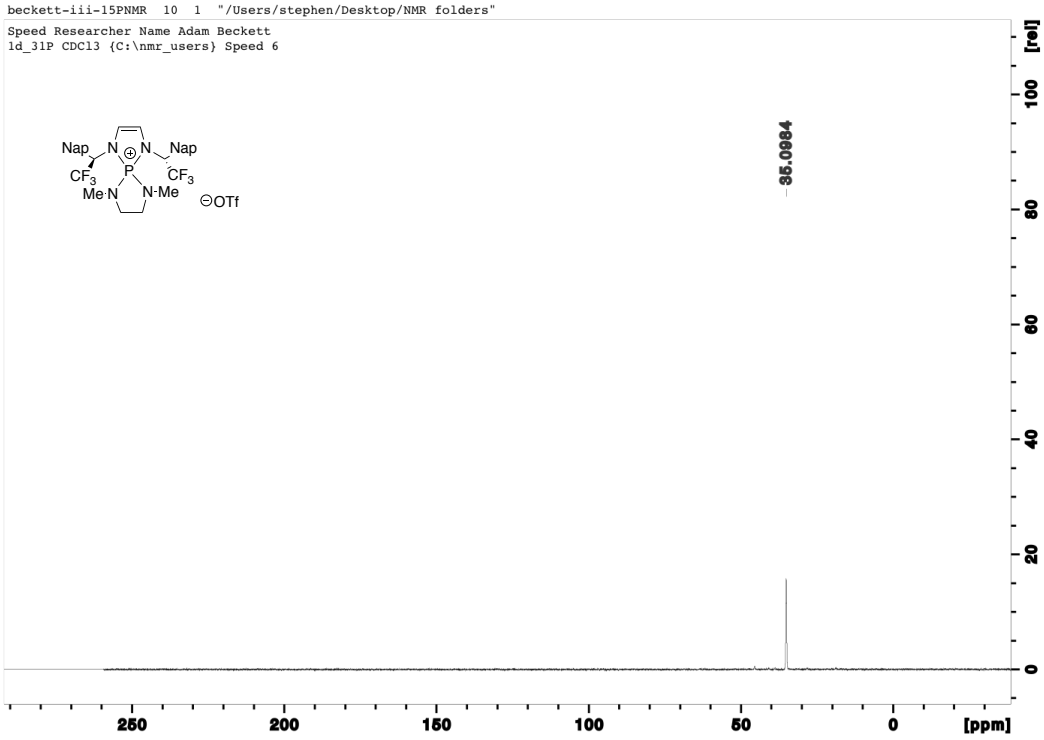


Figure S43. ^{31}P NMR spectrum of **XY-3.5** (202MHz, $CDCl_3$)

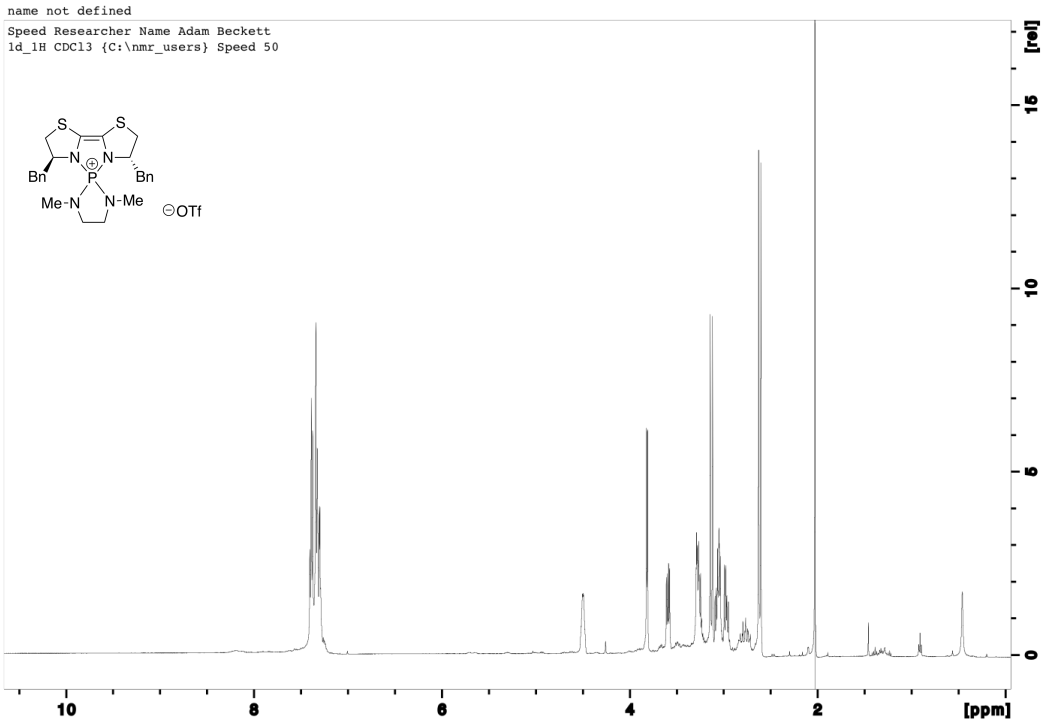


Figure S44. ^{1}H NMR spectrum of **XY-5.5** (500MHz, $CDCl_3$)

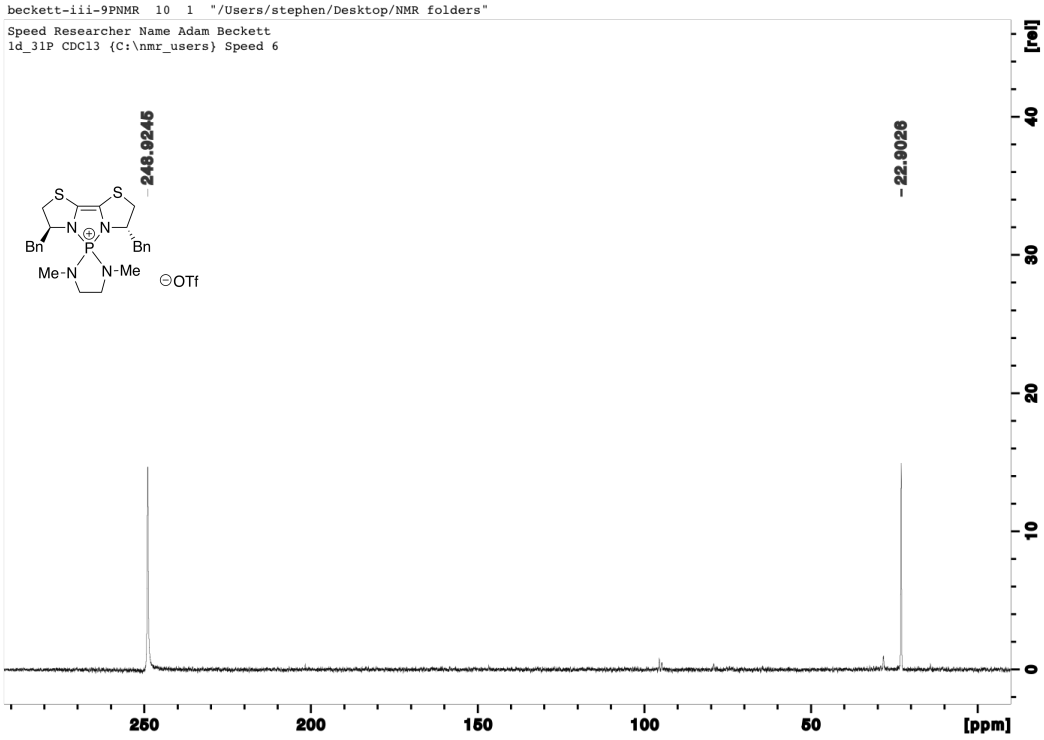


Figure S45. ^{31}P NMR spectrum of **XY-5.5** with impurities (202MHz, $CDCl_3$)

HPLC Data

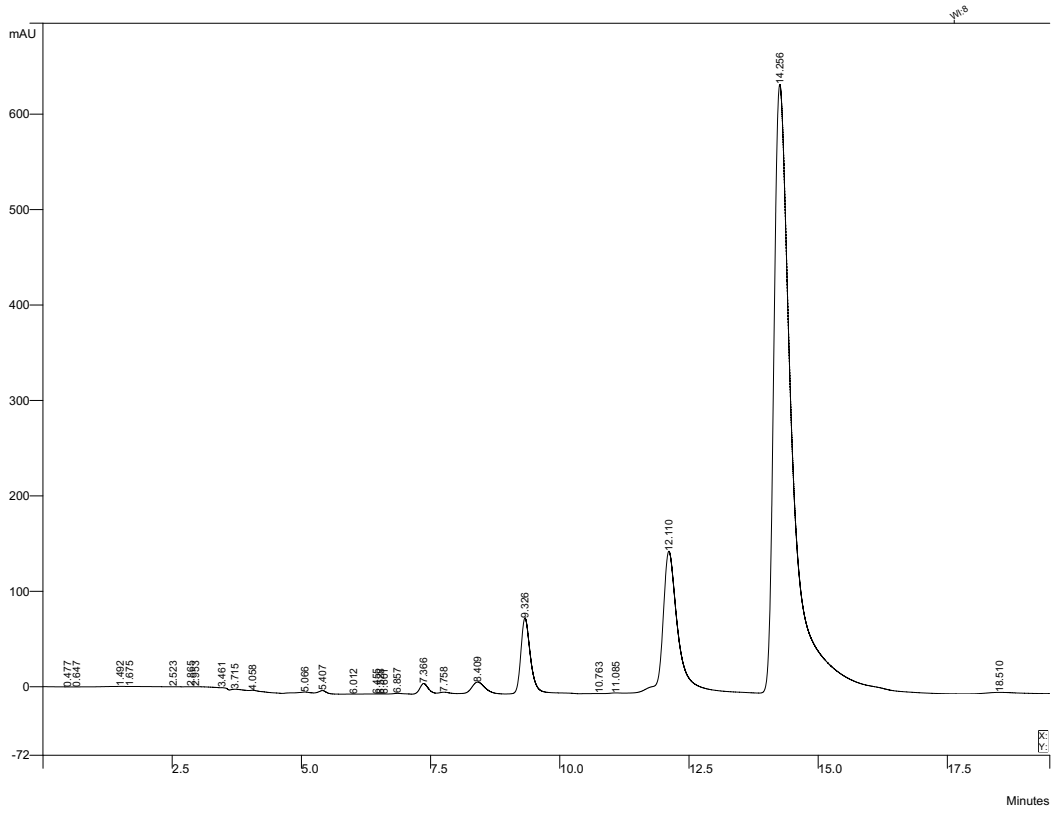


Figure S46. HPLC trace for imine substrate via **XY-1.2** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

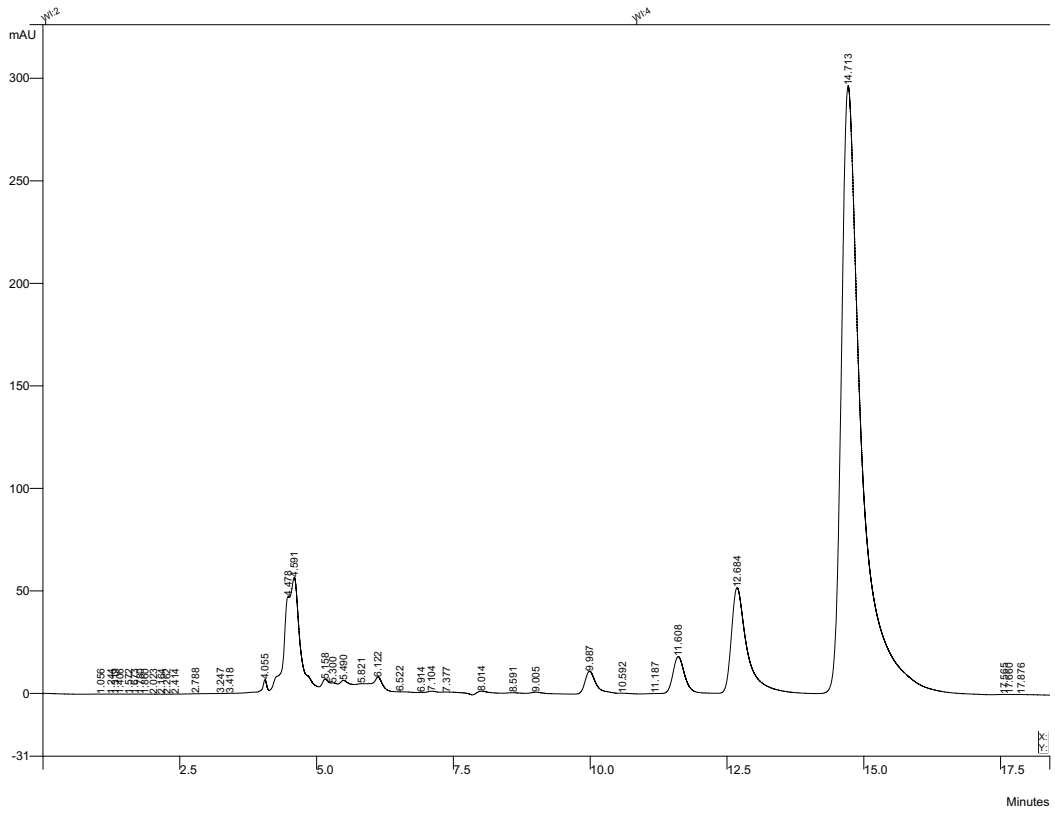


Figure S47. HPLC trace for imine substrate via **XY-1.3** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

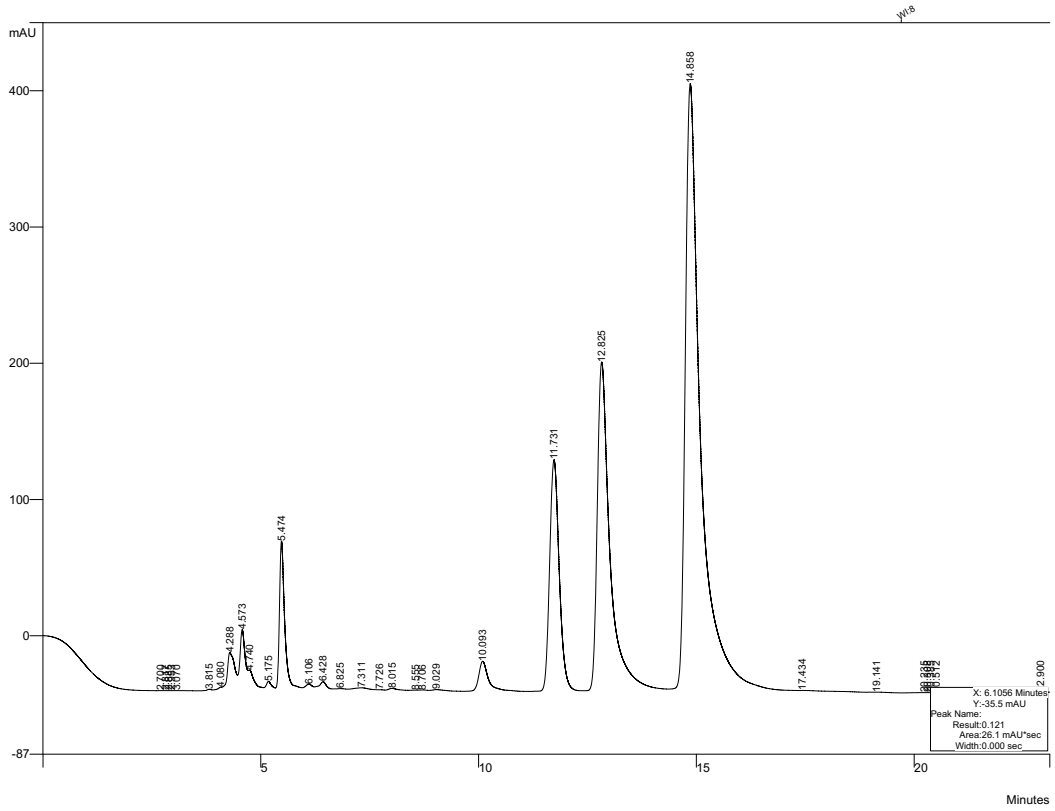


Figure S48. HPLC trace for imine substrate via **XY-1.4** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

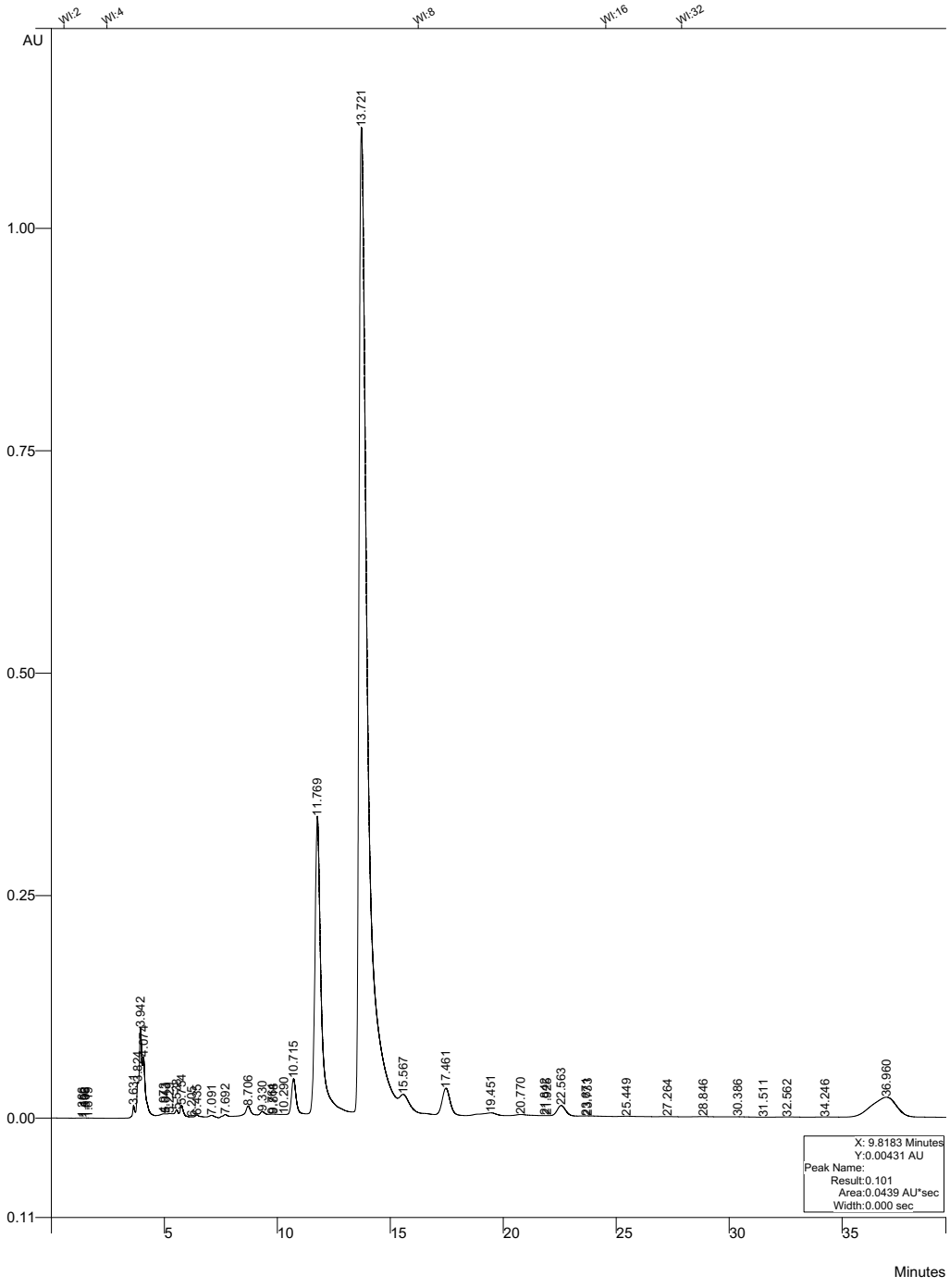


Figure S49. HPLC trace for imine substrate via **XY-2.3** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

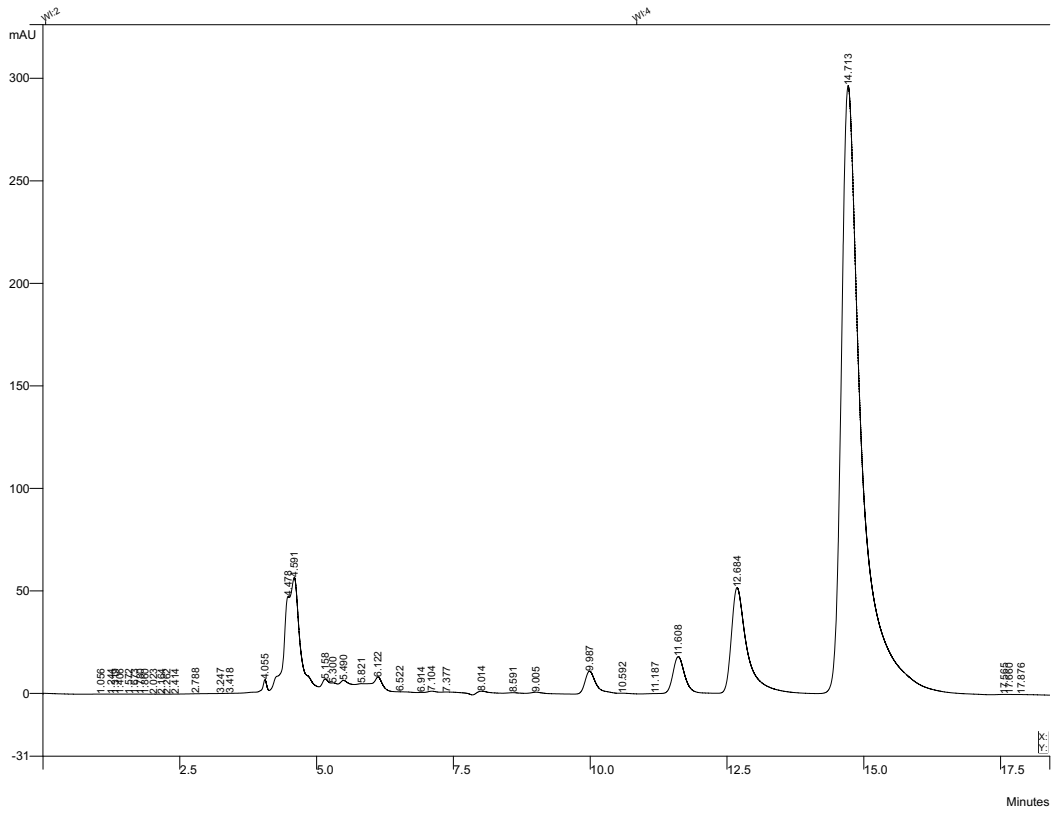


Figure S50. HPLC trace for imine substrate via **XY-2.4** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

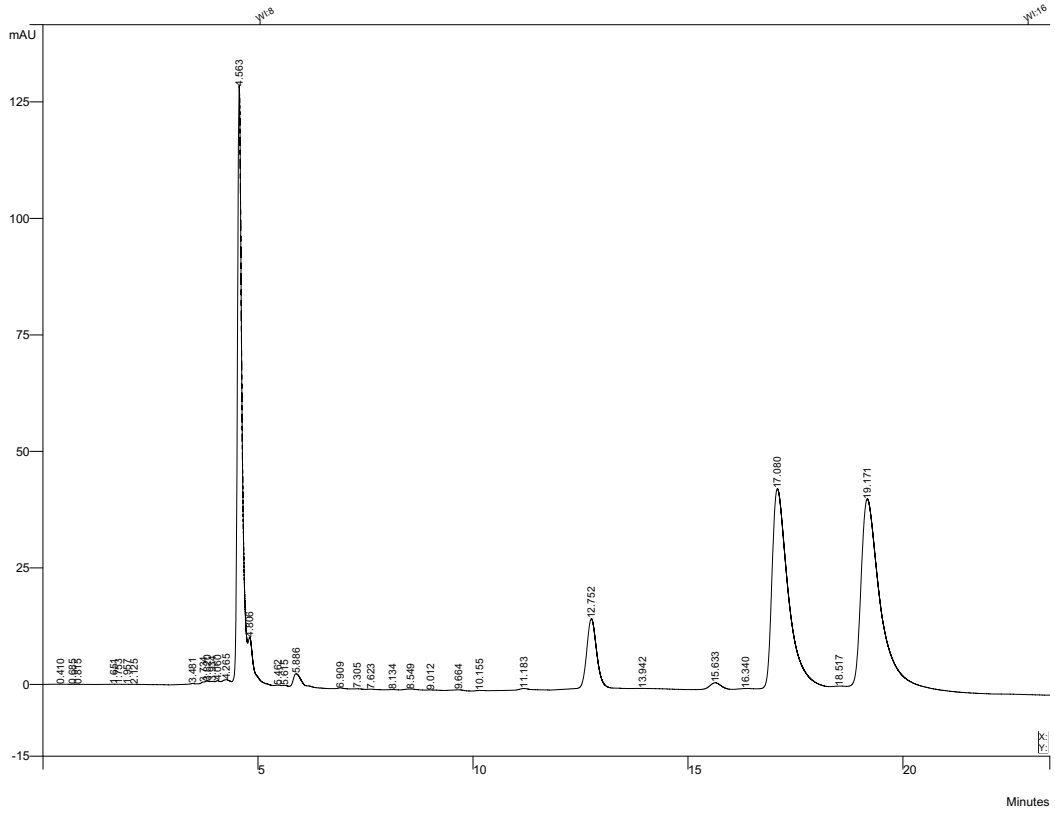


Figure S51. HPLC trace for imine substrate via **XY-2.5** catalyzed by hydroboration (Astec Cellulos DMP column, 99% *n*-hexane and 1% *i*PrOH)

References

(1) Adams, M. R.; Tien, C.-H.; Huchenski, B. S. N.; Ferguson, M. J.; Speed, A. W. H. Diazaphospholene Precatalysts for Imine and Conjugate Reductions. *Angew. Chem. Int. Ed.* **2017**, *56* (22), 6268–6271.

(2) Gracheva, I. A.; Shchegravina, E. S.; Schmalz, H.-G.; Beletskaya, I. P.; Fedorov, A. Yu. Colchicine Alkaloids and Synthetic Analogues: Current Progress and Perspectives. *J. Med. Chem.* **2020**, *63* (19), 10618–10651.

(3) A. Sheldon, R. Fundamentals of Green Chemistry: Efficiency in Reaction Design. *Chem. Soc. Rev.* **2012**, *41* (4), 1437–1451.

(4) Bayne, J. M.; Stephan, D. W. Phosphorus Lewis Acids: Emerging Reactivity and Applications in Catalysis. *Chem. Soc. Rev.* **2016**, *45* (4), 765–774.

(5) Leitao, E. M.; Jurca, T.; Manners, I. Catalysis in Service of Main Group Chemistry Offers a Versatile Approach to p -Block Molecules and Materials. *Nat. Chem.* **2013**, *5* (10), 817–829.

(6) Shende, V. S.; Singh, P.; Bhanage, B. M. Recent Trends in Organocatalyzed Asymmetric Reduction of Prochiral Ketones. *Catal. Sci. Technol.* **2018**, *8* (4), 955–969.

(7) Carroll, M. P.; Guiry, P. J. P,N Ligands in Asymmetric Catalysis. *Chem. Soc. Rev.* **2014**, *43* (3), 819–833.

(8) Janssen-Müller, D.; Schlepphorst, C.; Glorius, F. Privileged Chiral N-Heterocyclic Carbene Ligands for Asymmetric Transition-Metal Catalysis. *Chem. Soc. Rev.* **2017**, *46* (16), 4845–4854.

(9) Wilkins, L. C.; Melen, R. L. Enantioselective Main Group Catalysis: Modern Catalysts for Organic Transformations. *Coord. Chem. Rev.* **2016**, *324*, 123–139.

(10) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015**, *115* (13), 6621–6686.

(11) de Frémont, P.; Marion, N.; Nolan, S. P. Carbenes: Synthesis, Properties, and Organometallic Chemistry. *Coord. Chem. Rev.* **2009**, *253* (7), 862–892.

(12) Arduengo, A. J.; Harlow, R. L.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113* (1), 361–363.

(13) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115* (17), 9307–9387.

(14) Peris, E. Smart N-Heterocyclic Carbene Ligands in Catalysis. *Chem. Rev.* **2018**, *118* (19), 9988–10031.

(15) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in N-Heterocyclic Carbene (NHC)-Catalysed Benzoin Reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 444–461.

(16) Breslow, R. On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80* (14), 3719–3726.

(17) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. From Mono-Triazolium Salt to Bis-Triazolium Salt: Improvement of the Asymmetric Intermolecular Benzoin Condensation. *Adv. Synth. Catal.* **2008**, *350* (16), 2645–2651.

(18) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. Highly Enantioselective Benzoin Condensation Reactions Involving a Bifunctional Protic Pentafluorophenyl-Substituted Triazolium Precatalyst. *J. Org. Chem.* **2009**, *74* (23), 9214–9217.

(19) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-Dihydro-1H-1,2,4-Triazol-5-Ylidene, a New Stable Carbene. *Angew. Chem. Int. Ed. Engl.* **1995**, *34* (9), 1021–1023.

(20) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107* (12), 5606–5655.

(21) Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. Chiral Heterocylic Carbenes in Asymmetric Homogeneous Catalysis. *Angew. Chem. Int. Ed. Engl.* **1996**, *35* (23–24), 2805–2807.

(22) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. Chiral Imidazolylidine Ligands for Asymmetric Hydrogenation of Aryl Alkenes. *J. Am. Chem. Soc.* **2001**, *123* (36), 8878–8879.

(23) Yam, V. W.-W.; Lee, J. K.-W.; Ko, C.-C.; Zhu, N. Photochromic Diarylethene-Containing Ionic Liquids and N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2009**, *131* (3), 912–913.

(24) Hettmanczyk, L.; Manck, S.; Hoyer, C.; Hohloch, S.; Sarkar, B. Heterobimetallic Complexes with Redox-Active Mesoionic Carbenes as Metalloligands: Electrochemical Properties, Electronic Structures and Catalysis. *Chem. Commun.* **2015**, *51* (54), 10949–10952.

(25) Stephan, D. W. “Frustrated Lewis Pairs”: A Concept for New Reactivity and Catalysis. *Org. Biomol. Chem.* **2008**, *6* (9), 1535–1539.

(26) Lam, J.; Szkop, K. M.; Mosaferi, E.; Stephan, D. W. FLP Catalysis: Main Group Hydrogenations of Organic Unsaturated Substrates. *Chem. Soc. Rev.* **2019**, *48* (13), 3592–3612.

(27) Parks, D. J.; Piers, W. E. Tris(Pentafluorophenyl)Boron-Catalyzed Hydrosilation of Aromatic Aldehydes, Ketones, and Esters. *J. Am. Chem. Soc.* **1996**, *118* (39), 9440–9441.

(28) Liu, Y.; Du, H. Chiral Dienes as “Ligands” for Borane-Catalyzed Metal-Free Asymmetric Hydrogenation of Imines. *J. Am. Chem. Soc.* **2013**, *135* (18), 6810–6813.

(29) Erős, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. Catalytic Hydrogenation with Frustrated Lewis Pairs: Selectivity Achieved by Size-Exclusion Design of Lewis Acids. *Chem. – Eur. J.* **2012**, *18* (2), 574–585.

(30) Eisenberger, P.; Bailey, A. M.; Crudden, C. M. Taking the F out of FLP: Simple Lewis Acid–Base Pairs for Mild Reductions with Neutral Boranes via Borenium Ion Catalysis. *J. Am. Chem. Soc.* **2012**, *134* (42), 17384–17387.

(31) Spielmann, J.; Buch, F.; Harder, S. Early Main-Group Metal Catalysts for the Hydrogenation of Alkenes with H2. *Angew. Chem. Int. Ed.* **2008**, *47* (49), 9434–9438.

(32) Dunn, N. L.; Ha, M.; Radosevich, A. T. Main Group Redox Catalysis: Reversible PIII/PV Redox Cycling at a Phosphorus Platform. *J. Am. Chem. Soc.* **2012**, *134* (28), 11330–11333.

(33) Martin, D.; Soleilhavoup, M.; Bertrand, G. Stable Singlet Carbenes as Mimics for Transition Metal Centers. *Chem. Sci.* **2011**, *2* (3), 389–399.

(34) Chong, C. C.; Hirao, H.; Kinjo, R. A Concerted Transfer Hydrogenolysis: 1,3,2-Diazaphospholene-Catalyzed Hydrogenation of N=N Bond with Ammonia–Borane. *Angew. Chem. Int. Ed.* **2014**, *53* (13), 3342–3346.

(35) Gudat, D.; Haghverdi, A.; Nieger, M. Umpolung of P−H Bonds. *Angew. Chem. Int. Ed.* **2000**, *39* (17), 3084–3086.

(36) Gudat, D.; Haghverdi, A.; Hupfer, H.; Nieger, M. Stability and Electrophilicity of Phosphorus Analogues of Arduengo Carbenes—An Experimental and Computational Study. *Chem. – Eur. J.* **2000**, *6* (18), 3414–3425.

(37) Burck, S.; Gudat, D.; Nieger, M.; Du Mont, W.-W. P-Hydrogen-Substituted 1,3,2-Diazaphospholenes: Molecular Hydrides. *J. Am. Chem. Soc.* **2006**, *128* (12), 3946–3955.

(38) Chong, C. C.; Kinjo, R. Catalytic Hydroboration of Carbonyl Derivatives, Imines, and Carbon Dioxide. *ACS Catal.* **2015**, *5* (6), 3238–3259.

(39) Miaskiewicz, S.; Reed, J. H.; Donets, P. A.; Oliveira, C. C.; Cramer, N. Chiral 1,3,2-Diazaphospholenes as Catalytic Molecular Hydrides for Enantioselective Conjugate Reductions. *Angew. Chem. Int. Ed.* **2018**, *57* (15), 4039–4042.

(40) Rao, B.; Chong, C. C.; Kinjo, R. Metal-Free Regio- and Chemoselective Hydroboration of Pyridines Catalyzed by 1,3,2-Diazaphosphenium Triflate. *J. Am. Chem. Soc.* **2018**, *140* (2), 652–656.

(41) Hynes, T.; Welsh, E. N.; McDonald, R.; Ferguson, M. J.; Speed, A. W. H. Pyridine Hydroboration with a Diazaphospholene Precatalyst. *Organometallics* **2018**, *37* (6), 841–844.

(42) Lundrigan, T.; Welsh, E. N.; Hynes, T.; Tien, C.-H.; Adams, M. R.; Roy, K. R.; Robertson, K. N.; Speed, A. W. H. Enantioselective Imine Reduction Catalyzed by Phosphenium Ions. *J. Am. Chem. Soc.* **2019**, *141* (36), 14083–14088.

(43) Lundrigan, T.; Tien, C.-H.; Robertson, K. N.; Speed, A. W. H. Air and Water Stable Secondary Phosphine Oxides as Diazaphospholene Precatalysts. *Chem. Commun.* **2020**, *56* (58), 8027–8030.

(44) Leblanc, M.; Fagnou, K. Allocolchicinoid Synthesis via Direct Arylation. *Org. Lett.* **2005**, *7* (14), 2849–2852.

(45) Dasgeb, B.; Kornreich, D.; McGuinn, K.; Okon, L.; Brownell, I.; Sackett, D. L. Colchicine: An Ancient Drug with Novel Applications. *Br. J. Dermatol.* **2018**, *178* (2), 350–356.

(46) Besong, G.; Billen, D.; Dager, I.; Kocienski, P.; Sliwinski, E.; Tai, L. R.; Boyle, F. T. A Synthesis of (AR,7S)-(−)-N-Acetylcolchinol and Its Conjugate with a Cyclic RGD Peptide. *Tetrahedron* **2008**, *64* (21), 4700–4710.

(47) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. Synthesis of (S)-(−)-N-Acetylcolchinol Using Intramolecular Biaryl Oxidative Coupling. *Org. Biomol. Chem.* **2006**, *4* (11), 2193–2207.

(48) Leung, Y. Y.; Yao Hui, L. L.; Kraus, V. B. Colchicine—Update on Mechanisms of Action and Therapeutic Uses. *Semin. Arthritis Rheum.* **2015**, *45* (3), 341–350.

(49) Niel, E.; Scherrmann, J.-M. Colchicine Today. *Joint Bone Spine* **2006**, *73* (6), 672–678.

(50) Ravelli, R. B. G.; Gigant, B.; Curmi, P. A.; Jourdain, I.; Lachkar, S.; Sobel, A.; Knossow, M. Insight into Tubulin Regulation from a Complex with Colchicine and a Stathmin-like Domain. *Nature* **2004**, *428* (6979), 198–202.

(51) Jordan, M. A.; Wilson, L. Microtubules as a Target for Anticancer Drugs. *Nat. Rev. Cancer* **2004**, *4* (4), 253–265.

(52) Thomopoulou, P.; Sachs, J.; Teusch, N.; Mariappan, A.; Gopalakrishnan, J.; Schmalz, H.-G. New Colchicine-Derived Triazoles and Their Influence on Cytotoxicity and Microtubule Morphology. *ACS Med. Chem. Lett.* **2016**, *7* (2), 188–191.

(53) Alali, F. Q.; Tawaha, K.; El-Elimat, T.; Qasaymeh, R.; Li, C.; Burgess, J.; Nakanishi, Y.; Kroll, D. J.; Wani, M. C.; Oberlies, N. H. Phytochemical Studies and Cytotoxicity Evaluations of Colchicum Tunicatum Feinbr and Colchicum Hierosolymitanum Feinbr (Colchicaceae): Two Native Jordanian Meadow Saffrons. *Nat. Prod. Res.* **2006**, *20* (6), 558–566.

(54) Graening, T.; Friedrichsen, W.; Lex, J.; Schmalz, H.-G. Facile Construction of the Colchicine Skeleton By a Rhodium-Catalyzed Cyclization/Cycloaddition Cascade. *Angew. Chem. Int. Ed.* **2002**, *41* (9), 1524–1526.

(55) Djurdjevic, S.; Green, J. R. Allocolchicines via Intramolecular Nicholas Reactions: The Synthesis of NSC 51046. *Org. Lett.* **2007**, *9* (26), 5505–5508.

(56) Mehdi, M. A.; Djurdjevic, S.; Green, J. R. Lewis Acid Catalyzed Synthesis of Allocolchicinoids. *Synlett* **2015**, *26* (17), 2408–2412.

(57) Seganish, W. M.; DeShong, P. Application of Aryl Siloxane Cross-Coupling to the Synthesis of Allocolchicinoids. *Org. Lett.* **2006**, *8* (18), 3951–3954.

(58) Liu, X.; Hu, Y.-J.; Chen, B.; Min, L.; Peng, X.-S.; Zhao, J.; Li, S.; Wong, H. N. C.; Li, C.-C. Asymmetric Total Syntheses of Colchicine, β-Lumicolchicine, and Allocolchicinoid N-Acetylcolchinol-O-Methyl Ether (NCME). *Org. Lett.* **2017**, *19* (17), 4612–4615.

(59) Lan, X.-B.; Ye, Z.; Liu, J.; Huang, M.; Shao, Y.; Cai, X.; Liu, Y.; Ke, Z. Sustainable and Selective Alkylation of Deactivated Secondary Alcohols to Ketones by Non-Bifunctional Pincer N-Heterocyclic Carbene Manganese. *ChemSusChem* **2020**, *13* (10), 2557–2563.

(60) Pravst, I.; Zupan, M.; Stavber, S. Directed Regioselectivity of Bromination of Ketones with NBS: Solvent-Free Conditions versus Water. *Tetrahedron Lett.* **2006**, *47* (27), 4707–4710.

(61) Tsyganov, D. V.; Konyushkin, L. D.; Semenova, M. N.; Semenov, V. V. Synthesis of Analogues of Natural Antimitotic Glaziovianin A Based on Dill and Parsley Seed Essential Oils. *Mendeleev Commun.* **2016**, *26* (4), 285–287.

(62) Palleros, D. R. Solvent-Free Synthesis of Chalcones. *J. Chem. Educ.* **2004**, *81* (9), 1345.

(63) Udd, S.; Jokela, R.; Franzén, R.; Tois, J. Copper-Catalyzed Cyclization of Z-Oximes into 3-Methyl-1,2-Benzisoxazoles. *Tetrahedron Lett.* **2010**, *51* (7), 1030–1033.

(64) Cabrera, M.; Mastandrea, I.; Otero, G.; Cerecetto, H.; González, M. In Vivo Phase II-Enzymes Inducers, as Potential Chemopreventive Agents, Based on the Chalcone and Furoxan Skeletons. *Bioorg. Med. Chem.* **2016**, *24* (8), 1665–1674.

(65) Koprowski, M.; Szymańska, D.; Bodzioch, A.; Marciniak, B.; Różycka-Sokołowska, E.; Bałczewski, P. Synthesis of β-Ketophosphonates with Electron Rich β-Aryl Groups as Useful Organophosphorus Reagents in Lignans Synthesis. *Tetrahedron* **2009**, *65* (20), 4017–4024.

(66) Mirjafary, Z.; Abdoli, M.; Saeidian, H.; Boroon, S.; Kakanejadifard, A. Oxime Ethers as Versatile Precursors in Organic Synthesis: A Review. *RSC Adv.* **2015**, *5* (97), 79361–79384.

(67) Li, H.; Ma, B.; Liu, Q.-S.; Wang, M.-L.; Wang, Z.-Y.; Xu, H.; Li, L.-J.; Wang, X.; Dai, H.-X. Transformations of Aryl Ketones via Ligand-Promoted C−C Bond Activation. *Angew. Chem. Int. Ed.* **2020**, *59* (34), 14388–14393.

(68) Feuer, H.; Braunstein, D. M. Reduction of Oximes, Oxime Ethers, and Oxime Esters with Diborane. Novel Synthesis of Amines. *J. Org. Chem.* **1969**, *34* (6), 1817–1821.

(69) Reeske, G.; Cowley, A. H. One-Step Redox Route to N-Heterocyclic Phosphenium Ions. *Inorg. Chem.* **2007**, *46* (4), 1426–1430.

(70) Dube, J. W.; Farrar, G. J.; Norton, E. L.; Szekely, K. L. S.; Cooper, B. F. T.; Macdonald, C. L. B. A Convenient Method for the Preparation of N-Heterocyclic Bromophosphines: Excellent Precursors to the Corresponding N-Heterocyclic Phosphenium Salts. *Organometallics* **2009**, *28* (15), 4377–4384.

(71) Cheng, X.; Lu, H.; Lu, Z.; Enantioselective Benzylic C-H Arylation via Photoredox and Nickel Dual Catalysis. *Nat. Commun.* **2019**, *10* (1), 3549.

(72) Desimoni, G.; Faita, G.; Jørgensen, K. A. C2-Symmetric Chiral Bis(Oxazoline) Ligands in Asymmetric Catalysis. *Chem. Rev.* **2006**, *106* (9), 3561–3651.

(73) Dieck, H. T.; Dietrich, J. Diazadienes as Controlling Ligands in Catalysis, 51). Synthesis of Chiral Diazadienes R* – N = CR' – CR' = N – R*. *Chem. Ber.* **1984**, *117* (2), 694–701.

(74) Corey, E. J.; Imai, N.; Zhang, H. Y. Designed catalyst for enantioselective Diels-Alder addition from a C2-symmetric chiral bis(oxazoline)-iron(III) complex

(75) Cowley, A. H.; Kemp, R. A. Synthesis and Reaction Chemistry of Stable Two-Coordinate Phosphorus Cations (Phosphenium Ions). *Chem. Rev.* **1985**, *85* (5), 367–382.

(76) Mazieres, M. R.; Roques, C.; Khim, T.; Majoral, J. P.; Wolf, R.; Sanchez, M. Phosphenium Cations in Heterocyclic Chemistry. *Phosphorus Sulfur Silicon Relat. Elem.* **1990**, *49–50* (1–4), 309–312.

(77) Bordignon, B.; Chiron, J.; Fontés, M. Ascorbic Acid Derivatives as a New Class of Antiproliferative Molecules. *Cancer Lett.* **2013**, *338* (2), 317–327.

(78) Coyle, E. E.; Doonan, B. J.; Holohan, A. J.; Walsh, K. A.; Lavigne, F.; Krenske, E. H.; O'Brien, C. J. Catalytic Wittig Reactions of Semi- and Nonstabilized Ylides Enabled by Ylide Tuning. *Angew. Chem. Int. Ed.* **2014**, *53* (47), 12907–12911.